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P-2018/15525

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **NC2018/0007151**
Solicitud de patente a nombre de **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

Yo, CAROLINA DAZA MONTALVO identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, obrando como apoderada de la sociedad TAKEDA PHARMACEUTICAL COMPANY LIMITED, domiciliada en Osaka, Japón, solicitante de la patente de la referencia, en respuesta al oficio No. **12066** notificado electrónicamente el 30 de julio de 2021, relacionado con los requerimientos de fondo de la solicitud, y para el cual se solicitó prórroga de 30 días el 20 de octubre de 2021, atentamente me permito presentar la siguiente información:

1. Modificaciones a las Reivindicaciones y Claridad

Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo capítulo reivindicatorio, el cual consta de cuatro (4) reivindicaciones y reemplaza completamente el capítulo presentado anteriormente. Específicamente, se realizaron las siguientes modificaciones:

1.1 Se ha modificado la reivindicación 1, incluyendo las características de las antiguas reivindicaciones 3 y 5. Adicionalmente, se ha incluido la expresión *"cloruro de sodio a una concentración de aproximadamente 90 mM"*, con el fin de dar claridad a la presente invención. Dichas modificaciones se encuentran sustentadas, por ejemplo, en la página 46 en la sección "Descripción de Tratamientos" y en las antiguas reivindicaciones.

1.2 Se ha eliminado la antigua reivindicación 2 de acuerdo con las modificaciones realizadas a la reivindicación 1.

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1.3 Las reivindicaciones restantes, así como sus dependencias, fueron reenumeradas.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones de patentabilidad planteadas por el examinador en su concepto técnico.

En consecuencia, nos permitimos indicar que el presente capítulo reivindicatorio, que incluye cuatro (4) reivindicaciones, se ajusta a las disposiciones del artículo 30 de la Decisión 486/00.

2. Pago de tasas

En relación con el número de reivindicaciones, atentamente nos permitimos decir que no se adjunta tasa por concepto de reivindicaciones adicionales, toda vez que el nuevo capítulo reivindicatorio tiene igual número de reivindicaciones a las presentadas originalmente, y en esencia es el mismo objeto, pero definido con mayor claridad.

Por otra parte, me permito adjuntar recibo por concepto de pago de tasa de modificación a las reivindicaciones, según lo establecido en la **Resolución No. 59669 de 2020**.

3. Nivel Inventivo

El examinador establece que las reivindicaciones 1 a 7 carecen de nivel inventivo a la luz de las enseñanzas descritas en el documento WO2014/152232 (D1).

A este respecto, me permito decir que el artículo 18 de la Decisión 486 establece que "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*".

Lo anterior significa que el análisis de nivel inventivo **NO** es una comparación de los objetos de las anterioridades y la solicitud en estudio. El análisis de nivel inventivo **debe demostrar** la obviedad de la invención y establecer cómo ésta no contiene un salto cualitativo, que demuestre su altura inventiva, teniendo en cuenta que se hace

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necesario demostrar que la invención analizada carece de nivel inventivo y hubiese sido obvia para una persona versada en la materia.

De acuerdo con lo anterior, el solicitante desea manifestar respetuosamente su desacuerdo, ya que teniendo en cuenta las modificaciones presentadas en el nuevo capítulo reivindicatorio, se superan las objeciones realizadas, por cuanto **dichas características no se encuentran divulgadas en el documento citado por el examinador**.

De acuerdo con lo anterior y sin aceptar el rechazo, simplemente para adelantar el trámite, la reivindicación 1 se modifica como se describió anteriormente para recitar que la composición comprende 300 mg del anticuerpo y cloruro de sodio a una concentración de 90 mM y tiene un pH de 6,0. Nada en D1 habría indicado a un experto en la técnica que seleccionara los componentes específicos en los valores descritos.

Efectos superiores de la composición farmacéutica reclamada

Los resultados del estudio HELP de fase 3 descrito en el Ejemplo 1 de la presente solicitud demuestran que la composición farmacéutica reclamada proporciona efectos superiores en la prevención del ataque de HAE y/o en la reducción de la tasa de ataque de HAE en pacientes humanos. La tasa mensual media de ataques de HAE se redujo significativamente en al menos un 62,8% en comparación con el placebo en los pacientes que recibieron la composición farmacéutica reclamada durante todo el período de tratamiento (Ver, por ejemplo, "Test Product; Dose; and Mode of Administration" de Banjeeri et al., 2018, *JAMA*, 320(20): 2108-2121; Figura 1 de Riedl et al., 2020, Allergy, 75 (11): 2879-2887, copias de dichos documentos se adjuntan al presente memorial). Además, al menos un 30% más de pacientes tratados con la composición farmacéutica reclamada estuvieron libres de ataques durante el período de tratamiento en comparación con los pacientes tratados con placebo, y el número de ataques de HAE moderados y ataques de HAE graves se redujo en al menos un 34,9% y un 11,7%, respectivamente, en comparación con placebo (Ver, por ejemplo, la Figura 3 de Riedl et al). Además, al menos un 54% más de pacientes tratados con la composición farmacéutica reclamada tuvieron al menos un 50% de reducción en la tasa de ataque de HAE en comparación con los pacientes tratados con placebo (Ver, por ejemplo, la Figura 4 de Riedl). Además, al menos un 42,1% más de pacientes tratados con la composición farmacéutica reclamada estuvieron libres de ataques durante el estado estacionario en comparación con los pacientes tratados con placebo, y el número de ataques de HAE moderados y ataques de HAE graves se redujo en al menos un 30,4%

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y un 20,1%, respectivamente, en comparación con placebo (Ver, por ejemplo, la Figura 5).

Además, los resultados del estudio de extensión de etiqueta abierta (OLE) HELP de fase 3 descrito en el Ejemplo 2 de la presente solicitud también demuestran que la composición farmacéutica reclamada proporciona efectos superiores en la prevención del ataque de HAE y/o en la reducción de la tasa de ataque de HAE en pacientes humanos. La tasa de ataque de los pacientes tratados con la composición farmacéutica reclamada se redujo en al menos un 70% en los pacientes en comparación con el valor inicial (Ver, por ejemplo, Riedl et al., 2020, *J. Allergy Clin Immunol*. AB104, copias de dichos documentos se adjuntan al presente memorial). Además, el 57,9% de los pacientes estuvieron libres de ataques durante un período de más de 12 meses y el 78,0% de los pacientes estuvieron libres de ataques durante un período de más de 6 meses. Finalmente, los pacientes tratados con la composición farmacéutica reivindicada tuvieron una media de 27,3 días/mes sin crisis y una duración media sin crisis de 291,3 días. D1 no describe una composición farmacéutica que comprende DX-2930 y el vehículo farmacéuticamente aceptable mencionado, que puede usarse para tratar HAE, como se recita en las reivindicaciones modificadas.

Desarrollo de la composición farmacéutica reclamada

La selección de los componentes específicos y las concentraciones de las composiciones farmacéuticas reclamadas se basó en el desarrollo de una formulación de DX-2930 (también denominada lanadelumab) que permite una alta concentración del anticuerpo sin agregación durante el almacenamiento.

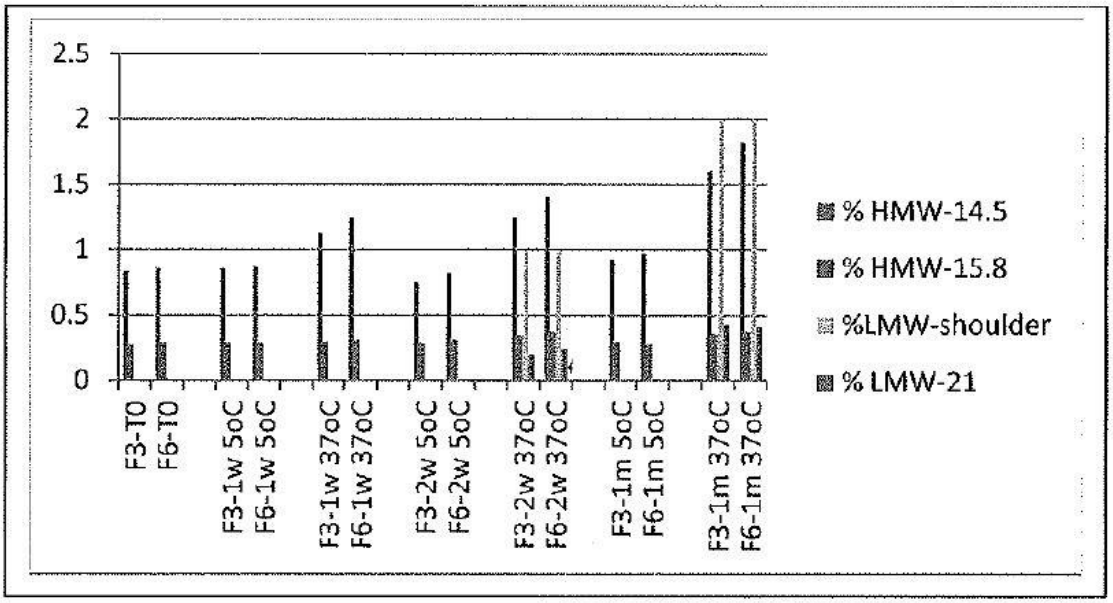
Brevemente, se determinó que la composición farmacéutica reclamada (denominada Fórmula 3 o "F3" en la Figura 30 a continuación) era estable y más resistente a la agregación de anticuerpos en diversas condiciones de almacenamiento (es decir, durante al menos un mes a temperatura ambiente) en comparación con una composición farmacéutica que comprende fosfato de sodio 30 mM, histidina 30 mM, trehalosa al 1% y NaCl 90 mM, pH 6,0 (denominada Fórmula 6 o "F6"), según se evalúa mediante cromatografía de exclusión por tamaño - cromatografía líquida de alta resolución (Estudio SEC-HPLC). Los resultados de este estudio se muestran a continuación en la Figura 30, proporcionada a partir de un informe sobre el desarrollo de la composición farmacéutica reclamada. Brevemente, se obtuvieron muestras que contenían DX-2930 en la composición farmacéutica reclamada (F3) u otra composición farmacéutica denominada Fórmula 6 (F6) en varios puntos de tiempo (0 semanas, 1

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semana, 2 semanas, 1 mes) después de la incubación en varias temperaturas (5°C, 37°C). Las muestras se analizaron mediante SEC-HPLC, que separa las moléculas en función del tamaño, por lo que el DX-2930 agregado aparecerá como una especie de alto peso molecular (% HMW) en comparación con el DX-2930 que no está agregado. Como se muestra a continuación, la composición farmacéutica reclamada ("F3") ha disminuido la agregación de DX-2930 (menor% HMW) en comparación con la formulación alternativa de Fórmula 6 ("F6"), particularmente después de 1 semana o más de incubación de la muestra. Por tanto, la selección de los componentes y concentraciones de la composición farmacéutica reclamada no habría sido obvia para un experto en la técnica porque no todas las formulaciones probadas dieron como resultado DX-2930 que no se agregara.

Figure 30: SEC-HPLC data comparison of DX2930 stability at T1 month

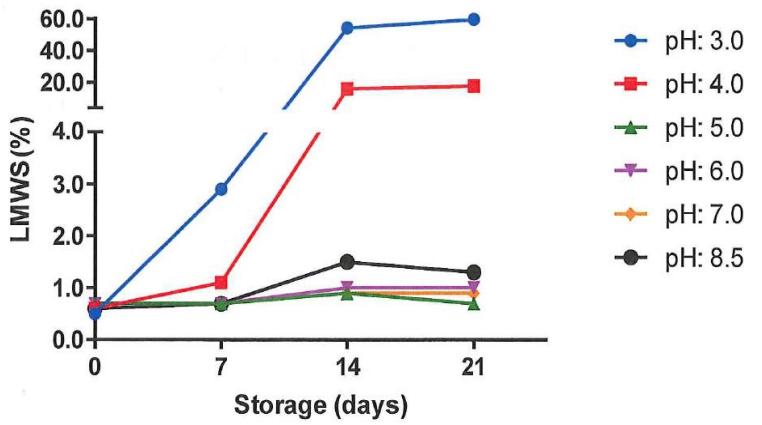


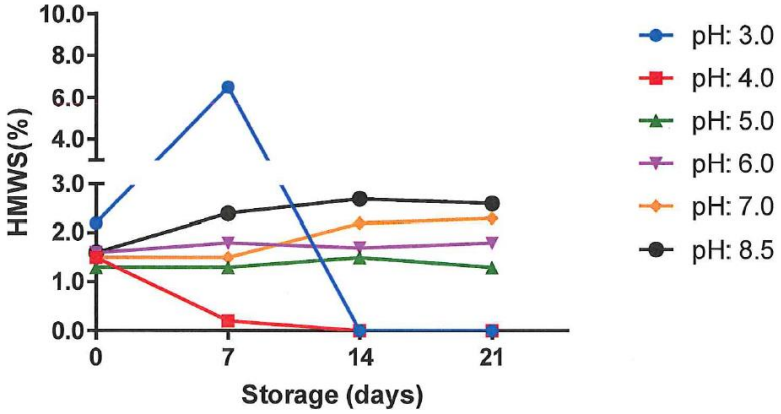
Además, se encontró que no todos los pH probados produjeron una formulación de anticuerpo estable. De hecho, como se muestra en las figuras siguientes de un informe sobre el efecto del pH en la agregación de anticuerpos, se encontró que el rango de pH óptimo de DX-2930 en una composición que comprende buffer citrato-fosfato 100 mM (fosfato disódico y ácido cítrico) y cloruro de sodio 50 mM era 5,0 - 7,0. Brevemente, DX-2930 se incubó en muestras de prueba que comprendían buffer citrato-fosfato con cloruro de sodio 50 mM a varios pH (3,0, 4,0, 5,0, 6,0, 7,0, 8,5) durante 21 días a temperatura ambiente. Se tomaron muestras de las diversas muestras de prueba DX-2930 en varios puntos de tiempo (0 días, 7 días, 14 días, 21 días) y se evaluaron

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mediante cromatografía de exclusión por tamaño (SEC). Debido a que SEC separa las moléculas según el tamaño, el DX-2930 agregado aparecerá como una especie de alto peso molecular (% HMWS) en comparación con el DX-2930 que no está agregado, y el DX-2930 degradado aparecerá como una especie de bajo peso molecular (% LMWS) en comparación con DX-2930 que no está degradado. Como se muestra a continuación, se produce una mayor degradación de DX-2930 (% de LMWS incrementado) a pH 3.0 y pH 4.0 en comparación con pH 6.0 y una mayor agregación de DX-2930 (mayor% de HMWS) ocurre a pH 7.0 y pH 8.5 en comparación con pH 6.0. Por tanto, la selección del pH de la composición farmacéutica reclamada no habría sido obvia para un experto en la técnica porque no todos los pH ensayados dieron como resultado DX-2930 que no se degradara ni se agregara.





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Además, no habría sido obvio para una persona experta en la técnica que un anticuerpo que comprende las CDR de las reivindicaciones modificadas (por ejemplo, DX-2930) sería estable (por ejemplo, no agregado, no degradado) y no presentaría problemas de viscosidad en un portador farmacéuticamente aceptable que comprende NaCl 90 mM. Típicamente, se agrega NaCl a una formulación de anticuerpo concentrado (por ejemplo, 300 mg) para mantener la estabilidad del anticuerpo y disminuir la viscosidad. Las formulaciones de anticuerpos monoclonales disponibles comercialmente comprenden típicamente 135 mM - 155 mM NaCl (ver, por ejemplo, la Tabla 1 de Wang et al., *J. Pharmaceutical Sci.*, 2007, 96 (1): 1-26, documento adjunto al presente memorial). Por lo tanto, una persona experta en la técnica no habría encontrado obvio que 300 mg de los anticuerpos reclamados serían estables y no presentarían problemas de viscosidad en una formulación de medicamento o anticuerpo que comprenda solo NaCl 90 mM.

De esta forma, teniendo en cuenta que el documento D1 **no menciona, describe o sugiere**, en forma individual o en combinación, todas las características técnicas reclamadas en el nuevo capítulo reivindicatorio presentado por el solicitante, **las nuevas reivindicaciones presentadas son novedosas, e inventivas sobre el estado del arte**.

En este sentido, y siguiendo el Manual Andino de Patentes, la presente invención tal y como se encuentra definida en las reivindicaciones 1 a 4, tiene diferencias con el estado del arte e implicó un nivel inventivo durante su desarrollo, por lo cual debe ser considerada como novedosa e inventiva según las disposiciones de los artículos 14, 16 y 18 de la Decisión 486.

4. Conclusión

Con las modificaciones introducidas y los argumentos presentados puede concluirse que:

i) La presente solicitud es clara, concisa y está debidamente soportada en la descripción, cumpliendo con los requerimientos del Artículo 30 de la Decisión 486; y

ii) Las reivindicaciones actuales son patentables sobre D1, cumpliendo así con los requerimientos del Artículo 18 de la Decisión 486.

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Por tanto, atentamente me permito solicitar a ese Despacho otorgar el privilegio de patente solicitado a la solicitud en estudio, toda vez que cumple a cabalidad con los requerimientos de la Decisión 486/00.

En consecuencia, solicitamos a ese Despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional.

5. Anexos

- Nuevo capítulo reivindicatorio conformado por 4 reivindicaciones.
- Banjeeri et al., 2018, *JAMA*
- Riedl et al., 2020, *Allergy*
- Riedl et al., 2020, *J. Allergy Clin Immunol.*
- Wang et al., *J. Pharmaceutical Sci.*
- Recibo por concepto de Tasa de modificaciones a las reivindicaciones.

Señora Directora,

CAROLINA DAZA MONTALVO
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TP-141563 CSJ
notificaciones@clarkemodet.com.co

REIVINDICACIONES MODIFICADAS

1. Una composición farmacéutica caracterizada porque comprende 300 mg de un anticuerpo que se une a la calicreína plasmática activa y un portador farmacéuticamente aceptable,

en donde el anticuerpo que se une a la calicreína plasmática activa comprende dominios determinantes de la complementariedad (CDRs) de cadena pesada como se definen en las SEQ ID NOs: 5-7 y CDRs de cadena ligera como se definen en las SEQ ID NOs: 8-10; y

en donde el portador farmacéuticamente aceptable comprende fosfato de sodio a una concentración de aproximadamente 30 mM, ácido cítrico a una concentración de aproximadamente 19 mM, histidina a una concentración de aproximadamente 50 mM, cloruro de socio a una concentración de aproximadamente 90 mM, y polisorbato 80 a una concentración de 0.01%,

en donde la composición farmacéutica tiene un pH de aproximadamente 6.0.

2. La composición farmacéutica de la reivindicación 1, en donde la composición farmacéutica es para administración subcutánea.

3. La composición farmacéutica de la reivindicación 1 o reivindicación 2, en donde el anticuerpo comprende una región variable de cadena pesada como se define en la SEQ ID NO: 3 y una región variable de cadena ligera como se define en la SEQ ID NO: 4.

4. La composición farmacéutica de la reivindicación 3, en donde el anticuerpo comprende una cadena pesada como se define en la SEQ ID NO: 1 y una cadena ligera como se define en la SEQ ID NO: 2.

Supplement

Protocol and Statistical Analysis plan for: Banerji A, Riedl MA, Bernstein JA, et al. Lanadelumab, a monoclonal antibody inhibitor of plasma kallikrein, for the prevention of hereditary angioedema attacks: a randomized clinical trial.

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-2930-03

Study Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-03
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-003943-20
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	Ryan Iarrobino PPD, Clinical Development 55 Network Drive, Burlington, MA 01803 USA Phone: PPD
Medical Monitor US and Canada:	PPD, M.D. Rho, Inc. PPD, PPD, PPD USA Phone: PPD
Medical Monitor Europe and Jordan:	PPD, M.D. Voisin Consulting PPD, PPD PPD, France Phone: PPD

	Date:
Original Protocol	14 September 2015

Confidentiality Statement

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PROTOCOL SIGNATURE PAGE

Study Title: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number: DX-2930-03

Final Date: 14 September 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
PPD, 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), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

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

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

Signed:_____ Date:_____

Investigator

Address: _____

_____

SYNOPSIS

Sponsor: Dyax Corp.
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate, citric acid, histidine, sodium chloride, and Tween 80
Study Title: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-03
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across the United States, Italy, United Kingdom, Germany, Canada and Jordan
Primary Objective: To evaluate the efficacy of DX-2930 in preventing HAE attacks
Secondary Objective: To evaluate the safety of repeated subcutaneous administrations of DX-2930
Tertiary Objectives: • To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930 • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the pharmacokinetics (PK) of chronically administered DX-2930 • To evaluate the effect of DX-2930 upon quality of life assessments
Study Design: This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in patients with Type I and Type II HAE. <u>Long-Term Prophylactic (LTP) Therapy Washout:</u> Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as

long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm the subject has successfully completed the 2 week washout period before they can enter the run-in period.

Run-In Period:

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

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be blocked by naïve vs. non-naïve subjects (subjects receiving active study drug in protocol DX-2930-02) as well as the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

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

Table 1. Treatment Period Dosing Schedule

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

Open-Label Extension (OLE) Study:

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

Follow-up Period:

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

Study Population:

The study will enroll approximately 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted either during the screening visit or during participation in study DX-2930-02.

Criteria for Inclusion:

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

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

Criteria for Exclusion:

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.

3. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
4. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
5. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
6. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate, 19 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Tween 80. Each vial contains a nominal concentration of 100 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered subcutaneously into the upper arm in a blinded manner.

For each 300 mg dose of DX-2930, each subject will receive a total of 3 mL, divided into 2 separate 1.5 mL SC injections of DX-2930. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

For each 150 mg dose of DX-2930, each subject will receive a total of 3 mL, divided into 2 separate 1.5 mL SC injections, where one injection is DX-2930 and the other is placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

Placebo; Dose; and Mode of Administration:

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate, 19 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Tween 80.

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

For each placebo dose, each subject will receive a total of 3 mL, divided into 2 separate 1.5 mL SC injections of placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

Duration of Treatment:

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

Duration of Study for Individual Subjects:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks in the double-blind study.

Prohibited Concomitant Treatments:

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

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

The use of short-term prophylactic treatment for HAE is permitted if medically indicated.

Management of Acute Attacks:

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

Safety Assessments:

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

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of

special interest (AESI). • Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR). • Physical examination. • Clinical laboratory testing (hematology, serum chemistry, coagulation, and urinalysis). • 12-Lead electrocardiogram (ECG).
Pharmacokinetic (PK) Assessments: Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to IMP administration on Day 0 and on Days 56 ± 3, 98 ± 3, 140 ± 3, and 182 ± 3. Additional samples will be collected on Days 210 ± 3 and 238± 3 during the follow-up period for any subjects not entering OLE.
Pharmacodynamic (PD) Assessments: Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to IMP administration on Day 0 and on Days 56 ± 3, 98 ± 3, 140 ± 3, and 182 ± 3. Additional samples will be collected on Days 210 ± 3 and 238 ± 3 during the follow-up period for any subjects not entering OLE.
Immunogenicity Assessments: Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56 ± 3, 98 ± 3, 140 ± 3, and 182 ± 3. Additional samples will be collected on Day 238 ± 3 during the follow-up period for any subjects not entering OLE.
C1-INH, C4 and C1q Assessments: Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02.
Quality of Life Assessments: Quality of life (QOL) assessments will be conducted prior to IMP administration on Day 0 and on Days 98 ± 3, and 182 ± 3. An additional QOL assessment will be conducted on Day 238 ± 3 for subjects not entering OLE.
Collection of HAE Attack Data: The collection, reporting and assessment of attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP). Site personnel will be trained on HAARP prior to screening subjects at their site. During screening, site personnel will train subjects and caregivers on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The subject (and caregiver) will confirm their understanding of what is required of them for reporting attacks to the site. At screening, subject HAE attack history will be collected. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack

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

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an HAE attack. In the situation that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subjects experience.

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

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

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

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

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

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to IMP, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to Dyax using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

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

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

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

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

Study Stopping Rules:

An Internal Study Safety Committee (SSC) will review blinded safety data at 50% of subjects completing Day 182, and *ad hoc* if needed. If necessary during a safety evaluation, the SSC may break the blind for individual subjects to determine if adverse events occurred in DX-2930 treated subjects.

Through the SSC review of safety data, the Sponsor may suspend dosing in the study at any

time for an important safety concern until the SSC can evaluate the potential signal and recommend an appropriate course of action.

If it is determined at any time that a dose group must be dropped due to an important safety signal, the sponsor may randomize the remaining unenrolled subjects into the remaining lower DX-2930 dosing arm(s) or placebo and continue enrollment for the remainder of the study in a double-blind fashion. If a dose is dropped due to an important safety signal, the highest remaining dose automatically becomes the primary dose comparison versus placebo. Subjects who had not yet completed the full treatment period in a dosing arm that has been dropped will rollover into a lower dosing arm in the Open-Label Extension Study, DX-2930-04, as determined by the SSC. Data for these subjects will be used up to the time at which it is decided to drop the dose in the efficacy analyses and in its entirety in the safety analyses.

Individual Stopping Rules:

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator and Medical Monitor, warrants discontinuation from further dosing for that subject's well-being. Subjects will continue to be followed through completion of all scheduled visits. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

Criteria for Evaluation:

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 14 ± 3 through Day 182 ± 3.

Primary Endpoint

- Number of HAE attacks per week

Secondary Endpoints (rank ordered)

1. Time to first attack, i.e. duration that a subject is attack-free until their first attack.
2. Number per week of HAE attacks requiring acute attack therapy use.
3. Number per week of moderate or severe HAE attacks.
4. Number per week of high-morbidity HAE attacks; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours) , hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Safety Measures:

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

- Physical examination
- 12-lead electrocardiogram (ECG)

Additional Measures:

- Pharmacodynamic effects
- Anti-drug antibody development
- Pharmacokinetic parameter determinations
- Quality of life assessments

Analysis Populations:

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

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

Sample Size Determination:

The sample size needed to test the primary hypothesis (alpha = 0.025, one-sided) in the Intent-to-treat (ITT) population to achieve a given power is calculated using the data and information from the DX-2930-02 study. Power analysis and sample size estimation was based on 1000 computer simulations using a mixed model repeated measures (MMRM) analysis of variance (ANOVA) for counts using the SAS generalized estimating equation (GEE) determination of statistical significance. Assumptions included that placebo subjects have an observed attack rate of 0.3 attacks per week during the treatment period, and are observed for 24 weeks of efficacy. Active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data / dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

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

Statistical Methods:

The primary analysis will be to compare the primary endpoint, which is the mean rate of Investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 14 through Day 182). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP will be conducted.

The HAE attack rates of the treated and placebo groups will be compared using MMRM ANOVA for counts using the GEE. The baseline attack rate for each subject as determined by the run-in period will be used as a continuous covariate in an analysis of covariance. For

each subject, the least squares mean will be calculated and adjusted for their baseline attack rate. A Poisson distribution will be assumed rather than a Gaussian distribution. Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. There will be no Last Observation Carried Forward (LOCF), as the HAE attack rate will be computed as the total number of attacks divided by the total duration of observation during the specified time period. Subject weeks for which completed observation is less than the full 168 hours within a week will be handled according to an *a priori* plan to be described in the Statistical Analysis Plan.

There are three active treatment arms ordered by highest total monthly dose; 1) Primary Treatment Arm: 300 mg DX-2930 every 2 weeks, 2) Secondary Treatment Arm: 300 mg DX-2930 every 4 weeks, and 3) Tertiary Treatment Arm: 150 mg DX-2930 every 4 weeks. For the primary endpoint, each of the three active treatment arms will be compared against placebo using a closed sequential testing procedure in which first, the primary active treatment arm is compared to placebo at significance level alpha and then, if there is statistical significance found, then the secondary treatment arm is tested against placebo at level alpha. If statistical significance is found for both the primary and secondary treatment arms, then the tertiary treatment arm shall be compared to placebo at significance level alpha.

Further, all secondary hypotheses for each active treatment group versus placebo are to be tested in a closed sequential methodology. The *a priori* order of testing the secondary hypotheses has been pre-specified above. In order to preserve the overall level alpha, secondary endpoints are not tested unless the primary endpoint is found to be statistically significant.

The first secondary endpoint, time to first HAE attack, will be tested using the log-rank test comparing each active treatment group vs placebo. The descriptive analysis will use life table summaries based on Kaplan Meier (KM) estimates. Subjects without any HAE attacks during the 24-week period and subjects without 24 weeks of observation will be right censored.

The second secondary endpoint, mean rate of HAE acute therapy use, will be tested using the MMRM model as described for the primary endpoint.

The third secondary endpoint, mean rate of moderate or severe HAE attacks, will be tested using the MMRM model as described for the primary endpoint.

The fourth secondary endpoint, mean rate of high-morbidity HAE attacks will be tested using the MMRM model as described for the primary endpoint.

Safety Analysis:

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

fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs and AESI will be produced.

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

Usage of concomitant medications (other than rescue mediations) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

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

Abnormal physical examination findings will be listed.

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

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

Date of Original Protocol: 14 September 2015

Study Activities Schedule

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

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

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

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. Subjects who have their run-in extended may not exit run-in early. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window.
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Day 98, and Day 238 can be serum or urine-based.
8. There is a ± 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to the last quantifiable concentration in plasma at time t
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last measurable concentration
BLA	Biologics License Application
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CL/F	apparent total plasma clearance after extravascular administration
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity

DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
FDA	Food and Drug Administration
FXI(a)	Factor XI (activated)
FXII(a)	Factor XII (activated)
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous

IWRS	Interactive Web-based Randomization System
K_i	inhibition constant
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pKal	Plasma kallikrein
PT	Prothrombin time
REB	Research Ethics Board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SM	Safety Management
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
SSC	Study Safety Committee
$t_{½}$	Terminal elimination half-life

t_{max}	Time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TT	Thrombin time
US	United States
Vd/F	Apparent volume of distribution during terminal phase after extravascular administration
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 DX-2930

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

1.2 Hereditary Angioedema

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

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

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

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

1.3 Therapeutic Rationale for DX-2930

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

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

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

1.4 Safety Rationale for DX-2930

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

Pharmacokinetic (PK) data from the Phase 1a clinical study in conjunction with data from the nonclinical toxicity studies support a wide safety margin. The mean C_{max} for human subjects treated at the highest dose of 3 mg/kg was approximately 14.5 µg/mL. As comparison, a mean C_{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 for systemically administered DX-2930.

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

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

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

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

1.6 DX-2930 Clinical Data

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

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

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

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

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

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

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

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

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days and were followed for 15 weeks after the second dose.

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

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

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

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

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

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive.

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

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

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

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

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

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

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

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

2.3 Tertiary Objectives

- To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930
- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the pharmacokinetics (PK) of chronically administered DX-2930
- To evaluate the effect of DX-2930 upon quality of life assessments

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

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

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

Long-Term Prophylactic (LTP) Therapy Washout:

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

Run-In Period:

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

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

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be blocked by naïve vs. non-naïve subjects (subjects receiving active study drug in protocol DX-2930-02) as well as the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

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

Table 1. Treatment Period Dosing Schedule

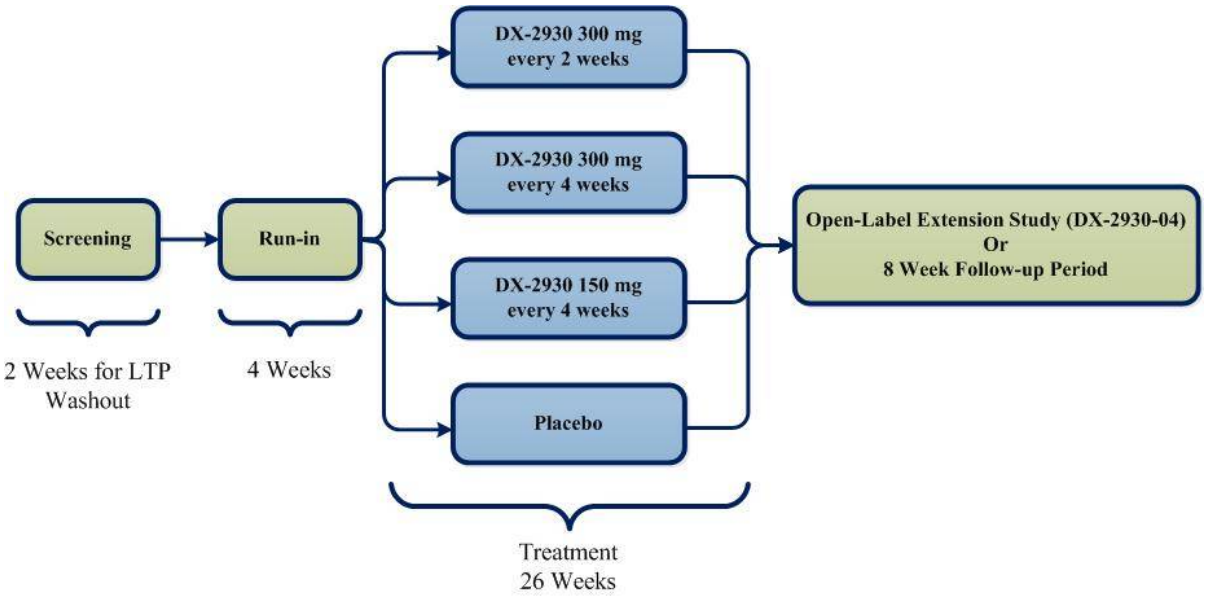
Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/ Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/ Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/ Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/ Week 4	DX-2930	DX-2930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

Open-Label Extension (OLE):

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

Figure 1 shows a schematic of the study design

Figure 1. Overview of the Study Design



Follow-up Period:

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

3.1.2 Safety Oversight and Stopping Rules

3.1.2.1 Study Safety Committee (SSC)

This study will be conducted under the oversight of an internal Study Safety Committee (SSC) that will review blinded safety data at 50% of subjects completing Day 182, and ad hoc if needed. The SSC may recommend actions to be taken by the Sponsor including but not limited to the following:

- Suspension of dosing in the study
- Suspension of dosing in a specific dosing arm
- Increase in subject post-dose monitoring period at the study site

Any action taken by the Sponsor as a result of an SSC recommendation may be temporary until the SSC can evaluate the potential signal and recommend an appropriate course of action.

3.1.2.2 Study Level Stopping Rules

If it is determined at any time that a dose group must be dropped due to an important safety signal, the Sponsor may randomize the remaining unenrolled subjects into the remaining lower DX-2930 dosing arm(s) or placebo and continue enrollment for the remainder of the study in a double-blind fashion. Subjects who had not yet completed the full treatment period in a dosing arm that has been dropped will rollover into a lower dosing arm in the Open-Label Extension Study, DX-2930-04, as determined by the SSC. Data for these subjects will be used up to the time at which it is decided to drop the dose in the efficacy analyses and in its entirety in the safety analyses.

3.1.2.3 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator and Medical Monitor, warrants discontinuation from further dosing for that subject's well-being. The subject will continue to be followed for the duration of the 26 week treatment period. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

3.1.3 Follow-up for Subjects Meeting Stopping Criteria

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

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

3.2 Rationale for Pivotal Dose Selection

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

In study DX-2930-02, two DX-2930 doses of 300 mg or greater administered 2 weeks apart resulted in a normalization of plasma 2-chain HMWK levels and a maximal 91% reduction in HAE attacks (DX-2930 Investigators Brochure). Steady-state trough concentrations following DX-2930 administration every 2 weeks would be approximately 27,000 ng/mL.

The maximum plasma concentration (C_{max}) obtained following ecallantide administration to treat an acute attack is similar to this trough concentration of DX-2930.

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

The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930 treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

3.3 Individual Subject Dosing and Follow-Up

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

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week wash-out period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study will enroll approximately 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted either during the screening visit or during participation in study DX-2930-02.

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

4.2 Inclusion Criteria

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

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
   - At least one of the following: age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

- Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from screening through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD, all types). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 60 days after the final study visit.

4.3 Exclusion Criteria

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior screening.
3. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
4. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
5. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
6. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding IMP administration, refer to the Pharmacy Manual.

5.1.1 DX-2930

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate, 19 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Tween 80. 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 in a blinded manner.

For each 300 mg dose of DX-2930, each subject will receive a total of 3 mL, divided into 2 separate 1.5 mL SC injections of DX-2930. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

For each 150 mg dose of DX-2930, each subject will receive a total of 3 mL, divided into 2 separate 1.5 mL SC injections, where one injection is DX-2930 and the other is placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

5.1.2 Placebo

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate, 19 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Tween 80.

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

For each placebo dose, each subject will receive a total of 3 mL, divided into 2 separate 1.5 mL SC injections of placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

5.2 Dosing and Follow-Up Schedule

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

5.3 Method of Assigning Subjects to Treatment Groups

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

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

5.4 Blinding and Unblinding

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

If necessary for the SSC to conduct a safety evaluation, the Sponsor may break the blind for individual subjects to determine if adverse events occurred in DX-2930 treated subjects.

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 from the time of screening up to administration of the first dose of IMP.

All information on concomitant therapy from the time of first dose of IMP through the final study visit (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's electronic Case Report Form (eCRF) and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.5.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, are permitted if not excluded in Section 5.5.2.
- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.5.2 Excluded Concomitant Therapies

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

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

5.6 Restrictions

5.6.1 Medical Interventions

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

5.6.2 Fluid and Food Intake

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

5.6.3 Activity

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

5.7 Treatment Compliance

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

5.8 Packaging and Labeling

The test products (DX-2930 and placebo) will be supplied by 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 (2ºC to 8ºC/36ºF to 46ºF) in the original carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

5.10 Investigational Medicinal Product Retention at Study Site

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

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

6 STUDY PROCEDURES

Please refer to the Study Activities Schedule, Appendix 1.

6.1 Informed Consent

Informed Consent and Assent forms must be approved for use by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study related activities. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Eligibility Review

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

6.3 Demographics and Medical History

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

6.4 Efficacy Assessments

6.4.1 Primary and Secondary Endpoints

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 14 ± 3 through Day 182 ± 3.

Primary Endpoint

- Number of HAE attacks per week

Secondary Endpoints (in rank order)

1. Time to first attack, i.e., duration that a subject is attack-free until their first attack.
2. Number per week of HAE attacks requiring acute attack therapy use.
3. Number per week of moderate or severe HAE attacks.
4. Number per week of high-morbidity HAE attacks; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours) , hemodynamically

significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

6.4.2 HAE Attack Information Collection

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

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

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

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

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

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

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

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

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

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

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

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

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

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

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region.

- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea.
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

6.5 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ± 15 minute window for all vital signs.

6.6 Physical Examination

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

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

- Dermatological
- Lymphatic

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Appendix 1). The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

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

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

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, PD, anti-drug antibodies. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each subject who does not rollover into the OLE will be approximately 271 mL. The total blood draw for each subject that does rollover into the OLE will be approximately 208 mL. Please refer to the Laboratory Manual for more information.

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

6.8.1.1 Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)

- Absolute platelet count

6.8.1.2 Coagulation

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

6.8.1.3 Chemistry

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

6.8.1.4 Urinalysis

- Bilirubin
- Glucose
- Ketones
- Blood
- Nitrite
- pH
- Protein

- Specific gravity
- Microscopy (if indicated by macroscopic findings)

6.8.1.5 Serology

HBsAg, HCV, and HIV tests

6.8.1.6 Pregnancy Test

Serum or urine pregnancy test

6.8.1.7 C1-INH Functional Assay

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

6.8.1.8 C4 Assay

Results of a C4 assay may be required for eligibility assessment. Samples will be drawn at the screening visit unless they were previously drawn and used for diagnostic confirmation in DX-2930-02. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.9 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Samples will be drawn at the screening visit if C1-INH and C4 samples are also being drawn. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.10 PK Sample Collection

As outlined in Section 6.9.

6.8.1.11 PD Sample Collection

As outlined in Section 6.10.

6.8.1.12 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained phlebotomist designated and/or approved by the study Investigator. Details for the collection,

processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

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

6.9 Pharmacokinetic Assessments

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

6.10 Pharmacodynamic Assessments

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

6.11 Plasma Anti-Drug Antibody Testing

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

6.12 Prior and Concomitant Therapy

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

6.13 Randomization

Subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be blocked by naïve vs. non-naïve subjects (subjects receiving active study drug in protocol DX-2930-02) as well as the baseline attack rate into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

6.14 Investigational Medicinal Product Treatment

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

6.15 Quality of Life Assessments

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

6.16 Adverse Event Reporting

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

6.16.1 Definitions

6.16.1.1 Adverse Event

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

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

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

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

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

6.16.1.2 Serious Adverse Event

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

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

6.16.1.3 Overdose

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

6.16.1.4 Planned Hospitalization

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

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after first administration of IMP through the Day 182±3 final follow-up visit or, in the event that onset time precedes first IMP administration, the AE increases in severity during the 182±3 day follow-up period.

6.16.1.6 Adverse Events of Special Interest (AESI)

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

HYPERSENSITIVITY REACTIONS

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

EVENTS OF DISORDERED COAGULATION

Bleeding AESI

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

Hypercoagulable AESI

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

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, from signing of the ICF through final follow-up on Day 182 ± 3.

- Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the Investigator.

- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

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

6.16.2.2 Monitoring of Safety Laboratory Assessments

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

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

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

In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 2) and the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

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

6.16.3.2 Assessment of Causality

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

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

The causal relationship between the study IMP and the AE will be assessed using one of the following categories:

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

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

Related: Factors consistent with an assessment of Related include:

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

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the Investigator, with discussion with the Medical Monitor as appropriate, or by the SSC for overall study AE review.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and

that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, will be considered an AE.

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

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

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

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-serious Adverse Events

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

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the 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.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to Dyax

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

- SAE
- AESI
- Overdose
- Cancer

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

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

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

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

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

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

6.16.5.5 Safety Contact Information

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

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

Dyax Pharmacovigilance Department
Contacts: PPD
Email: PPD
Phone (US): PPD

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

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

6.16.5.7 Unblinding a Subject's Treatment during the Trial

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

6.17 Subject Withdrawal

The Investigator may withdraw a subject from the trial for any of the reasons listed below. Any reason should be dicussed with the Medical Monitor prior to withdrawing a subject.

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

Subjects will continue to be followed through completion of all scheduled visits. The criteria used by the SSC regarding dose administration suspension and/or study discontinuation are provided in Section 3.1.2.

6.18 Appropriateness of Measurements

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

7 STUDY ACTIVITIES

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

7.1 Screening

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

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6); documentation of height and weight
- 12-Lead ECG (Section 6.7)
- Laboratory testing including, serology, hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms
- Subjects who are on LTP for HAE must complete a 2 week washout period, as confirmed by the Investigator, before entering the run-in period.

7.2 Run-in Period

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

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

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

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

The following procedures and assessments are to be performed on Day 0 prior to the first dose of IMP administration:

- Eligibility review (Section 6.2)
- Randomization to treatment (Section 6.13)
- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

7.4 Site Contact with the Subject

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

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)

- AE collection (Section 6.16)

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

period may be lengthened back to 2 hours at any time by the Sponsor based on SSC recommendation.

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

- 12-Lead ECG (Section 6.7)

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Urine pregnancy test (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)
- Discharge from study:
    - Subjects will be offered the option of enrolling in the DX-2930-04 Open Label Extension (OLE) study for continued treatment and safety follow-up.
    - Informed Consent obtained for study DX-2930-04
    - Subjects who consent to participate in DX-2930-04 will receive their first OLE dose following the completion of all double-blind assessments scheduled on Day 182.

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Urine pregnancy test (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)

7.18 Early Termination (ET)

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

8 QUALITY CONTROL AND ASSURANCE

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

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

9 DATA ANALYSIS / STATISTICAL METHODS

9.1 Sample Size Determination

The sample size needed to test the primary hypothesis (alpha = 0.025, one-sided) in the Intent-to-treat (ITT) population to achieve a given power is calculated using the data and information from the DX-2930-02 study. Power analysis and sample size estimation was based on 1000 computer simulations using a mixed model repeated measures (MMRM) analysis of variance (ANOVA) for counts using the SAS generalized estimating equation (GEE) determination of statistical significance. Assumptions included that placebo subjects have an observed attack rate of 0.3 attacks per week during the treatment period, and are observed for 24 weeks of efficacy. Active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data / dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

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

9.2 Analysis Populations

The analysis populations will be defined as follows:

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

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

9.3 Analysis of Disposition

The numbers of subjects randomized, completing, or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group.

9.4 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group.

9.5 Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

9.5.1 Pharmacokinetic Assessments:

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

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

Any concentrations reported below the lower limit of quantitation (LLOQ) will be assigned zero for summarizing concentration data, however, the PK parameter calculation of AUC will use either missing or zero for samples below LLOQ. Sample concentrations below the LLOQ will be assigned zero when they precede the first concentration not below the LLOQ. Sample concentrations following the last concentration not below the LLOQ will be assigned missing when below the LLOQ. If a sample concentration is below the LLOQ and between the first and last concentrations not below the LLOQ, then the assignment of missing or zero will be at the discretion of the PK specialists using physiological rationale.

Full details of the planned PK parameters will be included in the statistical analysis plan (SAP).

9.5.2 Pharmacodynamic Assessments:

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

9.5.3 Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56 ± 3, 98 ± 3, 140 ± 3, and 182 ± 3. Additional samples will be collected on Day 238± 3 during the follow-up period for any subjects not entering OLE

9.5.4 C1-INH and C4 Assessments:

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

9.6 Analysis of Primary and Secondary Efficacy Endpoints

The primary analysis will be to compare the primary endpoint, which is mean rate of Investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 14 through Day 182). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP will be conducted.

The HAE attack rates of the treated and placebo groups will be compared using MMRM ANOVA for counts using the GEE. The baseline attack rate for each subject as determined by the run-in period will be used as a continuous covariate in an analysis of covariance. The model will be based on two fixed effects (treatment group and prior use of DX-2930), the random effect will be the subject and the baseline attack rate will be a continuous covariate. For each subject, the least squares mean will be calculated and adjusted for their baseline attack rate. A Poisson distribution will be assumed rather than a Gaussian distribution. Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. There will be no Last Observation Carried Forward (LOCF), as the HAE attack rate will be computed as the total number of attacks divided by the total duration of observation during the specified time period. Subject weeks for which completed observation is less than the full 168 hours within a week will be handled according to an *a priori* plan to be described in the SAP.

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 rate of the mean event rate per week, for each dose level vs placebo and its 95% Confidence interval can also be estimated by transforming the above lsmean difference and its 95% CI confidence interval by the exponential function,

The percentage change in mean attack rate of each active 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.

Sample code for the above analysis is:

```
PROC GENMOD DATA = XXXX ;
WHERE  x<=visitn<=y;
        CLASS   Trta (REF = 'Placebo') usubjid;
        MODEL attack=trta priordx base/ DIST=poisson;
        REPEATED  SUBJECT=usubjid / CORR=ind;
        LSMEANS trta/DIFF CL ILINK;
        ODS OUTPUT diffs – meandiff  lsmeans = means;
RUN;
```

There are three active treatment arms ordered by highest total monthly dose; 1) Primary Treatment Arm: 300 mg DX-2930 every 2 weeks, 2) Secondary Treatment Arm: 300 mg DX-2930 every 4 weeks, and 3) Tertiary Treatment Arm: 150 mg DX-2930 every 4 weeks.

For the primary endpoint, each of the three active treatment arms will be compared against placebo using a closed sequential testing procedure in which first, the primary active treatment arm is compared to placebo at significance level alpha and then, if there is statistical significance found, then the secondary treatment arm is tested against placebo at level alpha. If statistical significance is found for both the primary and secondary treatment arms, then the tertiary treatment arm shall be compared to placebo at significance level alpha.

If a dose is dropped due to an important safety signal, the highest remaining dose automatically becomes the primary dose comparison versus placebo.

All secondary hypotheses for each active treatment group versus placebo are also to be tested in a closed sequential methodology. The *a priori* order of testing the secondary hypotheses has been pre-specified in Section 6.4.1. In order to preserve the overall alpha level, secondary endpoints are not tested unless the primary endpoint is found to be statistically significant.

The first secondary endpoint, time to first HAE attack, will be tested using the log-rank test comparing each active treatment group vs placebo. The descriptive summaries will use life table summaries based on Kaplan Meier (KM) estimates. Subjects without any HAE attacks during the 24-week period and subjects without 24 weeks of observation will be right censored.

The second secondary endpoint, reduction in HAE acute therapy use, will be tested using the MMRM model as described for the primary endpoint. The same SAS code used for the primary endpoint will be used but with a different endpoint.

The third secondary endpoint, reduction in moderate or severe HAE attacks, will be tested using the MMRM model as described for the primary endpoint. The same SAS code used for the primary endpoint will be used but with a different endpoint.

The fourth secondary endpoint, reduction in high-morbidity HAE attacks, will be tested using the MMRM model as described for the primary endpoint. The same SAS code used for the primary endpoint will be used but with a different endpoint.

9.7 Safety Analysis

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

AESI will be analyzed according to primary system Organ Classes (SOCs) and Preferred Terms (PTs) determined by the search of relevant Standardized MedDRA Queries (SMQs).

Summary tables with SOCs and PTs, from the SMQ searches, will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications (other than rescue mediations) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

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

Abnormal physical examination findings will be listed.

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

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

9.8 Analysis of Quality of Life Assessments

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

10 STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 2.

Table 2. Study Administrative Structure

Sponsor Contact:	Ryan Iarrobino PPD, Clinical Development 55 Network Drive, Burlington, MA 01803 Phone: PPD Email: PPD
Sponsor Medical Director:	PPD, MD PPD, Medical Research 55 Network Drive, Burlington, MA 01803 Phone: PPD Email: PPD
Medical Monitor (US, Canada):	PPD, MD Rho, Inc. PPD, PPD, PPD Phone: PPD Email: PPD
Medical Monitor (Jordan, Europe)	PPD, M.D. Voisin Consulting PPD, PPD PPD, France Phone: PPD Email: PPD
Study Monitoring (US):	Rho, Inc. PPD, PPD, PPD Phone: PPD
Study Monitoring (Jordan)	Triumpharma PPD, PPD PPD, PPD PPD, Jordan Phone: PPD
Study Monitoring (Canada)	Red Maple Trials Incorporated PPD, PPD PPD, PPD, Canada, PPD Phone: PPD
Study Monitoring (Europe)	Dyax Corp 55 Network Drive, Burlington, MA 01803 Phone: PPD

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

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

10.2 Ethical Conduct of the Study

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

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The Investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the study.

10.4 Subject Confidentiality

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

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

10.5 Study Monitoring

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

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

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

10.6 Case Report Forms and Study Records

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

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

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

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

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

10.7 Study Safety Committee

This study will be conducted under the oversight of an internal Study Safety Committee (SSC) that will review safety data at regular intervals throughout the course of the study.

10.8 Protocol Violations/Deviations

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

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

10.9 Access to Source Documentation and On-Site Audits

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

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

10.10 Data Generation and Analysis

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

will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.11 Retention of Data

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

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

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

10.12 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.

10.13 Publication and Disclosure Policy

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

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

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12 APPENDICES

Appendix 1 Study Activities Schedule

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

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

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 1 Study Activities Schedule

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

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

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

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. Subjects who have their run-in extended may not exit run-in early. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Day 98, and Day 238 can be serum or urine-based.

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

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

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

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Clinical Trial Protocol: DX-2930-03

Study Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-03
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-003943-20
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	Ryan Iarrobino PPD, Clinical Development 55 Network Drive, Burlington, MA 01803 USA Phone: PPD
Medical Monitor US and Canada:	PPD, M.D. Rho, Inc. PPD, PPD, PPD USA Phone: PPD
Medical Monitor Europe and Jordan:	PPD, M.D. Voisin Consulting PPD, PPD PPD, France Phone: PPD

	Date:
Original Protocol	14 September 2015
Amendment 1.0	14 December 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: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number: DX-2930-03

Amendment 1.0 Final Date: 14 December 2015

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

Signed:__PPD__ Date:__PPD__

Ryan Iarrobino
PPD, 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), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

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

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

Signed:_____ Date:_____
Investigator
Address: _____

_____

SYNOPSIS

Sponsor: Dyax Corp.
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80
Study Title: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-03
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across the United States, Italy, United Kingdom, Germany, Canada and Jordan
Primary Objective: To evaluate the efficacy of DX-2930 in preventing HAE attacks
Secondary Objective: To evaluate the safety of repeated subcutaneous administrations of DX-2930
Tertiary Objectives: • To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930 • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the pharmacokinetics (PK) of chronically administered DX-2930 • To evaluate the effect of DX-2930 upon quality of life assessments
Study Design: This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in patients with Type I and Type II HAE. <u>Long-Term Prophylactic (LTP) Therapy Washout:</u> Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum

2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm the subject has successfully completed the 2 week washout period before they can enter the run-in period.

Run-In Period:

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

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be blocked by naïve vs. non-naïve subjects (subjects receiving active study drug in protocol DX-2930-02) as well as the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

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

Table 1. Treatment Period Dosing Schedule

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

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

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

Study Population:
The study will enroll up to 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted either during the screening visit or during participation in study DX-2930-02. The study will aim to enroll at least 5 subjects who are 12 to 17 years of age.

Criteria for Inclusion:

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

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

Criteria for Exclusion:

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.

3. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
4. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
5. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
6. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

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

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

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

Placebo; Dose; and Mode of Administration:

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

Placebo doses will be administered to subjects randomized to the placebo treatment arm and in between doses of DX-2930 for subjects randomized to the 300 mg or 150 mg DX-2930

every 4 weeks treatment arms, according to the dosing schedule in Table 1.

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

Duration of Treatment:

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

Duration of Study for Individual Subjects:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks in the double-blind study.

Prohibited Concomitant Treatments:

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

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

The use of short-term prophylactic treatment for HAE is permitted if medically indicated.

Management of Acute Attacks:

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

Safety Assessments:

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

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI).
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR).
- Physical examination.
- Clinical laboratory testing (hematology, serum chemistry, coagulation, and urinalysis).
- 12-Lead electrocardiogram (ECG).

Pharmacokinetic (PK) Assessments:

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

Pharmacodynamic (PD) Assessments:

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

Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE.

C1-INH, C4 and C1q Assessments:

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

Quality of Life Assessments:

Quality of life (QOL) assessments will be conducted prior to IMP administration on Day 0 and on Days 98±3, and 182±3. An additional QOL assessment will be conducted on Day 238±3 for subjects not entering OLE.

Collection of HAE Attack Data:

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

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

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

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an HAE attack. In the situation that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subjects experience.

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

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

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

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

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

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already

provided to the site.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to IMP, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to Dyax using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

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

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

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

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

Study Stopping Rules:
An Internal Study Safety Committee (SSC) will review blinded safety data at 50% of subjects completing Day 182, and *ad hoc* if needed. If necessary during a safety evaluation, the SSC may break the blind for individual subjects to determine if adverse events occurred

in DX-2930 treated subjects.

Through the SSC review of safety data, the Sponsor may suspend dosing in the study at any time for an important safety concern until the SSC can evaluate the potential signal and recommend an appropriate course of action.

If it is determined at any time that a dose group must be dropped due to an important safety signal, the sponsor may randomize the remaining unenrolled subjects into the remaining lower DX-2930 dosing arm(s) or placebo and continue enrollment for the remainder of the study in a double-blind fashion. If a dose is dropped due to an important safety signal, the highest remaining dose automatically becomes the primary dose comparison versus placebo. Subjects who had not yet completed the full treatment period in a dosing arm that has been dropped will rollover into a lower dosing arm in the Open-Label Extension Study, DX-2930-04, as determined by the SSC. Data for these subjects will be used up to the time at which it is decided to drop the dose in the efficacy analyses and in its entirety in the safety analyses.

Individual Stopping Rules:

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through completion of all scheduled visits, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

Criteria for Evaluation:

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 14 through Day 182.

Primary Endpoint

- Number of HAE attacks per week

Secondary Endpoints (rank ordered)

1. Time to first attack, i.e. duration that a subject is attack-free until their first attack.
2. Number per week of HAE attacks requiring acute attack therapy use.
3. Number per week of moderate or severe HAE attacks.
4. Number per week of high-morbidity HAE attacks; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours) , hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Safety Measures:

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

Additional Measures:

- Pharmacodynamic (PD) effects
- Anti-drug antibody development
- Pharmacokinetics (PK)
- Quality of life assessments

Analysis Populations:

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

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

Sample Size Determination:

The sample size needed to test the primary hypothesis (alpha = 0.025, one-sided) in the Intent-to-treat (ITT) population to achieve a given power is calculated using the data and information from the DX-2930-02 study. Power analysis and sample size estimation was based on 1000 computer simulations using a mixed model repeated measures (MMRM) analysis of variance (ANOVA) for counts using the SAS generalized estimating equation (GEE) determination of statistical significance. Assumptions included that placebo subjects have an observed attack rate of 0.3 attacks per week during the treatment period, and are observed for 24 weeks of efficacy. Active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data / dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

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

Statistical Methods:

The primary analysis will be to compare the primary endpoint, which is the mean rate of Investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 14 through Day 182). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP will be conducted.

The HAE attack rates of the treated and placebo groups will be compared using MMRM ANOVA for counts using the GEE. The baseline attack rate for each subject as determined by the run-in period will be used as a continuous covariate in an analysis of covariance. For each subject, the least squares mean will be calculated and adjusted for their baseline attack rate. A Poisson distribution will be assumed rather than a Gaussian distribution. Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. There will be no Last Observation Carried Forward (LOCF), as the HAE attack rate will be computed as the total number of attacks divided by the total duration of observation during the specified time period. Subject weeks for which completed observation is less than the full 168 hours within a week will be handled according to an *a priori* plan to be described in the Statistical Analysis Plan.

There are three active treatment arms ordered by highest total monthly dose; 1) Primary Treatment Arm: 300 mg DX-2930 every 2 weeks, 2) Secondary Treatment Arm: 300 mg DX-2930 every 4 weeks, and 3) Tertiary Treatment Arm: 150 mg DX-2930 every 4 weeks. For the primary endpoint, each of the three active treatment arms will be compared against placebo using a closed sequential testing procedure in which first, the primary active treatment arm is compared to placebo at significance level alpha and then, if there is statistical significance found, then the secondary treatment arm is tested against placebo at level alpha. If statistical significance is found for both the primary and secondary treatment arms, then the tertiary treatment arm shall be compared to placebo at significance level alpha.

Further, all secondary hypotheses for each active treatment group versus placebo are to be tested in a closed sequential methodology. The *a priori* order of testing the secondary hypotheses has been pre-specified above. In order to preserve the overall level alpha, secondary endpoints are not tested unless the primary endpoint is found to be statistically significant.

The first secondary endpoint, time to first HAE attack, will be tested using the log-rank test comparing each active treatment group vs placebo. The descriptive analysis will use life table summaries based on Kaplan Meier (KM) estimates. Subjects without any HAE attacks during the 24-week period and subjects without 24 weeks of observation will be right censored.

The second secondary endpoint, mean rate of HAE acute therapy use, will be tested using the MMRM model as described for the primary endpoint.

The third secondary endpoint, mean rate of moderate or severe HAE attacks, will be tested using the MMRM model as described for the primary endpoint.

The fourth secondary endpoint, mean rate of high-morbidity HAE attacks will be tested using the MMRM model as described for the primary endpoint.

Safety Analysis:

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

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

Usage of concomitant medications (other than rescue medications) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

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

Abnormal physical examination findings will be listed.

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

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

Date of Amendment 1.0: 14 December 2015

Study Activities Schedule

Study Activities Schedule

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

Study Activities Schedule

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

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

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window.
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Day 98, and Day 238 can be serum or urine-based.
8. There is a ± 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to the last quantifiable concentration in plasma at time t
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last measurable concentration
BLA	Biologics License Application
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CL/F	apparent total plasma clearance after extravascular administration
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity

DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
FDA	Food and Drug Administration
FXI(a)	Factor XI (activated)
FXII(a)	Factor XII (activated)
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous

IWRS	Interactive Web-based Randomization System
K_i	inhibition constant
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pKal	Plasma kallikrein
PT	Prothrombin time
REB	Research Ethics Board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SM	Safety Management
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
SSC	Study Safety Committee
$t_{½}$	Terminal elimination half-life

t_{max}	Time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TT	Thrombin time
US	United States
Vd/F	Apparent volume of distribution during terminal phase after extravascular administration
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 DX-2930

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

1.2 Hereditary Angioedema

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

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

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

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

1.3 Therapeutic Rationale for DX-2930

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

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

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

1.4 Safety Rationale for DX-2930

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

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

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

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

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

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

1.6 DX-2930 Clinical Data

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

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

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

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

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

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

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

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

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days and were followed for 15 weeks after the second dose.

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

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

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

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

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

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

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

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

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

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

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

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

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

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

2.3 Tertiary Objectives

- To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930
- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the pharmacokinetics (PK) of chronically administered DX-2930
- To evaluate the effect of DX-2930 upon quality of life assessments

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

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

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

Long-Term Prophylactic (LTP) Therapy Washout:

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

Run-In Period:

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

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

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be blocked by naïve vs. non-naïve subjects (subjects receiving active study drug in protocol DX-2930-02) as well as the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

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

Table 1. Treatment Period Dosing Schedule

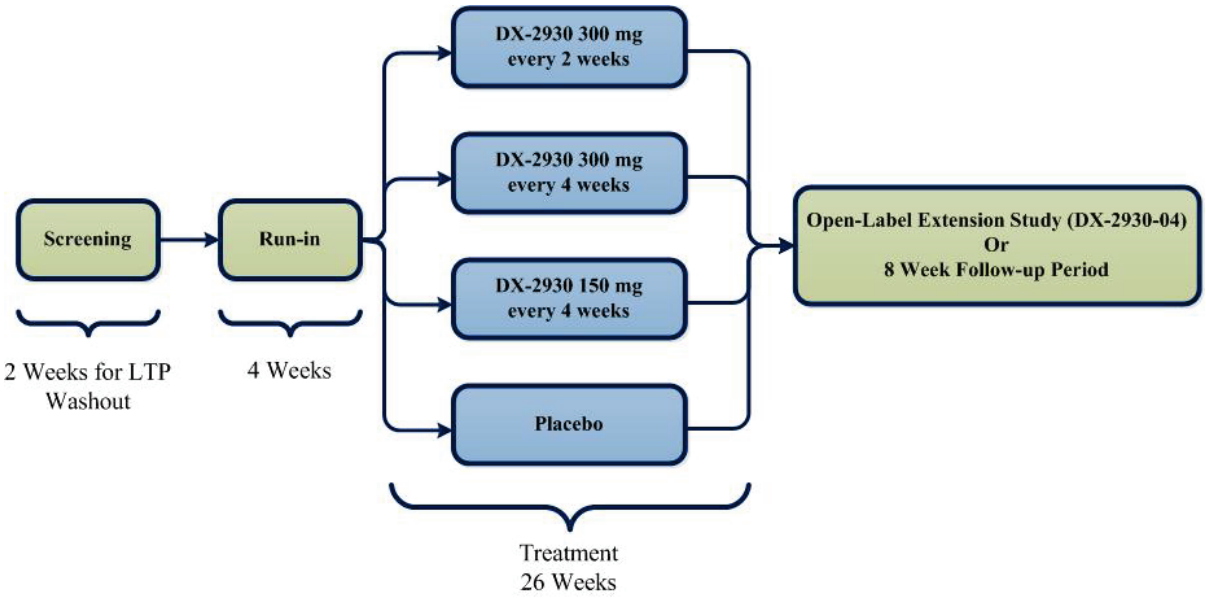
Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/ Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/ Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/ Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/ Week 4	DX-2930	DX-2930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

Open-Label Extension (OLE):

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

Figure 1 shows a schematic of the study design

Figure 1. Overview of the Study Design



Follow-up Period:

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

3.1.2 Safety Oversight and Stopping Rules

3.1.2.1 Study Safety Committee (SSC)

This study will be conducted under the oversight of an internal Study Safety Committee (SSC) that will review blinded safety data at 50% of subjects completing Day 182, and ad hoc if needed. The SSC may recommend actions to be taken by the Sponsor including but not limited to the following:

- Suspension of dosing in the study
- Suspension of dosing in a specific dosing arm
- Increase in subject post-dose monitoring period at the study site

Any action taken by the Sponsor as a result of an SSC recommendation may be temporary until the SSC can evaluate the potential signal and recommend an appropriate course of action.

3.1.2.2 Study Level Stopping Rules

If it is determined at any time that a dose group must be dropped due to an important safety signal, the Sponsor may randomize the remaining unenrolled subjects into the remaining lower DX-2930 dosing arm(s) or placebo and continue enrollment for the remainder of the study in a double-blind fashion. Subjects who had not yet completed the full treatment period in a dosing arm that has been dropped will rollover into a lower dosing arm in the Open-Label Extension Study, DX-2930-04, as determined by the SSC. Data for these subjects will be used up to the time at which it is decided to drop the dose in the efficacy analyses and in its entirety in the safety analyses.

3.1.2.3 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator, warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed for the duration of the 26 week treatment period, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

3.1.3 Follow-up for Subjects Meeting Stopping Criteria

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

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

3.2 Rationale for Pivotal Dose Selection

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

In study DX-2930-02, two DX-2930 doses of 300 mg or greater administered 2 weeks apart resulted in a normalization of plasma 2-chain HMWK levels and a maximal 91% reduction in HAE attacks (DX-2930 Investigators Brochure). Steady-state trough concentrations

following DX-2930 administration every 2 weeks would be approximately 27,000 ng/mL. The maximum plasma concentration (C_{max}) obtained following ecallantide administration to treat an acute attack is similar to this trough concentration of DX-2930.

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

The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930 treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

3.3 Individual Subject Dosing and Follow-Up

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

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week wash-out period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study will enroll up to 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted either during the screening visit or during participation in study DX-2930-02.

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in HAE patients as young as the age of 3 (Bork et al., 2003). In one case series of 49 pediatric HAE patients, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas, 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig, 2015; Zuraw, 2008). The study will aim to enroll at least 5 subjects who are 12 to 17 years of age.

4.2 Inclusion Criteria

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

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
   - At least one of the following: age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

- Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from screening through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD, all types). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 60 days after the final study visit.

4.3 Exclusion Criteria

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior screening.
3. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
4. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
5. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
6. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding IMP administration, refer to the Pharmacy Manual.

5.1.1 DX-2930

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm in a blinded manner.

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

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

5.1.2 Placebo

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

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

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

5.2 Dosing and Follow-Up Schedule

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

5.3 Method of Assigning Subjects to Treatment Groups

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

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

5.4 Blinding and Unblinding

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

If necessary for the SSC to conduct a safety evaluation, the Sponsor may break the blind for individual subjects to determine if adverse events occurred in DX-2930 treated subjects.

In the case of a concerning drug-related safety event, the Investigator has the ability to contact and consult with the Medical Monitor. In emergency situations, the Investigator may break the treatment code immediately, or as quickly as possible if he/she finds it is in the best interest of the trial subject. The investigator has unrestricted and immediate access to break the treatment code through the IWRS System. In the event of a drug-related, serious, unexpected AE, the Dyax Pharmacovigilance Department will be provided with the treatment assignment for the subject for the purpose of regulatory reporting.

5.5 Prior and Concomitant Therapy

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

All information on concomitant therapy from the time of first dose of IMP through the final study visit (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's electronic Case Report Form (eCRF) and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.5.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, are permitted if not excluded in Section 5.5.2.
- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.5.2 Excluded Concomitant Therapies

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

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

5.6 Restrictions

5.6.1 Medical Interventions

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

5.6.2 Fluid and Food Intake

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

5.6.3 Activity

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

5.7 Treatment Compliance

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

5.8 Packaging and Labeling

The test products (DX-2930 and placebo) will be supplied by 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 (2ºC to 8ºC/36ºF to 46ºF) in the original carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

5.10 Investigational Medicinal Product Retention at Study Site

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

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

6 STUDY PROCEDURES

Please refer to the Study Activities Schedule, Appendix 1.

6.1 Informed Consent

Informed Consent and Assent forms must be approved for use by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study related activities. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Eligibility Review

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

6.3 Demographics and Medical History

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

6.4 Efficacy Assessments

6.4.1 Primary and Secondary Endpoints

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 14through Day 182.

Primary Endpoint

- Number of HAE attacks per week

Secondary Endpoints (in Rank Order)

1. Time to first attack, i.e., duration that a subject is attack-free until their first attack.
2. Number per week of HAE attacks requiring acute attack therapy use.
3. Number per week of moderate or severe HAE attacks.
4. Number per week of high-morbidity HAE attacks; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours) , hemodynamically

significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

6.4.2 HAE Attack Information Collection

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

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

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

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

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

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

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

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

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

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

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

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

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

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

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

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

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

6.5 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ±15 minute window for all vital signs.

6.6 Physical Examination

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

- Height and weight (at Screening visit only)
- General appearance
- Ears, nose, and throat
- Head and Neck
- Ophthalmological
- Respiratory
- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Appendix 1). The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

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

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

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each subject who does not rollover into the OLE will be approximately 271 mL. The total blood draw for each subject that does rollover into the OLE will be approximately 208 mL. Please refer to the Laboratory Manual for more information.

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

6.8.1.1 Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

6.8.1.2 Coagulation

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

6.8.1.3 Chemistry

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

6.8.1.4 Urinalysis

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

6.8.1.5 Serology

HBsAg, HCV, and HIV tests

6.8.1.6 Pregnancy Test

Serum or urine pregnancy test

6.8.1.7 C1-INH Functional Assay

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

6.8.1.8 C4 Assay

Results of a C4 assay may be required for eligibility assessment. Samples will be drawn at the screening visit unless they were previously drawn and used for diagnostic confirmation in DX-2930-02. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.9 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Samples will be drawn at the screening visit if C1-INH and C4 samples are also being drawn. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.10 PK Sample Collection

As outlined in Section 6.9.

6.8.1.11 PD Sample Collection

As outlined in Section 6.10.

6.8.1.12 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

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

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

6.9 Pharmacokinetic Assessments

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

6.10 Pharmacodynamic Assessments

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

6.11 Plasma Anti-Drug Antibody Testing

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

6.12 Prior and Concomitant Therapy

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

6.13 Randomization

Subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be blocked by naïve vs. non-naïve subjects (subjects receiving active study drug in protocol DX-2930-02) as well as the baseline attack rate into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

6.14 Investigational Medicinal Product Treatment

Instructions for safe handling of IMP, preparation of each subcutaneous dose, and administration of IMP are provided in the Pharmacy Manual. Preparation and dispensing of the IMP will be handled by qualified site personnel as directed by the Principal Investigator

at the study site. The Principal Investigator or qualified site personnel will administer the assigned IMP. The requirements for maintaining IMP accountability are provided in Section 5.9 of this protocol.

6.15 Quality of Life Assessments

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

6.16 Adverse Event Reporting

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

6.16.1 Definitions

6.16.1.1 Adverse Event

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

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

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

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

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

6.16.1.2 Serious Adverse Event

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

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

6.16.1.3 Overdose

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

6.16.1.4 Planned Hospitalization

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

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

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

6.16.1.6 Adverse Events of Special Interest (AESI)

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

HYPERSENSITIVITY REACTIONS

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

EVENTS OF DISORDERED COAGULATION

Bleeding AESI

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

Hypercoagulable AESI

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

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

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

- Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the Investigator.

- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

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

6.16.2.2 Monitoring of Safety Laboratory Assessments

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

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

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

In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 2) and the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

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

6.16.3.2 Assessment of Causality

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

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

The causal relationship between the study IMP and the AE will be assessed using one of the following categories:

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

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

Related: Factors consistent with an assessment of Related include:

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

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the Investigator, with discussion with the Medical Monitor as appropriate, or by the SSC for overall study AE review.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and

that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, will be considered an AE.

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

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

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

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-Serious Adverse Events

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

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the 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.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to Dyax

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

- SAE
- AESI
- Overdose
- Cancer

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

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

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

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

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

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

6.16.5.5 Safety Contact Information

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

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

Dyax Pharmacovigilance Department
Contacts: PPD **or** PPD
Email: PPD
Phone (US): PPD

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

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

6.16.5.7 Unblinding a Subject's Treatment during the Trial

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

6.17 Subject Withdrawal

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

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

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study. The criteria used by the SSC regarding dose administration suspension and/or study discontinuation are provided in Section 3.1.2.

6.18 Appropriateness of Measurements

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

7 STUDY ACTIVITIES

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

7.1 Screening

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

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6); documentation of height and weight
- 12-Lead ECG (Section 6.7)
- Laboratory testing including, serology, hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms
- Subjects who are on LTP for HAE must complete a 2 week washout period, as confirmed by the Investigator, before entering the run-in period.

7.2 Run-in Period

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

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

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

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

The following procedures and assessments are to be performed on Day 0 prior to the first dose of IMP administration:

- Eligibility review (Section 6.2)
- Randomization to treatment (Section 6.13)
- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

7.4 Site Contact with the Subject

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

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

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

- 12-Lead ECG (Section 6.7)

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

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

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

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

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

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

period may be lengthened back to 2 hours at any time by the Sponsor based on SSC recommendation.

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

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

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Urine pregnancy test (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)
- Discharge from study:
    - Subjects will be offered the option of enrolling in the DX-2930-04 Open Label Extension (OLE) study for continued treatment and safety follow-up.
    - Informed Consent obtained for study DX-2930-04
    - Subjects who consent to participate in DX-2930-04 will receive their first OLE dose following the completion of all double-blind assessments scheduled on Day 182.

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- PK sample collection (Section 6.9)

- PD sample collection (Section 6.10)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

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

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Urine pregnancy test (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.15)

7.18 Early Termination (ET)

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

8 QUALITY CONTROL AND ASSURANCE

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

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

9 DATA ANALYSIS / STATISTICAL METHODS

9.1 Sample Size Determination

The sample size needed to test the primary hypothesis (alpha = 0.025, one-sided) in the Intent-to-treat (ITT) population to achieve a given power is calculated using the data and information from the DX-2930-02 study. Power analysis and sample size estimation was based on 1000 computer simulations using a mixed model repeated measures (MMRM) analysis of variance (ANOVA) for counts using the SAS generalized estimating equation (GEE) determination of statistical significance. Assumptions included that placebo subjects have an observed attack rate of 0.3 attacks per week during the treatment period, and are observed for 24 weeks of efficacy. Active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data / dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

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

9.2 Analysis Populations

The analysis populations will be defined as follows:

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

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

9.3 Analysis of Disposition

The numbers of subjects randomized, completing, or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group.

9.4 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group.

9.5 Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

9.5.1 Pharmacokinetic Assessments:

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

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

9.5.2 Pharmacodynamic Assessments:

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

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

9.5.3 Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE

9.5.4 C1-INH and C4 Assessments:

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

9.6 Analysis of Primary and Secondary Efficacy Endpoints

The primary analysis will be to compare the primary endpoint, which is mean rate of Investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 14 through Day 182). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP will be conducted.

The HAE attack rates of the treated and placebo groups will be compared using MMRM ANOVA for counts using the GEE. The baseline attack rate for each subject as determined by the run-in period will be used as a continuous covariate in an analysis of covariance. The model will be based on two fixed effects (treatment group and prior use of DX-2930), the

random effect will be the subject and the baseline attack rate will be a continuous covariate. For each subject, the least squares mean will be calculated and adjusted for their baseline attack rate. A Poisson distribution will be assumed rather than a Gaussian distribution. Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. There will be no Last Observation Carried Forward (LOCF), as the HAE attack rate will be computed as the total number of attacks divided by the total duration of observation during the specified time period. Subject weeks for which completed observation is less than the full 168 hours within a week will be handled according to an *a priori* plan to be described in the SAP.

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 rate of the mean event rate per week, for each dose level vs placebo and its 95% Confidence interval can also be estimated by transforming the above lsmean difference and its 95% CI confidence interval by the exponential function,

The percentage change in mean attack rate of each active 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.

Sample code for the above analysis is:

```
PROC GENMOD DATA = XXXX ;
WHERE  x<=visitn<=y;
        CLASS   Trta (REF = 'Placebo') usubjid;
        MODEL attack=trta priordx base/ DIST=poisson;
        REPEATED  SUBJECT=usubjid / CORR=ind;
        LSMEANS trta/DIFF CL ILINK;
        ODS OUTPUT diffs – meandiff  lsmeans = means;
RUN;
```

There are three active treatment arms ordered by highest total monthly dose; 1) Primary Treatment Arm: 300 mg DX-2930 every 2 weeks, 2) Secondary Treatment Arm: 300 mg DX-2930 every 4 weeks, and 3) Tertiary Treatment Arm: 150 mg DX-2930 every 4 weeks. For the primary endpoint, each of the three active treatment arms will be compared against placebo using a closed sequential testing procedure in which first, the primary active treatment arm is compared to placebo at significance level alpha and then, if there is statistical significance found, then the secondary treatment arm is tested against placebo at level alpha. If statistical significance is found for both the primary and secondary treatment arms, then the tertiary treatment arm shall be compared to placebo at significance level alpha.

If a dose is dropped due to an important safety signal, the highest remaining dose automatically becomes the primary dose comparison versus placebo.

All secondary hypotheses for each active treatment group versus placebo are also to be tested in a closed sequential methodology. The *a priori* order of testing the secondary hypotheses

has been pre-specified in Section 6.4.1. In order to preserve the overall alpha level, secondary endpoints are not tested unless the primary endpoint is found to be statistically significant.

The first secondary endpoint, time to first HAE attack, will be tested using the log-rank test comparing each active treatment group vs placebo. The descriptive summaries will use life table summaries based on Kaplan Meier (KM) estimates. Subjects without any HAE attacks during the 24-week period and subjects without 24 weeks of observation will be right censored.

The second secondary endpoint, reduction in HAE acute therapy use, will be tested using the MMRM model as described for the primary endpoint. The same SAS code used for the primary endpoint will be used but with a different endpoint.

The third secondary endpoint, reduction in moderate or severe HAE attacks, will be tested using the MMRM model as described for the primary endpoint. The same SAS code used for the primary endpoint will be used but with a different endpoint.

The fourth secondary endpoint, reduction in high-morbidity HAE attacks, will be tested using the MMRM model as described for the primary endpoint. The same SAS code used for the primary endpoint will be used but with a different endpoint.

9.7 Safety Analysis

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

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

Usage of concomitant medications (other than rescue medications) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

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

Abnormal physical examination findings will be listed.

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

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

9.8 Analysis of Quality of Life Assessments

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

10 STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 2.

Table 2. Study Administrative Structure

Sponsor Contact:	Ryan Iarrobino PPD, Clinical Development 55 Network Drive, Burlington, MA 01803 Phone: PPD Email: PPD
Sponsor Medical Director:	PPD, MD PPD, Medical Research 55 Network Drive, Burlington, MA 01803 Phone: PPD Email: PPD
Medical Monitor (US, Canada):	PPD, MD Rho, Inc. PPD, PPD, PPD Phone: PPD Email: PPD
Medical Monitor (Jordan, Europe)	PPD, M.D. Voisin Consulting PPD, PPD PPD, France Phone: PPD Email: PPD
Study Monitoring (US):	Rho, Inc. PPD, PPD, PPD Phone: PPD
Study Monitoring (Jordan)	Triumpharma PPD, PPD PPD, PPD PPD, Jordan Phone: PPD
Study Monitoring (Canada)	Red Maple Trials Incorporated PPD, PPD PPD, PPD, Canada, PPD Phone: PPD
Study Monitoring (Europe)	Dyax Corp 55 Network Drive, Burlington, MA 01803 Phone: PPD

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

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

10.2 Ethical Conduct of the Study

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

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The Investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the study.

10.4 Subject Confidentiality

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

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

10.5 Study Monitoring

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

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

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

10.6 Case Report Forms and Study Records

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

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

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

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

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

10.7 Study Safety Committee

This study will be conducted under the oversight of an internal Study Safety Committee (SSC) that will review safety data at regular intervals throughout the course of the study.

10.8 Protocol Violations/Deviations

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

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

10.9 Access to Source Documentation and On-Site Audits

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

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

10.10 Data Generation and Analysis

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

will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.11 Retention of Data

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

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

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

10.12 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.

10.13 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

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12 APPENDICES

Appendix 1 Study Activities Schedule

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

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

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 1 Study Activities Schedule

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

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

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

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Day 98, and Day 238 can be serum or urine-based.

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

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

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

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Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

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

(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

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

(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

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(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

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(Greater than 3 months of age)

GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

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(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microscopic >25		Gross hematuria

	cells/hpf	cells/hpf		

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(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

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(Greater than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
PARAMETER	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

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(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

HAE Attack Assessment and Reporting Procedures (HAARP)

Title:	HAE Attack Assessment and Reporting Procedures (HAARP)
Product Name:	DX-2930
Indication:	Prevention of angioedema attacks in patients with HAE
Sponsor:	Dyax Corp. 55 Network Drive Burlington, MA 01803
Original Date:	14 September 2015
Version:	v1.0

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1 PURPOSE

This document applies to clinical trials that involve investigator adjudication/assessment of angioedema attacks. The purpose of this document is to provide a definition of an HAE attack and to define a standardized set of procedures for the reporting and assessment of events reported by subjects to determine whether those events are true HAE attacks.

2 DEFINITION OF AN ATTACK

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

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

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (e.g., urticaria), the reported event persists well beyond the typical time course of an attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

Attack resolution is defined as the subject no longer having symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

Patient report of use of acute HAE attack treatment for an attack by itself is not confirmation that an attack occurred.

3 REPORTING AND ASSESSMENT OF ATTACK DATA

At screening for applicable clinical trials, subject HAE attack history will be collected by the site for entry into the clinical database. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant location(s), average duration, acute attack therapy use, and history of long-term prophylaxis.

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects < 18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is

unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

Site personnel will review the information provided by the subject or caregiver and solicit additional information as necessary to document the attack. Information documented by the site will be considered source for the study.

A designated individual at the site (the collector) will contact the subject or caregiver on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject or caregiver.

The Investigator or designee (the assessor) will review the attack information and evaluate if the event represents a confirmed HAE attack. If necessary for the evaluation, the investigator or designee may contact the subject to receive additional information.

3.1 Subject-Reported Symptoms

Subjects and caregivers can use any existing methods by which they track information about their attacks, or, if requested, memory aids can be provided by the study site. However, subjects (or a caregiver) will need to track attacks in such a way as to be able to contact the study site as soon as possible, but not later than 72 hours (3 full days) after the first symptoms appear, to report the information.

3.1.1 Attack Information

The following information should be provided by the subject (or caregiver) at the time they are reporting an attack to the site:

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

Subjects do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/ or at a scheduled study visit. Subjects should not withhold or delay any treatment they would normally receive to treat their attack in order contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/ or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

During screening, site personnel will train subjects on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The patient will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the subject's compliance with the reporting requirements throughout the study and may retrain the subject if necessary in order to maintain the integrity of the data provided to the site.

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack as stated in Section 2, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Caregiver Report

During screening, site personnel will train subject caregivers (if applicable) on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The caregiver will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the caregiver's compliance with the reporting requirements throughout the study and may retrain the caregiver if necessary in order to maintain the integrity of the data provided to the site.

3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/ or use of back-up contacts, should be established in case the subject is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits. The date and time for check-ins can be modified based on when the last contact with the subject was made, as outlined in the study protocol. When the site is contacted by a subject reporting symptoms of an attack the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be

established in case the subject misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

3.2.1 Review of subject report of symptoms

During contact with the subject, whether subject-initiated or a regular check-in, site personnel should ask the subject to provide them information about new or ongoing HAE attacks experienced.

The site will try to obtain all information necessary to document the attack completely. Missing information may impact the assessment of any attack and should be avoided whenever possible.

3.2.2 Documenting a Reported Attack

Complete and accurate documentation of each reported attack is important to making an Investigator assessment of the attack. The site should document the following information about each attack reported by the subject or caregiver:

- Date and time of contact with the subject
- Date and time the subject first experienced symptoms
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance was required
- If the attack has resolved or is ongoing. If the attack has resolved, the date and time the subject was no longer experiencing any symptoms of the attack
- Names of any medications used to treat the attack including HAE acute therapy or other non-HAE treatments
- If hospitalization occurred
- If a trip to the emergency department occurred

Additional probing questions about what the subject experienced to determine:

- If the subject only experienced prodromal symptoms
- If the subject experienced anything different than their typical attack
- If there were any possible alternative etiologies of the symptoms. For example, a viral gastroenteritis outbreak in the household could explain abdominal symptoms

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

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

The site will also document the date and time of investigator or designee review, the official designation of the event as an attack or not, and if applicable, the reason why an event is not considered an attack.

All reported attacks will be entered by site personnel into the electronic case report form (eCRF).

3.2.3 Site Training

Site personnel responsible for collecting attack information about subject HAE attacks will need to pass a "Collector" training assessment covering the following:

- definition of an HAE attack
- requirements of subjects and caretakers for reporting attacks
- reporting worsening symptoms and multiple attacks
- information to be collected from subjects and caregivers as well as the additional probing questions to gather context for the attack information provided
- assessment of attack severity
- entry of the attack data into the eCRF
- reporting HAE attacks as adverse events
- requirements for Investigator assessment of attacks

Trainings will be conducted prior to sites screening subjects. Trainings will be documented in the Trial Master File. Investigators and designees will be trained on these procedures as well and must pass an "Assessor" training in order to officially assess attacks for this study.

All responsible persons involved in the collection of information from subjects or assessing attacks must be listed on FDA Form 1572.

3.3 HAE attacks as Adverse Events

At the time of each contact and scheduled study visit, site personnel will ask if the subject experienced any adverse events or changes to the medications they are taking.

HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF.

Any AE reported to the site meeting criteria for a serious adverse event must be reported to Dyax using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack.

For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional

information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

4 INVESTIGATOR ATTACK ASSESSMENT

The Principal Investigator for a study site may identify a physician designee to assess patient symptom information and make attack determinations. Sites should be limited to two individuals responsible for assessing attacks, one of them being the Principal Investigator. Assessors must be experienced with HAE and familiar with the study subject's disease history.

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

Clinical Trial Protocol: DX-2930-03

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

	Date:
Original Protocol	14 September 2015
Amendment 1.0	14 December 2015
Amendment 2.0	21 April 2016

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: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number: DX-2930-03

Amendment 2.0 Final Date: 21 April 2016

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

Signed: PPD _____ Date: PPD

Jennifer Schranz, MD PPD

PPD , Clinical Development

300 Shire Way, Lexington, MA 02421

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

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

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

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

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

Signed:_____ Date:_____

Investigator

Address: _____

_____

SYNOPSIS

Sponsor: Dyax Corp. 55 Network Drive, Burlington, MA 01803 USA
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80
Study Title: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-03
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across the United States, Italy, United Kingdom, Germany, Canada and Jordan
Primary Objective: To evaluate the efficacy of DX-2930 in preventing HAE attacks
Secondary Objective: To evaluate the safety of repeated subcutaneous administrations of DX-2930
Tertiary Objectives: • To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930 • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the pharmacokinetics (PK) of chronically administered DX-2930 • To evaluate the effect of DX-2930 on health-related quality of life (QoL)
Study Design: This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in

patients with Type I and Type II HAE.

Long-Term Prophylactic (LTP) Therapy Washout:

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

Run-In Period:

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

Treatment Period:

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

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

Table 1. Treatment Period Dosing Schedule

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

Open-Label Extension (OLE) Study:

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

Follow-Up Period:

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

Study Population:

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

Criteria for Inclusion:

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

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
   - At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, and are willing and able to read, understand, and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
   - Females of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This includes progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable, or implantable), intra-uterine device (IUD, all types), or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective.
   - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study.
   - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 60 days after the final study visit.

Criteria for Exclusion:

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior DX-2930 study.
3. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.
2. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
3. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
4. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
5. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
6. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
7. Pregnancy or breastfeeding.
8. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

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

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

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

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

Placebo; Dose; and Mode of Administration:

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

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

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

Duration of Treatment:

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

Duration of Study for Individual Subjects:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks in the double-blind study.

Prohibited Concomitant Treatments:

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

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

- Any other investigational drug or device.

The use of short-term prophylactic treatment for HAE is permitted if medically indicated.

Management of Acute Attacks:

Acute HAE attacks during the study are to be managed in accord with the Investigator's usual care of their patients, including use of acute attack therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylaxis. Administration of the investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the patient receives any treatment for an HAE attack.

Safety Assessments:

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

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI).
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR).
- Physical examination.
- Clinical laboratory testing (hematology, serum chemistry, coagulation, and urinalysis).
- 12-Lead electrocardiogram (ECG).

Pharmacokinetic (PK) Assessments:

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

Pharmacodynamic (PD) Assessments:

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

Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE.

C1-INH, C4, and C1q Assessments:

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

Quality of Life Assessments:

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

Collection of HAE Attack Data:

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

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

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

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

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

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

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

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

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

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

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

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

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

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

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

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

the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household). To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.
Interim Analysis and Data Safety Monitoring Board: No interim analysis is planned for this study. During the study, patient safety will be monitored on a continuous basis by the Medical Monitor until the last patient completes his or her last scheduled study assessment. An independent Data Safety Monitoring Board (DSMB) will also be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The ongoing review of SAEs and other responsibilities of the DSMB are described in the DSMB Charter.
Individual Stopping Rules: Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through completion of all scheduled visits, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

Criteria for Evaluation:

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

Primary Efficacy Endpoint

- Number of Investigator-confirmed HAE attacks

Secondary Efficacy Endpoints (rank ordered)

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

Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Safety Measures:

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

Additional Measures:

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

Analysis Populations:

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

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

Sample Size Determination:

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

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

Statistical Methods:

The primary analysis will be to compare the primary endpoint, which is the number of Investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 0 through Day 182). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP or placebo (ITT population) will be conducted.

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

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

The primary endpoint will be tested by the following hypothesis:

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

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

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

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

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

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

Safety Analysis:

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

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

Usage of concomitant medications (other than rescue medications) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

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

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

Study Activities Schedule

Study Activities Schedule

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

Study Activities Schedule

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

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

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

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
AE-QoL	Angioedema-Quality of Life Questionnaire
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to the last quantifiable concentration in plasma at time t
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last measurable concentration
BLA	Biologics License Application
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CL/F	apparent total plasma clearance after extravascular administration
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report

DLT	Dose Limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
EQ5D	EuroQoL Group 5-Dimension Report Questionnaire
FWER	family-wise type 1 error rate
FDA	Food and Drug Administration
FXI(a)	Factor XI (activated)
FXII(a)	Factor XII (activated)
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug

INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing systems
IV	Intravenous
IWRS	Interactive Web-based Randomization System
K_i	inhibition constant
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LTP	Long-Term Prophylactic
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pKal	Plasma kallikrein
PT	Prothrombin time
QoL	Quality of Life
REB	Research Ethics Board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)

SGPT	Serum glutamic pyruvic transaminase (ALT)
SM	Safety Management
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
$t_{½}$	Terminal elimination half-life
t_{max}	Time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TT	Thrombin time
US	United States
Vd/F	Apparent volume of distribution during terminal phase after extravascular administration
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 DX-2930

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

1.2 Hereditary Angioedema

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

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

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

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

1.3 Therapeutic Rationale for DX-2930

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

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

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

1.4 Safety Rationale for DX-2930

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

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

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

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

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

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

1.6 DX-2930 Clinical Data

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

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

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

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

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

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

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

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

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days and were followed for 15 weeks after the second dose.

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

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

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

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

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

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

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

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

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

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

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

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

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

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

2.3 Tertiary Objectives

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

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

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

3.1.1.1 Long-Term Prophylactic (LTP) Therapy Washout

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

3.1.1.2 Run-In Period

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

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

3.1.1.3 Treatment Period

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

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

Table 1. Treatment Period Dosing Schedule

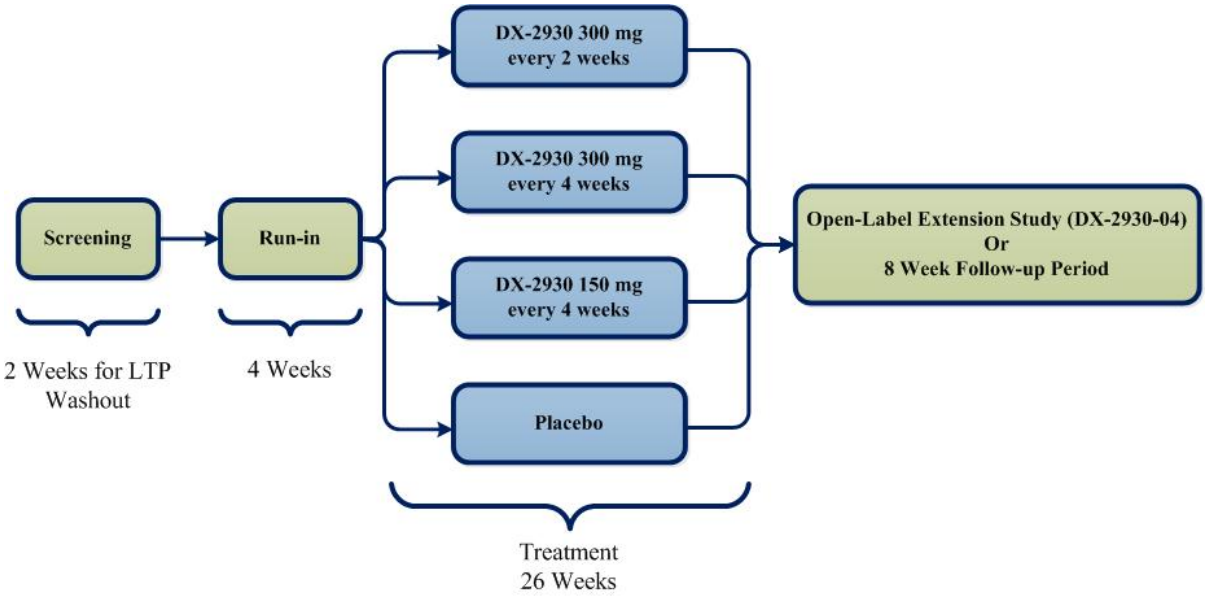
Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/Week 4	DX-2930	DX-2930	DX-2930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

3.1.1.4 Open-Label Extension (OLE)

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

Figure 1 shows a schematic of the study design.

Figure 1. Overview of the Study Design



3.1.1.5 Follow-Up Period

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

3.1.2 Safety Oversight and Stopping Rules

3.1.2.1 Interim Analysis and Data Safety Monitoring Board (DSMB)

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

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

3.1.2.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator, warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed for the duration of the 26 week treatment period, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

3.1.3 Follow-Up for Subjects Meeting Stopping Criteria

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

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

3.2 Rationale for Pivotal Dose Selection

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

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

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

The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930 treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

3.3 Individual Subject Dosing and Follow-Up

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

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week wash-out period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

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

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in HAE patients as young as the age of 3 (Bork et al., 2003). In one case series of 49 pediatric HAE patients, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas, 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig, 2015; Zuraw, 2008). The study will aim to enroll at least 5 subjects who are 12 to 17 years of age.

4.2 Inclusion Criteria

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

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
   - At least one of the following: age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

- Females of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This includes progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective.
- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 60 days after the final study visit.

4.3 Exclusion Criteria

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior DX-2930 study.
3. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
7. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
9. Pregnancy or breastfeeding.
10. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or

interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding IMP administration, refer to the Pharmacy Manual.

5.1.1 DX-2930

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm in a blinded manner.

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

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

5.1.2 Placebo

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

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

5.2 Dosing and Follow-Up Schedule

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

5.3 Method of Assigning Subjects to Treatment Groups

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

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

5.4 Blinding and Unblinding

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

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

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

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

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

5.5 Prior and Concomitant Therapy

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

All information on concomitant therapy from the time of first dose of IMP through the final study visit (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's electronic Case Report Form (eCRF) and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.5.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, are permitted if not excluded in Section 5.5.2. Acute HAE attacks during the study are to be managed in accord with the Investigator's usual care of their patients, including use of acute attack therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylaxis. Administration of the investigational product and study procedures will continue without alteration to the protocol specified study schedule, even if the patient receives any treatment for an HAE attack.
- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.5.2 Excluded Concomitant Therapies

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

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

5.6 Restrictions

5.6.1 Medical Interventions

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

5.6.2 Fluid and Food Intake

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

5.6.3 Activity

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

5.7 Treatment Compliance

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

5.8 Packaging and Labeling

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

5.9 Storage and Accountability

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

5.10 Investigational Medicinal Product Retention at Study Site

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

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

6 STUDY PROCEDURES

Please refer to the Study Activities Schedule, Appendix 1.

6.1 Informed Consent

Informed Consent and Assent forms must be approved for use by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study related activities. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Eligibility Review

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

6.3 Demographics and Medical History

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

6.4 Efficacy Assessments

6.4.1 Primary and Secondary Endpoints

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

Primary Efficacy Endpoint

- Number of Investigator-confirmed HAE attacks

Secondary Efficacy Endpoints (rank ordered)

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

Exploratory Efficacy Endpoints

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

- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

6.4.2 HAE Attack Information Collection

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

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

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

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

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

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

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

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

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

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

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

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

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

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

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

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

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

6.5 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ±15 minute window for all vital signs.

6.6 Physical Examination

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

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

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

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Appendix 1). The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

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

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

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each subject who does not rollover into the OLE will be approximately 271 mL. The total blood draw for each subject that does rollover into the OLE will be approximately 208 mL. Please refer to the Laboratory Manual for more information.

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

6.8.1.1 Hematology

- Hemoglobin

- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

6.8.1.2 Coagulation

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

6.8.1.3 Chemistry

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

- Potassium
- Sodium
- Total protein
- Uric acid

6.8.1.4 Urinalysis

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

6.8.1.5 Serology

HBsAg, HCV, and HIV tests

6.8.1.6 Pregnancy Test

Serum or urine pregnancy test

6.8.1.7 C1-INH Functional Assay

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the screening visit. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.8 C4 Assay

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

6.8.1.9 C1q Assay

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

6.8.1.10 PK Sample Collection

As outlined in Section 6.9.

6.8.1.11 PD Sample Collection

As outlined in Section 6.10.

6.8.1.12 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

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

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

6.9 Pharmacokinetic Assessments

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

6.10 Pharmacodynamic Assessments

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

6.11 Plasma Anti-Drug Antibody Testing

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

6.12 Prior and Concomitant Therapy

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

6.13 Randomization

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

6.14 Investigational Medicinal Product Treatment

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

6.15 Quality of Life Assessments

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

6.16 Adverse Event Reporting

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

6.16.1 Definitions

6.16.1.1 Adverse Event

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

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

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

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

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

6.16.1.2 Serious Adverse Event

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

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

6.16.1.3 Overdose

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

6.16.1.4 Planned Hospitalization

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

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

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

6.16.1.6 Adverse Events of Special Interest (AESI)

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

HYPERSENSITIVITY REACTIONS

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

EVENTS OF DISORDERED COAGULATION

Bleeding AESI

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

when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

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

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

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

- Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the Investigator.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects will continue to be followed through completion of all scheduled visits.

6.16.2.2 Monitoring of Safety Laboratory Assessments

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the Investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning.

In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 2) and the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

- GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required
- GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Any treatment-emergent ECG abnormality that is considered by the Investigator as clinically significant and requiring intervention/therapy will be assessed as a severe AE.

6.16.3.2 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the IMP, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between IMP exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the IMP.
- The AE resolved or improved with decreasing the dose or stopping use of the IMP (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study IMP and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the IMP); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of IMP); or
- The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the IMP).

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the Investigator, with discussion with the Medical Monitor as appropriate, or by the DSMB for overall study AE review.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) or DMID Pediatric Toxicity Tables (Appendix 3) will be used to assess severity. Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the Investigator with input from the Medical Monitor as needed.

Following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the Investigators Brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically

important functions *in vivo*. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-Serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to IMP, will be recorded on the AE page of the eCRF. In this study all HAE attacks reported by the subject, regardless of whether or not they are confirmed by the Investigator, will be captured as AEs.

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Sponsor's Pharmacovigilance Department using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The Investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the Investigator or qualified designee to the Sponsor's Pharmacovigilance Department:

- SAE
- AESI
- Overdose
- Cancer

The Investigator is to report any expedited safety observations from the list above to the Sponsor using the **SAE Reporting Form in the EDC system** within 24 hours of becoming aware of the event.

Any SAE reported to the Sponsor Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

The Investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The Investigator does not expect any further improvement or worsening of the event.
- Fatal outcome—if an autopsy is performed, the autopsy report is requested to be provided to the sponsor as soon as it is available.

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor or designee will report relevant safety information to concerned health authorities in accordance with local laws and regulations.

6.16.5.5 Safety Contact Information

Medical Safety Contact for US and Canada
PPD, MD
PPD, Clinical Development
300 Shire Avenue, MA 02421 USA
Phone: PPD
Email: PPD
Calls or emails received weekends, holidays, or weekdays between 8:00 pm and 8:00 am Eastern (US) time will be responded to the morning of the following business day.

24-Hour Medical Safety Contact for Europe and Middle East
PPD, MD, MBA
PPD
Phone: PPD
Email: PPD

Sponsor Pharmacovigilance Department
Email: PPD
Phone (US): PPD

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to IMP that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The Investigator will promptly inform his/her IRB/REB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

6.16.5.7 Unblinding a Subject's Treatment during the Trial

Requirements for emergency unblinding by the Investigator are detailed in Section 5.4. To assess an occurrence of a safety observation, the Sponsor Pharmacovigilance Department may unblind the treatment of any subject.

6.17 Subject Withdrawal

The Investigator may withdraw a subject from treatment with study drug for any of the reasons listed below.

- In the opinion of the Investigator, the subject is unable to comply with the requirements of the protocol for satisfactory completion or interpretation of study results (including use of prohibitive medications),
- A serious or intolerable AE occurs,
- A clinically significant change in a laboratory parameter occurs,
- The Sponsor or Investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study. The criteria used by the DSMB regarding dose administration suspension and/or study discontinuation are provided in Section 3.1.2.

6.18 Appropriateness of Measurements

This is a Phase 3 multi-center, randomized, double-blind, placebo-controlled study that is designed to evaluate the efficacy and safety of DX-2930 in prevention of HAE attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The randomized, placebo controlled study design is a standard approach for differentiation between the efficacy and safety profiles of an active and placebo treatment when administered to subjects. All of the measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product.

7 STUDY ACTIVITIES

Study activities are summarized by study visit in Appendix 1 (Study Activities Schedule).

7.1 Screening

The following procedures and assessments are to be performed during Screening:

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6); documentation of height and weight
- 12-Lead ECG (Section 6.7)
- Laboratory testing including, serology, hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms
- Subjects who are on LTP for HAE must complete a 2 week washout period, as confirmed by the Investigator, before entering the run-in period.
    - LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age.

7.2 Run-in Period

Subjects who were on LTP may enter run-in after successfully completing a 2 week washout of their LTP. All subjects will undergo a run-in period of 4 weeks to determine the baseline HAE attack rate (Section 6.4). The run-in period may be shortened to less than 4 weeks for any subject who experiences 3 Investigator-confirmed attacks before the 4 weeks have ended. The run-in period may be expanded by an additional 4 weeks if the subject does not meet the minimum attack requirement during the first 4 weeks.

The following will be collected on an ongoing basis during the run-in period by subjects (or caregivers) reporting symptoms of an HAE attack to the site or through regular site contact with the subject (or caregiver):

- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.3 Start of Treatment Period: Visit 1, Dose 1 (Day 0)

The following procedures and assessments are to be performed on Day 0 prior to the first dose of IMP administration:

- Eligibility review (Section 6.2)
- Randomization to treatment (Section 6.13)
- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.4 Site Contact with the Subject

Site personnel contact the subject once between scheduled study visits or approximately 7 days after their last contact with the subject to solicit for any HAE attack information not already reported by the subject.

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.5 Continuation of Treatment Period: Visit 2, Dose 2 (Day 14±3 Days)

On Day 14 the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.6 Continuation of Treatment Period: Visit 3, Dose 3 (Day 28±3 Days)

On Day 28, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.7 Continuation of Treatment Period: Visit 4, Dose 4 (Day 42 ±3 Days)

On Day 42, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)

- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.8 Continuation of Treatment Period: Visit 5, Dose 5 (Day 56±3 Days)

On Day 56, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.9 Continuation of Treatment Period: Visits 6 and 7, Doses 6 and 7 (Days 70 and 84, All ±3 Days)

On Days 70 and 84, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.

- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.10 Continuation of Treatment Period: Visit 8, Dose 8 (Day 98±3 Days)

On Day 98, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)

- AE collection (Section 6.16)

7.11 Continuation of Treatment Period: Visits 9 and 10, Doses 9 and 10 (Days 112 and 126, All ±3 Days)

On Days 112 and 126, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Pregnancy test, serum or urine (females) on Day 126±3 (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL on Day 126±3 (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.12 Continuation of Treatment Period: Visit 11, Dose 11 (Day 140±3 Days)

On Day 140, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)

- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.13 Continuation of Treatment Period (Day 144±1 Day)

This ECG assessment may be conducted through an at-home visit by a nurse or technician or at the study site. The date, time and collection location of this ECG and its results will be documented in the source documents and eCRF.

- 12-Lead ECG (Section 6.7)

7.14 Continuation of Treatment Period: Visits 12 and 13, Doses 12 and 13 (Days 154 and 168, All ±3 Days)

On Days 154 and 168, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Pregnancy test, serum or urine (females) on Day 154±3 (Section 6.8)

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL on Day 154±3 (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.15 Completion of Treatment Period: Visit 14, Day 182±3 Days

On Day 182, the following procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Urine pregnancy test (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)
- Discharge from study:
  - Subjects will be offered the option of enrolling in the DX-2930-04 Open Label Extension (OLE) study for continued treatment and safety follow-up.
  - Informed Consent obtained for study DX-2930-04
  - Subjects who consent to participate in DX-2930-04 will receive their first OLE dose following the completion of all double-blind assessments scheduled on Day 182.

7.16 Follow-up Period (Subjects Not Continuing in Open-Label Extension Study): Visit 15, Day 210 ±3 Days

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.17 Final Follow-up Visit (Subjects Not Continuing in Open-Label Extension Study): Visit 16, Day 238±3 Days

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

7.18 Early Termination (ET)

Subjects that terminate early from the study will undergo (if possible) all of the assessments and procedures scheduled for Day 182.

8 QUALITY CONTROL AND ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management services, Rho, Inc. will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The site staff should assist in all aspects of audit/inspection.

9 DATA ANALYSIS / STATISTICAL METHODS

9.1 General Considerations

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, PPD, PPD, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group. For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, treatment differences, p-values, and 95% confidence intervals for least squares mean treatment differences will be provided. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal statistical hypothesis testing will be performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure as described in Section 9.12.5.

9.2 Sample Size Determination

Power analysis and sample size estimation was based on 1000 computer simulations using a generalized linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

For a treatment effect of 60% reduction in attacks as compared to placebo, assuming a placebo attack rate of 0.3 attacks per week over a 26 week period for an average total of 7.8 attacks during the treatment period, a sample size of 24 actively treated subjects for the primary active treatment arm and 36 placebo subjects would provide at least 95% power (at alpha=0.025, one-sided). A 60% reduction is well below the smallest expected reduction in attacks, for in the DX-2930-02 study, we observed reductions of attacks of near 100%. These sample sizes will also provide adequately sized safety population for evaluation. Up to 120 subjects (approximately 80 subjects in the 3 active treatment groups and 40 in the placebo group) may be enrolled to account for potential early dropouts during the study.

9.3 Method of Assigning Study Subjects to Treatment Groups

Subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive repeated SC administrations of DX-2930 or placebo. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization will be performed centrally and stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks. Permuted blocks will be used to ensure that approximately equal numbers of subjects are assigned each treatment within strata.

9.4 Analysis Populations

The analysis populations will be defined as follows:

Intent-to-treat (ITT) Population: will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received. The primary efficacy analyses will be carried out with the ITT Population.

Safety Population: will include all subjects who are administered at least 1 dose of active IMP or placebo. Subjects will be analyzed according to the treatment they actually received. All safety analyses will use the Safety Population.

9.5 Analysis of Disposition

The numbers of subjects randomized, completing, or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group and overall for the ITT and safety populations.

9.6 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group and overall for the ITT and safety populations.

9.7 Treatment Compliance and Extent of Exposure

Treatment compliance and extent of exposure will be described by calculating the percentage of planned doses received by the subject and the total number of doses received by the subject and summarized by treatment group for the ITT and safety populations.

9.8 Analysis of Primary and Secondary Efficacy Endpoints

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint, number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182), will be compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the efficacy evaluation period will be used as an offset variable in the model.

From this model, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group will be estimated. These estimates will be reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \lambda_{DX\text{-}2930} / \lambda_{placebo} = 1 \text{ versus } H_1: \lambda_{DX\text{-}2930} / \lambda_{placebo} \neq 1$$

$\lambda_{DX\text{-}2930}$ refers to the mean Investigator-confirmed HAE attack rate in the DX-2930 group and $\lambda_{Placebo}$ refers to the mean Investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean Investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of Investigator-confirmed HAE attacks during the efficacy evaluation period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage change in mean Investigator-confirmed HAE attack rate of each active treatment group from the attack rate of placebo will be calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

All efficacy analyses will be conducted using the ITT population.

In order to maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure will be used for the comparisons of each of the active treatment groups with the placebo group with equal weights for each test set at 1.67% significance level ($\alpha/3$).

9.8.2 Secondary Efficacy Endpoints

The rank-ordered secondary efficacy endpoints are as follows:

1. Number of Investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation period.
2. Number of moderate or severe Investigator-confirmed HAE attacks during the efficacy evaluation period.

The secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint.

To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant. The testing procedure is detailed in Section 9.12.5.

9.8.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

The exploratory efficacy endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment effect.

9.9 Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

9.9.1 Pharmacokinetic Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3 and 182±3. Additional samples will be collected on Days 210±3, and 238±3 during the follow-up period for any subjects not entering OLE.

Plasma concentrations of DX-2930 will be summarized with descriptive statistics by nominal PK sampling time.

9.9.2 Pharmacodynamic Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3, and 238±3 during the follow-up period for any subjects not entering OLE.

Plasma kallikrein activity will be summarized with descriptive statistics by nominal PD sampling time.

9.9.3 Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE

9.9.4 C1-INH and C4 Assessments:

Samples will be obtained for C1-INH, C4 and C1q assays at screening for eligibility assessment.

9.10 Safety Analysis

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The number and percentage of subjects with TEAEs will be displayed for each treatment group by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Serious AEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs and AESI will be produced.

AESI will be analyzed according to primary system Organ Classes (SOCs) and Preferred Terms (PTs) determined by the search of relevant Standardized MedDRA Queries (SMQs). Summary tables with SOCs and PTs, from the SMQ searches, will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications (other than rescue medications) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

Actual values and change from screening in vital signs and clinical laboratory tests will be summarized for each treatment group with descriptive statistics at each assessment obtained. For all laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice-versa.

Abnormal physical examination findings will be listed.

The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed for each of the treatment groups.

Additional analyses of AEs, SAEs, severe AEs, AESI, and abnormal findings will be based on the timing (Study Day) and number of prior doses of study medication. The incidence of AEs by month from the start of study medication will be examined and the incidence among the four treatment arms will be compared. The rate of study discontinuation among the four treatment arms will also be compared.

9.11 Analysis of Quality of Life Assessments

Quality of life data will be obtained using the EQ5D Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the AE-QoL Questionnaire at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional QoL assessment will be conducted on Day 238±3 for subjects not entering OLE.

9.12 Statistical/Analytic Issues

9.12.1 Adjustment for Covariates

The analysis of the primary and secondary efficacy adjusts for the normalized baseline HAE attack rate. No additional covariate adjustment is planned.

9.12.2 Handling of Dropouts or Missing Data

All available data will be included in the analysis. The length of time a subject was observed during the efficacy evaluation period will be included as a variable in the generalized linear model to adjust for differences in follow-up time.

9.12.3 Interim Analysis and Data Monitoring

No interim analyses are planned. However, an independent DSMB will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DSMB review will be conducted according to the DSMB Charter and DSMB SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

9.12.4 Multicenter Studies

Data from all study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

9.12.5 Multiple Comparisons/Multiplicity

The global family-wise Type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 6.4.1) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach with branches for each active treatment group to placebo group comparison will be utilized in which each family of statistical tests will be conducted in a sequential manner. Specifically, a three-branch general gatekeeping procedure with three families of hypotheses will be defined as follows:

- Family 1 (F_1): Hypothesis tests for the primary efficacy endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{11}, H_{12}, and H_{13}).
- Family 2 (F_2): Hypothesis tests for the first ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{21}, H_{22}, and H_{23}).
- Family 3 (F_3): Hypothesis tests for the second ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{31}, H_{32}, and H_{33}).

The 3 sets of hypotheses in F1, F2, and F3 will be tested in a fixed sequence within each active treatment group to placebo group comparison or branch. Testing within a branch will continue in sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests within the branch.

Within a family, hypotheses will be tested using a conservative Bonferroni-based procedure with equal weights for each test set at 1.67% significance level ($\alpha/3$). If the null hypothesis for a test is rejected, α will be propagated entirely to the next test in the sequence, which will then be tested at the 1.67% significance level.

To further illustrate this approach, the test for the primary endpoint will be conducted first at the 1.67% significance level for each active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 1.67% significance level. The testing sequence will continue in order through the remaining secondary endpoints for each active treatment group to placebo comparison or branch as long as the null hypothesis is rejected at the 1.67% significance level.

Testing within the last family (F3) will utilize the remaining α by applying the Holm-Bonferroni procedure.

9.12.6 Sensitivity Analyses

Sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results from the primary analysis method. These analyses will be described in the statistical analysis plan.

10 STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 2.

Table 2. Study Administrative Structure

Sponsor Contact/Sponsor Medical Director:	Jennifer Schranz, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD
Medical Monitor (US, Canada):	PPD, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD Email: PPD
Medical Monitor (Jordan, Europe)	PPD, MD, MBA Voisin Consulting PPD, PPD PPD, France Phone: PPD Email: PPD
Study Monitoring (US):	Rho, Inc. PPD, PPD, PPD Phone: PPD
Study Monitoring (Jordan)	Triumpharma PPD, PPD PPD, PPD PPD, Jordan Phone: PPD
Study Monitoring (Canada)	Red Maple Trials Incorporated PPD, PPD PPD, PPD, Canada, PPD Phone: PPD
Study Monitoring (Europe)	Dyax Corp. 55 Network Drive, Burlington, MA 01803 Phone: PPD

10.1 Institutional Review Board/Research Ethics Board/Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the Investigator and approved in writing by the IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent and assent forms, any consent or assent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects prior to implementation. The Investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the

IRB/REB/IEC. The Investigator must provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

10.2 Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the International Conference on Harmonisation (ICH) guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements [in accordance with United States Investigational New Drug (IND) regulations (21 CFR 56)].

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The Investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the study.

10.4 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number and birth date (if allowed based on local data protection regulations), not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the Investigator.

The Investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

10.5 Study Monitoring

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety

assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator.

10.6 Case Report Forms and Study Records

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the clinical sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, source data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving randomized study dug.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

A Trial Master File will be maintained by the Sponsor (or designee). All documents and other materials that pertain to the conduct of the trial, quality of the data, and compliance with GCPs will be collected in the Trial Master File.

10.7 Data Safety Monitoring Board

An independent DSMB will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study.

The DSMB will adhere to a prospectively determined Charter, which will be written by the Sponsor and approved by the DSMB. The Charter will define the responsibilities of the DSMB and Sponsor, the number and timing of the DSMB meetings, the conduct of the meetings, and the data sets to be reviewed by the DSMB. Further details regarding the DSMB can be found in the DSMB charter.

10.8 Protocol Violations/Deviations

The Investigator will be instructed not to deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the Investigator should contact their Sponsor representative to discuss the appropriate course of action.

The Investigator should document all protocol deviations/violations in the subject's eCRF and source documents or the Investigator Site File if appropriate. In the event of a significant deviation/violation, the Investigator should notify the Sponsor representative. Significant deviations/violations include, but are not limited to those that increase the health risk to the subject, or confound interpretation of primary study assessments. The Investigator will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects or others to his or her IRB/REB/IEC.

10.9 Premature Closure of the Study

If the Sponsor, Investigator, DSMB, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated overall or at a specific site after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to, the following:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

10.10 Access to Source Documentation and On-Site Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The Investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study.

The Investigator will be responsible for the accuracy of the data entered in the eCRF. The Investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

10.11 Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitors will meet with the Investigators and staff shortly before the start of the trial to review the procedures for study conduct and documentation. During the study, the monitors will visit the sites to verify record keeping and adherence to the protocol. For this study, eCRFs will be used. The monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure accuracy and consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.12 Data Handling Considerations

Data that may potentially unblind the treatment assignment (i.e., investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

10.13 Retention of Data

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and IMP dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the responsible Investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible Investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will

accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

10.14 Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the Investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.15 Publication and Disclosure Policy

All information concerning DX-2930, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's advanced written consent. A description of this clinical study may also be available on other externally facing public websites and registries. A summary of the study results may be potentially disclosed as per local and country specific requirements.

The information developed in this study will be used by the Sponsor in connection with the continued development of DX-2930 and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

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12 APPENDICES

Appendix 1 Study Activities Schedule

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 1 Study Activities Schedule

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			Visit 1 Dose 1 Day 0	Site Check-in[4]	Visit 2 Dose 2 Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visits 6 and 7 Doses 6 and 7 Days 70 and 84	Visit 8 Dose 8 Day 98	Visits 9 and 10 Doses 9 and 10 Days 112 and 126	Visit 11 Dose 11 Day 140	Day 144±1	Visits 12 and 13 Doses 12 and 13 Days 154 and 168	Visit 14 Day 182	Visit 15 Day 210	Visit 16 Day 238
Informed Consent	X																
Eligibility Review	X		X														
Long-term prophylactic therapy washout[5]	X																
Randomization			X														
Blinded IMP Treatment			X		X	X	X	X	X	X	X	X		X			
Demographic and Medical History	X																
C1-INH, C1q and C4 Testing[6]	X																
Pregnancy Test[7] (females)	X		X			X		X		X	X			X	X		X
Vital Signs[8]	X		X		X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination[9]	X		X			X		X		X		X			X		X
12-Lead ECG[10]	X		X					X					X		X		X
Clinical Laboratory Testing[11]	X		X			X		X		X		X			X		X
Serologies: HBsAg, HCV, and HIV	X																
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

Study Activities Schedule

	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
HAE Attack Data[12]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Quality of Life Assessments[13]			X			X		X		X	X			X	X		X
PK Blood Sampling			X					X		X		X			X	X	X
PD Sample Collection			X					X		X		X			X	X	X
Plasma Anti-Drug Antibody Testing			X					X		X		X			X		X
Discharge from Study[14,15]															X		X

ECG = Electrocardiogram; PK = Pharmacokinetic; PD = Pharmacodynamic; IMP = Investigational Medicinal Product

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum or urine-based.

8. There is a ± 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.
9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema-Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES
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Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

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(Greater than 3 months of age)

GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microscopic >25		Gross hematuria

	cells/hpf	cells/hpf		

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
PARAMETER	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

HAE Attack Assessment and Reporting Procedures (HAARP)

Title:	HAE Attack Assessment and Reporting Procedures (HAARP)
Product Name:	DX-2930
Indication:	Prevention of angioedema attacks in patients with HAE
Sponsor:	Dyax Corp. 55 Network Drive Burlington, MA 01803
Original Date:	14 September 2015
Version:	v1.0

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1 PURPOSE

This document applies to clinical trials that involve investigator adjudication/assessment of angioedema attacks. The purpose of this document is to provide a definition of an HAE attack and to define a standardized set of procedures for the reporting and assessment of events reported by subjects to determine whether those events are true HAE attacks.

2 DEFINITION OF AN ATTACK

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (e.g., urticaria), the reported event persists well beyond the typical time course of an attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

To be counted as a unique attack distinct from their previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Attack resolution is defined as the subject no longer having symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

Patient report of use of acute HAE attack treatment for an attack by itself is not confirmation that an attack occurred.

3 REPORTING AND ASSESSMENT OF ATTACK DATA

At screening for applicable clinical trials, subject HAE attack history will be collected by the site for entry into the clinical database. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant location(s), average duration, acute attack therapy use, and history of long-term prophylaxis.

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects < 18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is

unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

Site personnel will review the information provided by the subject or caregiver and solicit additional information as necessary to document the attack. Information documented by the site will be considered source for the study.

A designated individual at the site (the collector) will contact the subject or caregiver on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject or caregiver.

The Investigator or designee (the assessor) will review the attack information and evaluate if the event represents a confirmed HAE attack. If necessary for the evaluation, the investigator or designee may contact the subject to receive additional information.

3.1 Subject-Reported Symptoms

Subjects and caregivers can use any existing methods by which they track information about their attacks, or, if requested, memory aids can be provided by the study site. However, subjects (or a caregiver) will need to track attacks in such a way as to be able to contact the study site as soon as possible, but not later than 72 hours (3 full days) after the first symptoms appear, to report the information.

3.1.1 Attack Information

The following information should be provided by the subject (or caregiver) at the time they are reporting an attack to the site:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Subjects do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/ or at a scheduled study visit. Subjects should not withhold or delay any treatment they would normally receive to treat their attack in order contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/ or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

During screening, site personnel will train subjects on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The patient will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the subject's compliance with the reporting requirements throughout the study and may retrain the subject if necessary in order to maintain the integrity of the data provided to the site.

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack as stated in Section 2, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Caregiver Report

During screening, site personnel will train subject caregivers (if applicable) on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The caregiver will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the caregiver's compliance with the reporting requirements throughout the study and may retrain the caregiver if necessary in order to maintain the integrity of the data provided to the site.

3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/ or use of back-up contacts, should be established in case the subject is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits. The date and time for check-ins can be modified based on when the last contact with the subject was made, as outlined in the study protocol. When the site is contacted by a subject reporting symptoms of an attack the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be

established in case the subject misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

3.2.1 Review of subject report of symptoms

During contact with the subject, whether subject-initiated or a regular check-in, site personnel should ask the subject to provide them information about new or ongoing HAE attacks experienced.

The site will try to obtain all information necessary to document the attack completely. Missing information may impact the assessment of any attack and should be avoided whenever possible.

3.2.2 Documenting a Reported Attack

Complete and accurate documentation of each reported attack is important to making an Investigator assessment of the attack. The site should document the following information about each attack reported by the subject or caregiver:

- Date and time of contact with the subject
- Date and time the subject first experienced symptoms
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance was required
- If the attack has resolved or is ongoing. If the attack has resolved, the date and time the subject was no longer experiencing any symptoms of the attack
- Names of any medications used to treat the attack including HAE acute therapy or other non-HAE treatments
- If hospitalization occurred
- If a trip to the emergency department occurred

Additional probing questions about what the subject experienced to determine:

- If the subject only experienced prodromal symptoms
- If the subject experienced anything different than their typical attack
- If there were any possible alternative etiologies of the symptoms. For example, a viral gastroenteritis outbreak in the household could explain abdominal symptoms

The overall severity of the subject's attack will be determined by the site using the following definitions:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance needed
- Severe: Marked limitation in activity, assistance required

The site will also document the date and time of investigator or designee review, the official designation of the event as an attack or not, and if applicable, the reason why an event is not considered an attack.

All reported attacks will be entered by site personnel into the electronic case report form (eCRF).

3.2.3 Site Training

Site personnel responsible for collecting attack information about subject HAE attacks will need to pass a "Collector" training assessment covering the following:

- definition of an HAE attack
- requirements of subjects and caretakers for reporting attacks
- reporting worsening symptoms and multiple attacks
- information to be collected from subjects and caregivers as well as the additional probing questions to gather context for the attack information provided
- assessment of attack severity
- entry of the attack data into the eCRF
- reporting HAE attacks as adverse events
- requirements for Investigator assessment of attacks

Trainings will be conducted prior to sites screening subjects. Trainings will be documented in the Trial Master File. Investigators and designees will be trained on these procedures as well and must pass an "Assessor" training in order to officially assess attacks for this study.

All responsible persons involved in the collection of information from subjects or assessing attacks must be listed on FDA Form 1572.

3.3 HAE attacks as Adverse Events

At the time of each contact and scheduled study visit, site personnel will ask if the subject experienced any adverse events or changes to the medications they are taking.

HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF.

Any AE reported to the site meeting criteria for a serious adverse event must be reported to Dyax using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack.

For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional

information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

4 INVESTIGATOR ATTACK ASSESSMENT

The Principal Investigator for a study site may identify a physician designee to assess patient symptom information and make attack determinations. Sites should be limited to two individuals responsible for assessing attacks, one of them being the Principal Investigator. Assessors must be experienced with HAE and familiar with the study subject's disease history.

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

Clinical Trial Protocol: DX-2930-03

Study Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-03
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-003943-20
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	Jennifer Schranz, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD
Medical Monitor US and Canada:	PPD, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD
Medical Monitor Europe and Jordan:	PPD, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD

	Date:
Original Protocol	14 September 2015
Amendment 1.0	14 December 2015
Amendment 2.0	21 April 2016
Amendment 3.0	09 January 2017

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PROTOCOL SIGNATURE PAGE

Study Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-03
Amendment 3.0 Final Date:	09 January 2017

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The signature of the Sponsor representative indicates that the Sponsor will comply with all Sponsor obligations detailed in applicable regulations and guidelines and will ensure the Investigator is informed of all relevant information that becomes available.

Signed PPD Date: PPD

Jennifer Schra[redacted], MD PPD
PPD Clinical Development
300 Shire Way, Lexington, MA 02421

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, GCP, and all applicable regulatory requirements and guidelines as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Dyax Corp. and my Institutional Review Board (IRB), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

I further agree that Dyax Corp. or their designees shall have access to any source documents from which eCRF information may have been generated.

By signing this protocol, I agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP to which it conforms.

Signed:_____ Date:_____
Investigator

Address: _____

_____

AMENDMENT SUMMARY AND RATIONALE

Amendment 3 to Protocol DX-2930-03 includes the following revisions:

- Added efficacy measure to assess the number of Investigator-confirmed HAE attacks occurring on Day 14 through Day 182 to rank ordered secondary efficacy endpoints for inclusion in the multiple testing procedure (third in the rank order) to better understand the exposure-response relationship since data from Phase 1b study (DX-2930-02) suggested that lanadelumab (DX-2930) has a mean elimination half-life of approximately 14 days where it is anticipated that 50% steady state is achieved in HAE subjects and lanadelumab exposure reaches reasonable levels associated with therapeutic effect.
- Updated the multiplicity procedure by adding the "Family 4 (F4)" hypothesis test to the 3-branch general gatekeeping procedure (previously with 3 families of hypotheses) for the third ranked secondary efficacy endpoint.

Noteworthy changes to the protocol are captured in the table below. Additional minor revisions in grammar, spelling, punctuation, and format have been made for clarity and are not reflected in the summary of changes.

Summary of Changes from Previous Version

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3.0**	**Amendment Date** **09 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated administrative information to reflect current contact information for the Sponsor's Medical Monitor -for Europe and Jordan to PPD, MD		Title Page, Section 10 Study Administrative Structure
Specified that Dyax Corp is an indirect, wholly-owned subsidiary of Shire plc.		Title Page, Study Synopsis, Section 10
Clarified that primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 0 **(after study drug administration)** through Day 182, **unless otherwise specified**.		Study Synopsis, Section 6.4.1
Specified that primary and 1st and 2nd rank ordered secondary efficacy endpoints will be assessed **during the efficacy evaluation period (Day 0 through Day 182)** to be consistent with other sections (Sections 9.8.1 and 9.8.2-Analysis of Primary and Secondary Efficacy Endpoints).		Study Synopsis, Section 6.4.1, Section 9.8.2
Added efficacy measure to assess the number of Investigator-confirmed HAE attacks occurring on Day 14 through Day 182 to rank ordered secondary efficacy endpoints for inclusion in the multiple testing procedure (third in the rank order) to better understand the exposure-response relationship since data from Phase 1b study (DX2930-02) suggested that lanadelumab has a mean elimination half-life of approximately 14 days where it is anticipated that 50% steady state is achieved in HAE subjects and lanadelumab exposure reaches reasonable levels associated with therapeutic effect.		Study Synopsis, Section 6.4.1, Section 9.8.2
Removed incorrect contact information provided for 24-hour medical safety		Section 6.16.5.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3.0**	**Amendment Date** **09 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
contact for US, Canada, Europe, and Middle East.		
Updated the multiplicity procedure by adding the "Family 4 (F4)" hypothesis test to the 3-branch general gatekeeping procedure (previously with 3 families of hypotheses) for the third ranked secondary efficacy endpoint.		Section 9.12.5
Replaced the table for the study activities schedule (a repetition) in Appendix 1 with the Protocol History. Numbered the table for the study activities schedule (that follows the Study Synopsis) as Table 1. Removed cross-reference to the treatment period dosing schedule in the Study Synopsis.		Section 12, Appendix 1 Study Activities Schedule, Study Synopsis.

SYNOPSIS

Sponsor: Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc 55 Network Drive, Burlington, MA 01803 USA
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80
Study Title: HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-03
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across the United States, Italy, United Kingdom, Germany, Canada and Jordan
Primary Objective: To evaluate the efficacy of DX-2930 in preventing HAE attacks
Secondary Objective: To evaluate the safety of repeated subcutaneous administrations of DX-2930
Tertiary Objectives: • To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930 • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the pharmacokinetics (PK) of chronically administered DX-2930 • To evaluate the effect of DX-2930 on health-related quality of life (QoL)
Study Design: This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in

patients with Type I and Type II HAE.

Long-Term Prophylactic (LTP) Therapy Washout:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm the subject has successfully completed the 2 week washout period before they can enter the run-in period.

Run-In Period:

Screened subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. Only subjects meeting a minimum baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered screen failures. Subjects who screen fail will not be allowed to rescreen into the study.

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in the table below.

Treatment Period Dosing Schedule

Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/Week 4	DX-2930	DX-2930	DX-2930	Placebo
4	Day 42/Week 6	DX-2930	Placebo	Placebo	Placebo
5	Day 56/Week 8	DX-2930	DX-2930	DX-2930	Placebo
6	Day 70/Week 10	DX-2930	Placebo	Placebo	Placebo
7	Day 84/Week 12	DX-2930	DX-2930	DX-2930	Placebo
8	Day 98/Week 14	DX-2930	Placebo	Placebo	Placebo
9	Day 112/Week 16	DX-2930	DX-2930	DX-2930	Placebo
10	Day 126/Week 18	DX-2930	Placebo	Placebo	Placebo
11	Day 140/Week 20	DX-2930	DX-2930	DX-2930	Placebo
12	Day 154/Week 22	DX-2930	Placebo	Placebo	Placebo
13	Day 168/Week 24	DX-2930	DX-2930	DX-2930	Placebo
--	Day 182/Week 26	No Dose	No Dose	No Dose	No Dose

Open-Label Extension (OLE) Study:

Subjects who complete the treatment period will be offered the option of enrolling in an open-label extension (OLE) study that will be described in a separate protocol (DX-2930-04).

Follow-Up Period:

Subjects who do not participate in the OLE will undergo safety and additional evaluations (i.e., PK and PD) during an 8 week follow-up period. Subjects (or caregivers) will be instructed to inform the site of any HAE attack they experience for up to 30 days after the final follow-up visit.

Study Population:

The study will enroll up to 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit. The study will aim to enroll at least 5 subjects who are 12 to 17 years of age.

Criteria for Inclusion:

Subjects must meet the following criteria to be enrolled in this study:

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
   - At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, and are willing and able to read, understand, and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
   - Females of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This includes progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable, or implantable), intra-uterine device (IUD, all types), or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective.
   - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study.
   - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 60 days after the final study visit.

Criteria for Exclusion:

Subjects who meet any of the following criteria will be excluded from the study:

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III),

idiopathic angioedema, or recurrent angioedema associated with urticaria.

2. Participation in a prior DX-2930 study.
3. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
7. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
9. Pregnancy or breastfeeding.
10. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered subcutaneously into the upper arm in a blinded manner.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of DX-2930. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

For each 150 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections, where one injection is DX-2930 and the other is placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

Placebo; Dose; and Mode of Administration:

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0

with 0.01% Polysorbate 80.

Placebo doses will be administered to subjects randomized to the placebo treatment arm and in between doses of DX-2930 for subjects randomized to the 300 mg or 150 mg DX--2930 every 4 weeks treatment arms, according to the table for dosing schedule.

For each placebo dose, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

Duration of Treatment:

Subjects will receive a dose of blinded IMP every 2 weeks during the 26-week treatment period for a total of 13 doses. The first dose of IMP will be administered on Day 0 and the last dose of IMP will be administered on Day 168. There will be a ±3-day window around each study visit, with a maximum of 17 days or a minimum of 11 days between any 2 doses. Subjects will be monitored at the study site through 2 hours post-dose for the first 4 doses with the ability to reduce this time to 1 hour for the remaining doses based on the discretion of the Investigator and the absence of safety signals. A follow-up visit will occur on Day 182.

Duration of Study for Individual Subjects:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks in the double-blind study.

Prohibited Concomitant Treatments:

Use of the following treatments will not be permitted during the study:

- Long-term prophylaxis for HAE (e.g., use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy).
- Androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone).
- Any other investigational drug or device.

The use of short-term prophylactic treatment for HAE is permitted if medically indicated.

Management of Acute Attacks:

Acute HAE attacks during the study are to be managed in accord with the Investigator's usual care of their patients, including use of acute attack therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylaxis. Administration of the investigational product and study

procedures will continue without alteration to the protocol-specified study schedule, even if the patient receives any treatment for an HAE attack.

Safety Assessments:

The following assessments will be conducted according to the Study Activities Schedule:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI).
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR).
- Physical examination.
- Clinical laboratory testing (hematology, serum chemistry, coagulation, and urinalysis).
- 12-Lead electrocardiogram (ECG).

Pharmacokinetic (PK) Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

Pharmacodynamic (PD) Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE.

C1-INH, C4, and C1q Assessments:

Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.

Quality of Life Assessments:

Quality-of-life (QoL) data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema-Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28 ±3, 56 ±3, 98±3, 126 ±3, 154 ±3, and 182±3. An additional QoL assessment will be conducted on Day 238±3 for subjects not entering OLE.

Collection of HAE Attack Data:

The collection, reporting and assessment of attacks in this study will be done in accordance

with the HAE Attack Assessment and Reporting Procedures (HAARP). Site personnel will be trained on HAARP prior to screening subjects at their site.

During screening, site personnel will train subjects and caregivers on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The subject (and caregiver) will confirm their understanding of what is required of them for reporting attacks to the site.

At screening, subject HAE attack history will be collected. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), average duration, acute attack therapy use, and history of long-term prophylaxis.

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an HAE attack. In the situation that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subjects experience. Weekly communication between the patients and the site, including reports of HAE attacks, must be documented in the eCRF.

Subjects (or caregivers) will be asked to provide the following information when reporting an attack:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Site personnel will review the information provided and solicit additional information as necessary to document the attack, as described in the HAARP.

Site personnel will contact the subject or caregiver on a weekly basis or approximately 7 days after last contact with the subject throughout the run-in period. If the subject experiences 1 or more Investigator-confirmed HAE attacks by end of week 4, the subject will have fulfilled the run-in requirement and may proceed to enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks can exit the run-in period early and proceed to enrollment and randomization. If the subject experiences no Investigator-confirmed HAE attacks by the end of week 4, the subject will remain in the run-in period for an additional 4 weeks. The maximum duration of the run-in period is 8 weeks. If run-in has been extended and the subject has 2 or more Investigator-confirmed HAE attacks by the end of week 8, the subject will have fulfilled the run-in requirement and may proceed to the double-blind treatment period. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in will be considered a screen fail.

During the treatment period site personnel will contact the subject or caregiver once between scheduled study visits or approximately 7 days after last contact to solicit for any HAE attack

information not already reported.

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to IMP, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to the Sponsor using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

Emergency department visits for HAE attacks and HAE attacks resulting in hospital admissions will be captured.

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Interim Analysis and Data Safety Monitoring Board:

No interim analysis is planned for this study. During the study, patient safety will be monitored on a continuous basis by the Medical Monitor until the last patient completes his or her last scheduled study assessment.

An independent Data Safety Monitoring Board (DSMB) will also be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The ongoing review of SAEs and other responsibilities of the DSMB are described in the DSMB Charter.

Individual Stopping Rules:

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through completion of all scheduled visits, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

Criteria for Evaluation:

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 0 (after study drug administration) through Day 182, unless otherwise specified.

Primary Efficacy Endpoint

- Number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182)

Secondary Efficacy Endpoints (rank ordered)

1. Number of Investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation period (Day 0 through Day 182)
2. Number of moderate or severe Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182)
3. Number of Investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Safety Measures:

- Adverse events (AEs) including serious adverse events (SAEs) and adverse events of special interest (AESI)
- Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis)
- Vitals signs including blood pressure, heart rate, body temperature and respiratory rate
- Physical examination
- 12-lead electrocardiogram (ECG)

Additional Measures:

- Pharmacodynamic (PD) effects
- Anti-drug antibody development
- Pharmacokinetics (PK)
- Health-related quality of life assessments

Analysis Populations:

Intent-to-treat (ITT) Population: will include all randomized subjects who are

administered at least 1 dose of active IMP or placebo. The primary efficacy analyses will be carried out with the ITT Population.

Safety Population: will include all subjects who are administered at least 1 dose of active IMP or placebo. All safety analyses will use the Safety Population.

Sample Size Determination:

Power analysis and sample size estimation was based on 1000 computer simulations using a generalized linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

For a treatment effect of 60% reduction in attacks as compared to placebo, assuming a placebo attack rate of 0.3 attacks per week over a 26 week period for an average total of 7.8 attacks during the treatment period, a sample size of 24 actively treated subjects for the primary active treatment arm and 36 placebo subjects would provide at least 95% power (at alpha=0.025, one-sided). A 60% reduction is well below the smallest expected reduction in attacks, for in the DX-2930-02 study, we observed reductions of attacks of near 100%. These sample sizes will also provide adequately sized safety population for evaluation. Up to 120 subjects (approximately 80 subjects in the 3 active treatment groups and 40 in the placebo group) may be enrolled to account for potential early dropouts during the study.

Statistical Methods:

The primary analysis will be to compare the primary endpoint, which is the number of Investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 0 through Day 182). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP or placebo (ITT population) will be conducted.

The primary efficacy endpoint, number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182), will be compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the efficacy evaluation period will be used as an offset variable in the model.

From this model, the least squares mean rate and standard error for each treatment group as well as the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group will be estimated. These estimates will be reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \lambda_{DX\text{-}2930} / \lambda_{placebo} = 1 \text{ versus } H_1: \lambda_{DX\text{-}2930} / \lambda_{placebo} \neq 1$$

Where $\lambda_{DX\text{-}2930}$ refers to the mean Investigator-confirmed HAE attack rate in the DX-2930

group and $\lambda_{placebo}$ refers to the mean Investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean Investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of Investigator-confirmed HAE attacks during the efficacy evaluation period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage change in mean Investigator-confirmed HAE attack rate of each active treatment group from the attack rate of placebo will be calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

In order to maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure will be used for the comparisons of each of the active treatment groups with the placebo group with equal weights for each test set at 1.67% significance level ($\alpha/3$).

The rank ordered secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint. To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant.

Safety Analysis:

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The number and percentage of subjects with TEAEs will be displayed for each treatment group by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Serious AEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs and AESI will be produced.

AESI will be analyzed according to primary System Organ Classes (SOCs) and Preferred Terms (PTs) determined by the search of relevant Standardized MedDRA Queries (SMQs). Summary tables with SOCs and PTs, from the SMQ searches, will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications (other than rescue medications) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

Actual values and change from baseline in vital signs and clinical laboratory tests will be summarized for each treatment group with descriptive statistics at each assessment obtained.

For all laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice versa. Abnormal physical examination findings will be listed. The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed for each of the treatment groups. Additional analyses of AEs, SAEs, severe AEs, AESI, and abnormal findings will be based on the timing (Study Day) and number of prior doses of study medication. The incidence of AEs by month from the start of study medication will be examined and the incidence among the four treatment arms will be compared. The rate of study discontinuation among the four treatment arms will also be compared.
Date of Amendment 3.0: 09 January 2017

Table 1. Study Activities Schedule

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			Visit 1 Dose 1 Day 0	Site Check-in[4]	Visit 2 Dose 2 Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visits 6 and 7 Doses 6 and 7 Days 70 and 84	Visit 8 Dose 8 Day 98	Visits 9 and 10 Doses 9 and 10 Days 112 and 126	Visit 11 Dose 11 Day 140	Day 144±1	Visits 12 and 13 Doses 12 and 13 Days 154 and 168	Visit 14 Day 182	Visit 15 Day 210	Visit 16 Day 238
Informed Consent	X																
Eligibility Review	X		X														
Long-term Prophylactic Therapy Washout[5]	X																
Randomization			X														
Blinded IMP Treatment			X		X	X	X	X	X	X	X	X		X			
Demographic and Medical History	X																
C1-INH, C1q and C4 Testing[6]	X																
Pregnancy Test[7] (females)	X		X			X		X		X	X			X	X		X
Vital Signs[8]	X		X		X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination[9]	X		X			X		X		X		X			X		X
12-Lead ECG[10]	X		X					X					X		X		X
Clinical Laboratory Testing[11]	X		X			X		X		X		X			X		X
Serologies: HBsAg, HCV, and HIV	X																
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

Table 1. Study Activities Schedule

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			Visit 1 Dose 1 Day 0	Site Check-in[4]	Visit 2 Dose 2 Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visits 6 and 7 Doses 6 and 7 Days 70 and 84	Visit 8 Dose 8 Day 98	Visits 9 and 10 Doses 9 and 10 Days 112 and 126	Visit 11 Dose 11 Day 140	Day 144±1	Visits 12 and 13 Doses 12 and 13 Days 154 and 168	Visit 14 Day 182	Visit 15 Day 210	Visit 16 Day 238
HAE Attack Data[12]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Quality of Life Assessments[13]			X			X		X		X	X			X	X		X
PK Blood Sampling			X					X		X		X			X	X	X
PD Sample Collection			X					X		X		X			X	X	X
Plasma Anti-Drug Antibody Testing			X					X		X		X			X		X
Discharge from Study[14,15]															X		X

BP = blood Pressure; C1-INH = C1 Inhibitor; C_{max} = Maximum plasma drug concentration; ECG = Electrocardiogram; HAE = hereditary Angioedema; HbsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency virus; HR = Heart Rate; IMP = Investigational Medicinal Product; LTP = Long-term Prophylactic; OLe = Open-label Extension; PD = Pharmacodynamic; PK = Pharmacokinetic; RR = Resting Rate

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window.
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can

Table 1. Study Activities Schedule

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	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			Visit 1 Dose 1 Day 0	Site Check-in[4]	Visit 2 Dose 2 Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visits 6 and 7 Doses 6 and 7 Days 70 and 84	Visit 8 Dose 8 Day 98	Visits 9 and 10 Doses 9 and 10 Days 112 and 126	Visit 11 Dose 11 Day 140	Day 144±1	Visits 12 and 13 Doses 12 and 13 Days 154 and 168	Visit 14 Day 182	Visit 15 Day 210	Visit 16 Day 238

enter the run-in period.

6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum- or urine-based.
8. There is a ±15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.
9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Self-Report Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema Quality of Life Questionnaire (AE-QoL) at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
AE-QoL	Angioedema-Quality of Life Questionnaire
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to the last quantifiable concentration in plasma at time t
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last measurable concentration
BLA	Biologics License Application
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CL/F	apparent total plasma clearance after extravascular administration
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report

DLT	Dose Limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
EQ5D	EuroQoL Group 5-Dimension Report Questionnaire
FWER	family-wise type I error rate
FDA	Food and Drug Administration
FXI(a)	Factor XI (activated)
FXII(a)	Factor XII (activated)
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug

INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing systems
IV	Intravenous
IWRS	Interactive Web-based Randomization System
K_i	inhibition constant
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LTP	Long-Term Prophylactic
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pKal	Plasma kallikrein
PT	Prothrombin time
QoL	Quality of Life
REB	Research Ethics Board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)

SGPT	Serum glutamic pyruvic transaminase (ALT)
SM	Safety Management
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
$t_{½}$	Terminal elimination half-life
t_{max}	Time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TT	Thrombin time
US	United States
Vd/F	Apparent volume of distribution during terminal phase after extravascular administration
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 DX-2930

DX-2930 is a fully human IgG1 recombinant monoclonal antibody that binds specifically to active plasma kallikrein. DX-2930 is being developed for prophylactic treatment of angioedema attacks in patients with hereditary angioedema (HAE), a serious and life-threatening disease.

1.2 Hereditary Angioedema

HAE is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs and/or genitalia (Zuraw, 2008). Swelling may last up to five or more days; most patients suffer multiple attacks per year. HAE is an orphan disorder. The exact prevalence of HAE is unknown, but current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Nordenfelt et al., 2014; Roche et al., 2005).

Swelling in the larynx can obstruct the airways and cause death from asphyxiation (Bork et al., 2012; Bork et al., 2000). Approximately 50% of all HAE patients will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack (Bork et al., 2003; Bork et al., 2006).

Abdominal attacks are often associated with nausea, vomiting, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Zuraw, 2008).

Approximately 85% of patients have Type I HAE, characterized by very low production of functionally normal C1-INH protein, while the remaining approximately 15% of patients have Type II HAE and produce normal or elevated levels of a functionally impaired C1-INH (Zuraw, 2008). In patients with Types I and II HAE, uncontrolled plasma kallikrein generation results in excess bradykinin release from high-molecular weight kininogen (HMWK) and vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells (Zuraw, 2008). Clinical suspicion of Types I and II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are markedly reduced at all times in blood from most patients.

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Davis, 2006; Kaplan and Joseph, 2010). In normal physiology, C1-INH regulates the activity of plasma kallikrein as well as a variety of other proteases, such as C1r, C1s, factor XIa, and factor XIIa. Plasma kallikrein regulates the release of bradykinin from high molecular weight kininogen (HMWK). Due to a deficiency of C1-INH in HAE, uncontrolled plasma kallikrein activity occurs and leads to the excessive generation of bradykinin. Bradykinin is a vasodilator which is thought to be

responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain (Craig et al., 2012; Zuraw et al., 2013). Intervening at the level of bradykinin production with a plasma kallikrein inhibitor therefore represents an attractive and rational therapeutic strategy for HAE. Indeed, the importance of plasma kallikrein as a drug target in HAE has been validated through the observed effectiveness of Kalbitor® (ecallantide), a peptide that specifically targets plasma kallikrein, which was approved by the FDA for the treatment of acute HAE attacks (Kalbitor® Package Insert, 2015).

DX-2930 is a highly potent and specific inhibitor of plasma kallikrein (K_i = 125 pM). X-ray crystallography of DX-2930 combined with plasma kallikrein demonstrates DX-2930 binding to the active site of kallikrein (Kenniston et al., 2014).

1.4 Safety Rationale for DX-2930

Safety data from the Phase 1a clinical study, a first-in-human study with DX-2930 in healthy subjects did not identify any safety concerns. Single doses up to 3 mg/kg of DX-2930 were well-tolerated. There were no dose-limiting toxicities, serious adverse events, or any other safety concerns identified.

Pharmacokinetic (PK) data from the Phase 1a and 1b clinical studies in conjunction with data from the nonclinical toxicity studies support a wide safety margin. The mean C_{max} for human subjects treated at a dose of 300 mg on Days 1 and 15 was approximately 27 μg/mL. As comparison, a mean C_{max} of 744 μg /mL was observed following dosing of monkeys with 50 mg/kg DX-2930 SC weekly for 6 months resulting in a safety margin of approximately 28-fold. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date for systemically administered DX-2930.

Safety data is also available from the Phase 1b study, a multiple-ascending dose study in HAE patients. In this study, two doses of DX-2930 up to 400 mg administered 14 days apart were well-tolerated. There were no dose-limiting toxicities, serious adverse events in any DX-2930 treated subjects, or any other safety concerns identified in this study of HAE patients. Pharmacokinetic data from the 1b study found that the drug exposure following two administrations of DX-2930 (up to a maximum of 400 mg) was substantially less than that attained and evaluated in the nonclinical toxicity studies.

For additional detail regarding the safety rationale for DX-2930, please refer to the DX-2930 Investigator's Brochure.

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

For detail regarding the nonclinical findings, please refer to the DX-2930 Investigator's Brochure.

1.6 DX-2930 Clinical Data

The clinical development program to date for DX-2930 consists of 2 studies to evaluate the safety, tolerability, and PK of DX-2930, including a Phase 1a single-ascending dose study in

healthy subjects and a Phase 1b multiple-ascending dose study in HAE patients. These studies are summarized in the following sections.

1.6.1 Single-Ascending Dose Study in Healthy Subjects (DX-2930-01)

DX-2930-01 was a Phase 1a randomized, double-blind, placebo-controlled study in healthy subjects to evaluate the safety, tolerability, and PK following a single, SC dose of DX-2930. Participating subjects were randomized to receive placebo or active study drug within one of the following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. For each dosing cohort, 6 subjects were randomized to receive active drug and 2 subjects to receive placebo.

A total of 32 subjects enrolled in the study and were randomized. The treatment groups were well balanced for demographic characteristics. The actual dose of DX-2930 administered to subjects ranged from 6.2 mg (in the 0.1 mg/kg group) to 300 mg (in the 3.0 mg/kg group) across all cohorts.

Based on the safety analysis, a single administration of DX-2930 was well tolerated up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. There were no deaths, SAEs, or subject discontinuations due to adverse events (AEs) during the study. Furthermore, there was no significant imbalance between placebo and DX-2930 for any particular treatment-emergent adverse event (TEAE). The most commonly reported TEAE was headache, which occurred at a rate of 25% for both DX-2930 and placebo.

The PK profile demonstrated linear, dose-dependent drug exposure with a mean half-life of approximately 17 to 21 days across dose groups. Results from two exploratory biomarker assays provide evidence for an important pharmacodynamic effect of DX-2930 in humans.

For additional detail regarding the single dose, clinical study in healthy subjects, please refer to the DX-2930 Investigator's Brochure.

1.6.2 Multiple-Ascending Dose Study in HAE Patients (DX-2930-02)

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days and were followed for 15 weeks after the second dose.

A total of 37 subjects were randomized and treated with DX-2930 or placebo. One subject in the 400 mg dose group received a single dose of DX-2930 and, following several unsuccessful attempts to schedule their second dose, was replaced. This subject returned for a single follow-up visit before being lost to follow-up for reasons not related to the study. Routine C1-INH testing revealed that one other subject did not have HAE Type I or II, despite a historical lab test indicating otherwise.

Subject demographics were balanced in terms of age, race, ethnicity and BMI. There were slightly more females in the DX-2930 group than in the placebo group (66.7% versus 53.8%).

The most common AEs reported were HAE attacks, injection site pain, and headache. The rates were not appreciably higher in the DX-2930 subjects compared to placebo. Two subjects were reported to have 3 related severe TEAEs. One of these was a DX-2930 subject (30 mg) with injection site pain lasting 1 minute and one was a DX-2930 subject (400 mg) with worsening headache lasting 1 minute and night sweats.

No safety signals were identified for vital signs, physical examinations, clinical laboratory tests, or electrocardiograms (ECG). Results suggest DX-2930 was well tolerated in this study with no evidence of dose-limiting toxicity at doses up to 400 mg.

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive. No samples were positive for neutralizing activity.

The pharmacokinetic analysis for all subjects in the 30, 100, 300, and 400 mg doses showed drug levels in HAE subjects were dose-dependent and exhibited a prolonged half-life of approximately 2 weeks, typical of a human monoclonal antibody. C_{max} drug levels increased with increasing dose, as expected. These parameters are consisted with values obtained in healthy subjects in study DX-2930-01.

A Western blot assay showed pre-dose baseline levels of mean 2-chain high-molecular-weight kininogen (HMWK) in unactivated plasma collected from HAE patients was approximately 50%. A statistically significant reduction in 2-chain HMWK levels was observed on study days 8 and 22 in the 300 and 400 mg dose groups compared to pre-dose levels, levels similar to that observed in healthy subjects. This outcome demonstrates the pharmacodynamic activity of DX-2930 and its ability to effectively normalize the instability of HAE plasma in this assay.

Primary efficacy analyses were based on subjects in the 300 mg, 400 mg, and placebo dose groups who reported having at least 2 attacks in the 3 months prior to study entry (0.15 attacks/week). Of those subjects treated with 300 or 400 mg DX-2930, 15 of 16 subjects met these criteria. Of the placebo treated subjects, 11 of 13 subjects met these criteria.

The baseline HAE attack rates (attacks/week) were 0.39 attacks per week in the placebo group, 0.33 attacks per week in the 300 mg group, 0.55 attacks per week in the 400 mg group and 0.49 attacks per week in the 300 and 400 mg combined group. During the pre-specified, primary efficacy interval of 6 weeks (from days 8 to 50; corresponding to a period of notable drug exposure), the HAE attack rate, adjusted for baseline attack rate, was 0 in the 300 mg group and 0.045 attacks per week in the 400 mg group, compared to 0.37 attacks per week in the placebo group. This resulted in a 100% reduction vs placebo for the 300 mg DX-2930 group ($P < 0.0001$) and an 88% reduction vs placebo for 400 mg DX-2930 ($P = 0.005$). During this primary efficacy interval, 100% of subjects in the 300 mg group ($P = 0.026$) and 82% of subjects in the 400 mg group ($P = 0.03$) were attack-free compared with 27% of subjects in the placebo group.

The data from this study demonstrate proof of concept of the ability of DX-2930 to prevent acute attacks of HAE. A statistically significant finding of HAE attack prevention by DX-2930 was

observed. DX-2930 was well tolerated in HAE subjects up to 400 mg. Drug exposure appears to be dose-proportional and consistent with the results obtained in healthy subjects in study DX-2930-01. Pharmacodynamic effect assays provide evidence that DX-2930 has a direct effect on plasma kallikrein activity in patient plasma.

For additional detail regarding the multiple dose, clinical study in HAE subjects, please refer to the DX-2930 Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of DX-2930 in preventing HAE attacks.

2.2 Secondary Objective

To evaluate the safety of repeated subcutaneous administrations of DX-2930.

2.3 Tertiary Objectives

- To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930
- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the pharmacokinetics (PK) of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health-related quality of life (QoL)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute attacks in patients with Type I and Type II HAE. This double-blind study is planned to be followed by an open-label extension (OLE) that is described in a separate protocol (DX-2930-04).

Subjects aged 12 and over with a documented diagnosis of Type I or Type II HAE who experience at least 1 attack per 4 weeks during the run-in period will be eligible. Up to 120 subjects may be enrolled to provide 108 that complete. Subjects will be enrolled from sites in the United States, Canada, Italy, Germany, United Kingdom and Jordan.

3.1.1.1 Long-Term Prophylactic (LTP) Therapy Washout

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. These criteria ensure that patients who should remain on LTP do not washout for this study, but do allow the enrollment of appropriate patients with severe disease while minimizing their time off LTP. Current treatment guidelines recognize two different standard of care approaches to treating HAE, which include LTP and on-demand therapy (Cicardi et al., 2012; Craig et al., 2012; Zuraw et al., 2013). Throughout the study, subjects will be permitted to treat acute HAE attacks in accord with the Investigator's usual care of their patients. Thus, those subjects who stop their LTP to enter the study and are subsequently randomized to the placebo group will still be managed with no reduction in their standard of care. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.

3.1.1.2 Run-In Period

Screened subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. Only subjects meeting a minimum baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during

run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail. Subjects who screen fail will not be allowed to rescreen into the study.

3.1.1.3 Treatment Period

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in Table 2.

Table 2. Treatment Period Dosing Schedule

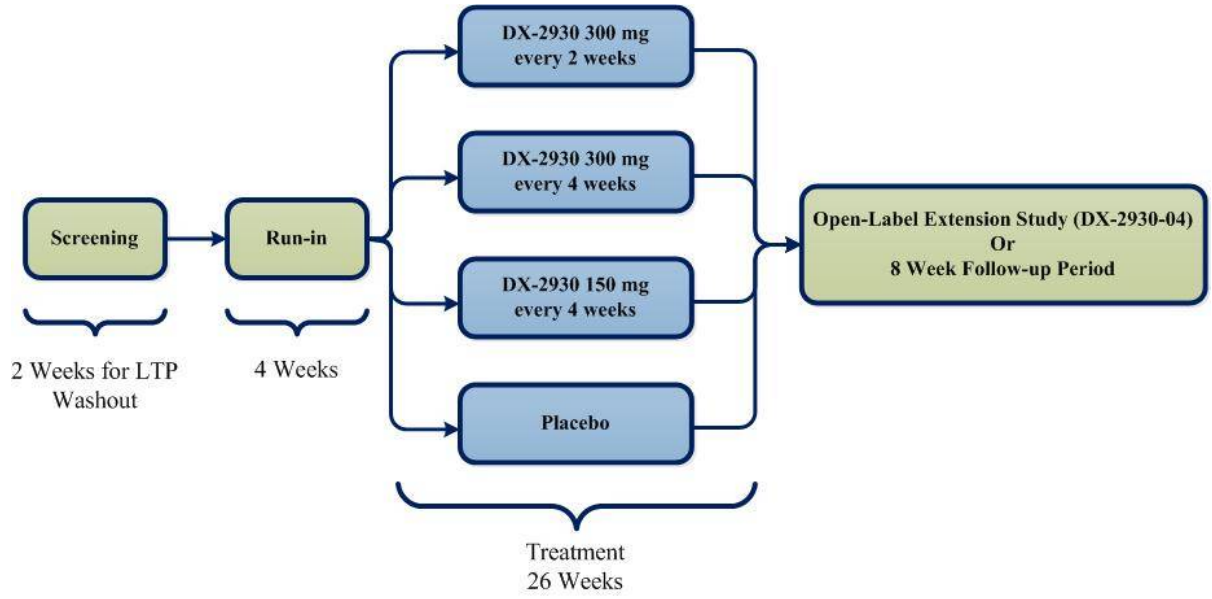
Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/Week 4	DX-2930	DX-2930	DX-2930	Placebo
4	Day 42/Week 6	DX-2930	Placebo	Placebo	Placebo
5	Day 56/Week 8	DX-2930	DX-2930	DX-2930	Placebo
6	Day 70/Week 10	DX-2930	Placebo	Placebo	Placebo
7	Day 84/Week 12	DX-2930	DX-2930	DX-2930	Placebo
8	Day 98/Week 14	DX-2930	Placebo	Placebo	Placebo
9	Day 112/Week 16	DX-2930	DX-2930	DX-2930	Placebo
10	Day 126/Week 18	DX-2930	Placebo	Placebo	Placebo
11	Day 140/Week 20	DX-2930	DX-2930	DX-2930	Placebo
12	Day 154/Week 22	DX-2930	Placebo	Placebo	Placebo
13	Day 168/Week 24	DX-2930	DX-2930	DX-2930	Placebo
--	Day 182/Week 26	No Dose	No Dose	No Dose	No Dose

3.1.1.4 Open-Label Extension (OLE)

Subjects who complete the treatment period will be offered the option of enrolling in an open-label extension (OLE) study that will be described in a separate protocol (DX-2930-04).

Figure 1 shows a schematic of the study design.

Figure 1. Overview of the Study Design



3.1.1.5 Follow-Up Period

Subjects who do not participate in the OLE will undergo safety and additional evaluations (i.e., PK and PD) during an 8 week follow-up period. Subjects (or caregivers) will be instructed to inform the site of any HAE attack they experience for up to 30 days after the final follow-up visit.

3.1.2 Safety Oversight and Stopping Rules

3.1.2.1 Interim Analysis and Data Safety Monitoring Board (DSMB)

No interim analysis is planned for this study. During the study, patient safety will be monitored on a continuous basis by the Medical Monitor until the last patient completes his or her last scheduled study assessment.

An independent data safety monitoring board (DSMB) will also be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study (see Section 10.7 for a description of the DSMB and its role). The ongoing review of SAEs and other responsibilities of the DSMB are described in the DSMB Charter.

3.1.2.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator, warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on

such matters. Subjects will continue to be followed for the duration of the 26 week treatment period, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

3.1.3 Follow-Up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, vital sign, or ECG finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

3.2 Rationale for Pivotal Dose Selection

The dose rationale is based on the pharmacodynamic bioactivity, PK, safety, and efficacy of DX-2930 from the Phase 1 clinical studies and nonclinical studies. Together, these attributes provide the rationale for the selected doses and regimens to achieve drug levels likely to prevent a majority of HAE attacks. Based on these considerations, 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks were identified as the dosing regimens for evaluation.

In study DX-2930-02, two DX-2930 doses of 300 mg or greater administered 2 weeks apart resulted in a normalization of plasma 2-chain HMWK levels and a maximal 91% reduction in HAE attacks (DX-2930 Investigators Brochure). Steady-state trough concentrations following DX-2930 administration every 2 weeks would be approximately 27,000 ng/mL. The maximum plasma concentration (C_{max}) obtained following ecallantide administration to treat an acute attack is similar to this trough concentration of DX-2930.

It is possible that lower drug levels would prevent attacks following prophylactic treatment than those required for acute attack treatment, since systemic drug exposure could attenuate contact system activation through the inhibition of plasma kallikrein-mediated FXII activation. As such, 2 dosing regimens of DX-2930 administered monthly are being evaluated. Doses of 300 mg or 150 mg DX-2930 administered every 4 weeks would result in a steady-state trough concentration of approximately 9,500 and 4,750 ng/mL, respectively. These trough levels bracket the C_{max} observed in the 100 mg dose group in study DX-2930-02, which demonstrated a slight, but not statistically significant, reduction in 2-chain HMWK levels.

The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930 treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

3.3 Individual Subject Dosing and Follow-Up

Subjects will receive a dose of blinded IMP every 2 weeks during the 26 week Treatment Period for a total of 13 doses. The first dose of IMP will be administered on Day 0 and the last dose of IMP will be administered on Day 168. There will be a ± 3 day window around each study visit, with a maximum of 17 days or a minimum of 11 days between any two doses. After each dose, subjects will be monitored at the study site through 2 hours post-dose for the first 4 doses with the ability to reduce this time to 1 hour for the remaining doses based on the discretion of the Investigator and the absence of safety signals. A follow-up visit will occur on Day 182.

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week wash-out period prior to the start of run-in. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study will enroll up to 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in HAE patients as young as the age of 3 (Bork et al., 2003). In one case series of 49 pediatric HAE patients, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas, 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig, 2015; Zuraw, 2008). The study will aim to enroll at least 5 subjects who are 12 to 17 years of age.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
   - At least one of the following: age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver provides informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
   - Females of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This includes progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD, all types) or

intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective.

- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 60 days after the final study visit.

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior DX-2930 study.
3. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
7. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
9. Pregnancy or breastfeeding.
10. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding IMP administration, refer to the Pharmacy Manual.

5.1.1 DX-2930

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm in a blinded manner.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of DX-2930. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

For each 150 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections, where one injection is DX-2930 and the other is placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

5.1.2 Placebo

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Polysorbate 80.

Placebo doses will be administered to subjects randomized to the placebo treatment arm and in between doses of DX-2930 for subjects randomized to the 300 mg or 150 mg DX-2930 every 4 weeks treatment arms, according to the dosing schedule in Table 2.
For each placebo dose, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

5.2 Dosing and Follow-Up Schedule

Details of subject dosing and follow-up are included in the Study Activities Schedule, Table 1.

5.3 Method of Assigning Subjects to Treatment Groups

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned an identification number. Subjects will be assigned to one of the DX-2930 or placebo treatment groups via an Interactive Web-based Randomization System (IWRS). Use of the IWRS will be outlined in the Operations Manual.

5.4 Blinding and Unblinding

Subjects will be randomized to receive 300 mg DX-2930 every 2 weeks, 300 mg DX-2930 every 4 weeks, 150 mg DX-2930 every 4 weeks or placebo every 2 weeks in a double-blind fashion. Subjects, caregivers for subjects under 18 years of age, Investigators and site personnel will be blinded to the treatment administered until the study is complete. The Sponsor will be blinded to the treatment administered until all subject involvement in the treatment period is complete and primary statistical analyses have been conducted.

The treatment code for an individual patient may only be broken by the Investigator or Sponsor or the DSMB for reasons of patient safety or in an emergency when knowledge of the study drug administered would be important for the treatment of the patient.

The Investigator must document the date, time and reason for the code break. The Investigator should follow the instructions within the IWRS System should a code break be required. In the case of a concerning drug-related safety event, the Investigator has the ability to contact and consult with the Medical Monitor. In emergency situations, the Investigator may break the treatment code immediately or as quickly as possible if he/she finds it is in the best interest of the trial subject. The Investigator has unrestricted and immediate access to break the treatment code through the IWRS System.

The Data and Safety Monitoring Board (DSMB), in consultation with the Medical Monitor, may also request unblinding of an individual patient's treatment assignment for reasons of safety.

In the event of a drug-related, serious, unexpected AE, the Sponsor's Pharmacovigilance Department will be provided with the treatment assignment for the subject for the purpose of regulatory reporting.

5.5 Prior and Concomitant Therapy

Reasonable efforts will be made to determine all relevant treatments received by the subject from the time of screening up to administration of the first dose of IMP.

All information on concomitant therapy from the time of first dose of IMP through the final study visit (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's electronic Case Report Form (eCRF) and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.5.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, are permitted if not excluded in Section 5.5.2. Acute HAE attacks during the study are to be managed in accord with the Investigator's usual care of their patients, including use of acute attack

therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylaxis. Administration of the investigational product and study procedures will continue without alteration to the protocol specified study schedule, even if the patient receives any treatment for an HAE attack.

- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.5.2 Excluded Concomitant Therapies

Use of the following treatments will not be permitted during the study:

- Long-term prophylaxis for HAE (e.g., use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy).
- Androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone).
- Any other investigational drug or device.

5.6 Restrictions

5.6.1 Medical Interventions

Medical interventions deemed necessary by the Investigator for the health and well-being of the subject will not be excluded during this study.

5.6.2 Fluid and Food Intake

There are no restrictions on fluid and food intake. Subjects may continue their usual dietary regimens.

5.6.3 Activity

There are no activity restrictions. Subjects may continue their usual activity regimens.

5.7 Treatment Compliance

All doses of the IMP will be administered during clinic visits under the direct supervision of the Investigator or qualified site personnel designated by the Investigator.

5.8 Packaging and Labeling

The test products (DX-2930 and placebo) will be supplied by the Sponsor and packaged and labeled according to applicable local and regulatory requirements for investigational studies.

5.9 Storage and Accountability

All supplies of the investigational products (DX-2930 and placebo) must be stored refrigerated (2ºC to 8ºC/36ºF to 46ºF) in the original carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

5.10 Investigational Medicinal Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the IMP throughout the clinical study. All IMP received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. IMP accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used IMP should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the IMP have been established, and that appropriate records of the disposal are documented and maintained. No unused IMP may be disposed until fully accounted for by the Sponsor monitor (or designee).

6 STUDY PROCEDURES

Please refer to the Study Activities Schedule, Table 1.

6.1 Informed Consent

Informed Consent and Assent forms must be approved for use by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study related activities. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Eligibility Review

The Investigator or qualified site personnel will confirm that all Inclusion and Exclusion criteria have been met.

6.3 Demographics and Medical History

Demographics: date of birth (alternatively age or year of birth, if full date of birth is not allowed to be collected for legal reasons), sex, race and ethnicity (where locally permitted) and medical history will be obtained from the subject and recorded in source documents and the eCRF. Medical history will capture the subject's current relevant medical status (current disease processes), past relevant medical status (past disease processes), history of surgery, allergies and concomitant medications.

6.4 Efficacy Assessments

6.4.1 Primary and Secondary Endpoints

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 0 (after study drug administration) through Day 182, unless otherwise specified

Primary Efficacy Endpoint

- Number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182)

Secondary Efficacy Endpoints (rank ordered)

1. Number of Investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation period (Day 0 through Day 182)
2. Number of moderate or severe Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182)
3. Number of Investigator confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

6.4.2 HAE Attack Information Collection

The collection, reporting and assessment of attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP) (Appendix 4). Site personnel will be trained on HAARP prior to screening subjects at their site.

During screening, site personnel will train subjects and caregivers on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The subject (and caregiver) will confirm their understanding of what is required of them for reporting attacks to the site.

At screening, subject HAE attack history will be collected. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), average duration, acute attack therapy use, and history of long-term prophylaxis.

During the study, subjects (or caregivers, in the event the subject is < 18 years old) will be instructed to notify and report details to the study site within 72 hours of the onset of an HAE attack. In the event that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subjects experience. Weekly communication between the patients and the site, including reports of HAE attacks, must be documented in the eCRF.

Subjects (or caregivers) will be asked to provide the following information when reporting an attack:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Site personnel will review the information provided and solicit additional information as necessary to document the attack, as described in HAARP.

Subjects washing out of LTP will be contacted by the site at the end of the 2 week washout period. The Investigator must confirm the subject has successfully completed the 2 week washout period before they can enter the run-in period. Confirmation of washout will be captured in the eCRF.

Site personnel will contact the subject or caregiver weekly, or approximately 7 days after their last contact with the subject, throughout the run-in period. If the subject experiences 1 or more Investigator-confirmed HAE attacks by the end of week 4, the subject will have fulfilled the run-in requirement and may proceed to enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks can exit the run-in period early and proceed to enrollment and randomization. If the subject experiences no Investigator-confirmed HAE attacks the end of the subject will remain in the run-in period for an additional 4 weeks. The maximum duration of the run-in period is 8 weeks. If run-in has been extended and the subject has 2 or more Investigator-confirmed HAE attacks by the end of week 8, the subject will have fulfilled the run-in requirement and may proceed to the double-blind treatment period. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in will be considered a screen fail.

During the treatment period site personnel will contact the subject or caregiver once between scheduled study visits or approximately 7 days after their last contact to solicit for any HAE attack information not already reported.

Throughout the duration of the double-blind study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to the Sponsor using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

Emergency department visits for HAE attacks and HAE attacks resulting in hospital admissions will be captured.

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region.
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea.
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

6.5 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Table 1). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ±15 minute window for all vital signs.

6.6 Physical Examination

A physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Table 1). The findings of each examination will be recorded on the source documents and eCRF. The physical examination will include the body systems listed below:

- Height and weight (at Screening visit only)
- General appearance
- Ears, nose, and throat
- Head and Neck
- Ophthalmological

- Respiratory
- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Table 1). The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Laboratory testing will be performed according to the Study Activities Schedule (Table 1).

Laboratory testing includes general safety parameters (hematology, coagulation, urinalysis, and serum chemistry), serology, pregnancy tests, C1-INH functional assay, C4 assay, C1q assay, PK samples, PD samples, and plasma anti-drug antibody testing. All laboratory tests will be performed using established and validated methods.

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each subject who does not rollover into the OLE will be approximately 271 mL. The total blood draw for each subject that does rollover into the OLE will be approximately 208 mL. Please refer to the Laboratory Manual for more information.

Laboratory testing will include the following as specified in the Study Activities Schedule (Table 1).

6.8.1.1 Hematology

- Hemoglobin

- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

6.8.1.2 Coagulation

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- International Normalized Ratio (INR)

6.8.1.3 Chemistry

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Blood urea nitrogen (BUN)
- Calcium
- Carbon dioxide (CO2)
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Glucose
- Phosphate
- Magnesium

- Potassium
- Sodium
- Total protein
- Uric acid

6.8.1.4 Urinalysis

- Bilirubin
- Glucose
- Ketones
- Blood
- Nitrite
- pH
- Protein
- Specific gravity
- Microscopy (if indicated by macroscopic findings)

6.8.1.5 Serology

HBsAg, HCV, and HIV tests

6.8.1.6 Pregnancy Test

Serum or urine pregnancy test

6.8.1.7 C1-INH Functional Assay

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the screening visit. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.8 C4 Assay

Results of a C4 assay may be required for eligibility assessment. Samples will be drawn at the screening visit. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.9 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Samples will be drawn at the screening visit. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.10 PK Sample Collection

As outlined in Section 6.9.

6.8.1.11 PD Sample Collection

As outlined in Section 6.10.

6.8.1.12 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained phlebotomist designated and/or approved by the study Investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

6.9 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.10 Pharmacodynamic Assessments

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.11 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 238±3 during the follow-up period for any subjects not entering OLE.

6.12 Prior and Concomitant Therapy

The Sponsor representatives and Investigator at the site conducting the trial will review and evaluate prior and concomitant medication usage on an ongoing basis. All prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from the time of screening through the duration of the study will be regarded as concomitant medications and must be documented in the source documents and eCRF.

6.13 Randomization

Subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

6.14 Investigational Medicinal Product Treatment

Instructions for safe handling of IMP, preparation of each subcutaneous dose, and administration of IMP are provided in the Pharmacy Manual. Preparation and dispensing of the IMP will be handled by qualified site personnel as directed by the Principal Investigator at the study site. The Principal Investigator or qualified site personnel will administer the assigned IMP. The requirements for maintaining IMP accountability are provided in Section 5.9 of this protocol.

6.15 Quality of Life Assessments

Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment will be conducted on Day 238±3 for subjects not entering OLE.

6.16 Adverse Event Reporting

Adverse events will be collected from signing of the informed consent through the last study visit.

6.16.1 Definitions

6.16.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject whether or not it appears to have a causal relationship with the treatment administered.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or

participation in a clinical study, whether or not directly related to the medicinal product or study participation.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency during the course of the study.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, will, in itself, be considered an AE. Laboratory or diagnostic testing abnormalities that reflect or are part of a known underlying medical condition are not, in themselves, AEs; rather, the underlying medical condition leading to the abnormalities would be reported as the AE.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 6.16.5.2.

6.16.1.2 Serious Adverse Event

A SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: “Life-threatening” refers to a situation in which the subject was at substantial risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization; Note: Does not include hospitalization for observation with release within 24 hours. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is considered to be an important medical event defined as those that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

6.16.1.3 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of DX-2930 is considered a dose that is two-fold higher than the intended dose for the subject.

6.16.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of IMP is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after first administration of IMP through the final follow-up visit or, in the event that onset time precedes first IMP administration, the AE increases in severity during the follow-up period.

6.16.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be captured and monitored during this study. **Investigators will report all AESI to the Sponsor, regardless of causality, using the same timelines as described for SAE reporting.** The following describe the AESI and the criteria for reporting AESI.

HYPERSENSITIVITY REACTIONS

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

EVENTS OF DISORDERED COAGULATION

Bleeding AESI

Although aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon, as a precautionary measure in evaluating the safety of DX-2930, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (aPTT, PT, INR) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a thrombotic or embolic etiology.

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, from signing of the ICF through the final follow-up visit.

- Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the Investigator.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects will continue to be followed through completion of all scheduled visits.

6.16.2.2 Monitoring of Safety Laboratory Assessments

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the Investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning.

In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 2) and the

Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

- GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required
- GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Any treatment-emergent ECG abnormality that is considered by the Investigator as clinically significant and requiring intervention/therapy will be assessed as a severe AE.

6.16.3.2 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the IMP, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between IMP exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the IMP.
- The AE resolved or improved with decreasing the dose or stopping use of the IMP (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study IMP and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the IMP); or

- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of IMP); or
- The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the IMP).

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the Investigator, with discussion with the Medical Monitor as appropriate, or by the DSMB for overall study AE review.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) or DMID Pediatric Toxicity Tables (Appendix 3) will be used to assess severity. Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the Investigator with input from the Medical Monitor as needed.

Following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the Investigators Brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically important functions *in vivo*. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-Serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to IMP, will be recorded on the AE page of the eCRF. In this study all HAE attacks reported by the subject, regardless of whether or not they are confirmed by the Investigator, will be captured as AEs.

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Sponsor's Pharmacovigilance Department using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The Investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the Investigator or qualified designee to the Sponsor's Pharmacovigilance Department:

- SAE
- AESI
- Overdose
- Cancer

The Investigator is to report any expedited safety observations from the list above to the Sponsor using the **SAE Reporting Form in the EDC system** within 24 hours of becoming aware of the event.

Any SAE reported to the Sponsor Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

The Investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The Investigator does not expect any further improvement or worsening of the event.
- Fatal outcome—if an autopsy is performed, the autopsy report is requested to be provided to the sponsor as soon as it is available.

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor or designee will report relevant safety information to concerned health authorities in accordance with local laws and regulations.

6.16.5.5 Safety Contact Information

24-Hour Medical Safety Contact for US, Canada, Europe, and Middle East

Sponsor Pharmacovigilance Department
Email: PPD
Phone (US): PPD

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to IMP that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The Investigator will promptly inform his/her IRB/REB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

6.16.5.7 Unblinding a Subject's Treatment during the Trial

Requirements for emergency unblinding by the Investigator are detailed in Section 5.4. To assess an occurrence of a safety observation, the Sponsor Pharmacovigilance Department may unblind the treatment of any subject.

6.17 Subject Withdrawal

The Investigator may withdraw a subject from treatment with study drug for any of the reasons listed below.

- In the opinion of the Investigator, the subject is unable to comply with the requirements of the protocol for satisfactory completion or interpretation of study results (including use of prohibitive medications),

- A serious or intolerable AE occurs,
- A clinically significant change in a laboratory parameter occurs,
- The Sponsor or Investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study. The criteria used by the DSMB regarding dose administration suspension and/or study discontinuation are provided in Section 3.1.2.

6.18 Appropriateness of Measurements

This is a Phase 3 multi-center, randomized, double-blind, placebo-controlled study that is designed to evaluate the efficacy and safety of DX-2930 in prevention of HAE attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The randomized, placebo controlled study design is a standard approach for differentiation between the efficacy and safety profiles of an active and placebo treatment when administered to subjects. All of the measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product.

7 STUDY ACTIVITIES

Study activities are summarized by study visit in Table 1 (Study Activities Schedule).

7.1 Screening

The following procedures and assessments are to be performed during Screening:

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6); documentation of height and weight
- 12-Lead ECG (Section 6.7)
- Laboratory testing including, serology, hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms
- Subjects who are on LTP for HAE must complete a 2 week washout period, as confirmed by the Investigator, before entering the run-in period.
    - LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age.

7.2 Run-in Period

Subjects who were on LTP may enter run-in after successfully completing a 2 week washout of their LTP. All subjects will undergo a run-in period of 4 weeks to determine the baseline HAE attack rate (Section 6.4). The run-in period may be shortened to less than 4 weeks for any subject who experiences 3 Investigator-confirmed attacks before the 4 weeks have ended. The run-in period may be expanded by an additional 4 weeks if the subject does not meet the minimum attack requirement during the first 4 weeks.

The following will be collected on an ongoing basis during the run-in period by subjects (or caregivers) reporting symptoms of an HAE attack to the site or through regular site contact with the subject (or caregiver):

- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.3 Start of Treatment Period: Visit 1, Dose 1 (Day 0)

The following procedures and assessments are to be performed on Day 0 prior to the first dose of IMP administration:

- Eligibility review (Section 6.2)
- Randomization to treatment (Section 6.13)
- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.4 Site Contact with the Subject

Site personnel contact the subject once between scheduled study visits or approximately 7 days after their last contact with the subject to solicit for any HAE attack information not already reported by the subject.

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.5 Continuation of Treatment Period: Visit 2, Dose 2 (Day 14±3 Days)

On Day 14 the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.6 Continuation of Treatment Period: Visit 3, Dose 3 (Day 28±3 Days)

On Day 28, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.7 Continuation of Treatment Period: Visit 4, Dose 4 (Day 42 ±3 Days)

On Day 42, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)

- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.8 Continuation of Treatment Period: Visit 5, Dose 5 (Day 56±3 Days)

On Day 56, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.9 Continuation of Treatment Period: Visits 6 and 7, Doses 6 and 7 (Days 70 and 84, All ±3 Days)

On Days 70 and 84, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)

- AE collection (Section 6.16)

7.10 Continuation of Treatment Period: Visit 8, Dose 8 (Day 98±3 Days)

On Day 98, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.11 Continuation of Treatment Period: Visits 9 and 10, Doses 9 and 10 (Days 112 and 126, All ±3 Days)

On Days 112 and 126, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Pregnancy test, serum or urine (females) on Day 126±3 (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL on Day 126±3 (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.12 Continuation of Treatment Period: Visit 11, Dose 11 (Day 140±3 Days)

On Day 140, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)

- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.13 Continuation of Treatment Period (Day 144±1 Day)

This ECG assessment may be conducted through an at-home visit by a nurse or technician or at the study site. The date, time and collection location of this ECG and its results will be documented in the source documents and eCRF.

- 12-Lead ECG (Section 6.7)

7.14 Continuation of Treatment Period: Visits 12 and 13, Doses 12 and 13 (Days 154 and 168, All ±3 Days)

On Days 154 and 168, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Pregnancy test, serum or urine (females) on Day 154±3 (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL on Day 154±3 (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.15 Completion of Treatment Period: Visit 14, Day 182±3 Days

On Day 182, the following procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Urine pregnancy test (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)
- Discharge from study:
    - Subjects will be offered the option of enrolling in the DX-2930-04 Open Label Extension (OLE) study for continued treatment and safety follow-up.
    - Informed Consent obtained for study DX-2930-04

- Subjects who consent to participate in DX-2930-04 will receive their first OLE dose following the completion of all double-blind assessments scheduled on Day 182.

7.16 Follow-up Period (Subjects Not Continuing in Open-Label Extension Study): Visit 15, Day 210 ±3 Days

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.17 Final Follow-up Visit (Subjects Not Continuing in Open-Label Extension Study): Visit 16, Day 238±3 Days

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

7.18 Early Termination (ET)

Subjects that terminate early from the study will undergo (if possible) all of the assessments and procedures scheduled for Day 182.

8 QUALITY CONTROL AND ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management services, Rho, Inc. will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The site staff should assist in all aspects of audit/inspection.

9 DATA ANALYSIS / STATISTICAL METHODS

9.1 General Considerations

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, PPD, PPD, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group. For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, treatment differences, p-values, and 95% confidence intervals for least squares mean treatment differences will be provided. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal statistical hypothesis testing will be performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure as described in Section 9.12.5.

9.2 Sample Size Determination

Power analysis and sample size estimation was based on 1000 computer simulations using a generalized linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

For a treatment effect of 60% reduction in attacks as compared to placebo, assuming a placebo attack rate of 0.3 attacks per week over a 26 week period for an average total of 7.8 attacks during the treatment period, a sample size of 24 actively treated subjects for the primary active treatment arm and 36 placebo subjects would provide at least 95% power (at alpha=0.025, one-sided). A 60% reduction is well below the smallest expected reduction in attacks, for in the DX-2930-02 study, we observed reductions of attacks of near 100%. These sample sizes will also provide adequately sized safety population for evaluation. Up to 120 subjects (approximately 80 subjects in the 3 active treatment groups and 40 in the placebo group) may be enrolled to account for potential early dropouts during the study.

9.3 Method of Assigning Study Subjects to Treatment Groups

Subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive repeated SC administrations of DX-2930

or placebo. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization will be performed centrally and stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks. Permuted blocks will be used to ensure that approximately equal numbers of subjects are assigned each treatment within strata.

9.4 Analysis Populations

The analysis populations will be defined as follows:

Intent-to-treat (ITT) Population: will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received. The primary efficacy analyses will be carried out with the ITT Population.

Safety Population: will include all subjects who are administered at least 1 dose of active IMP or placebo. Subjects will be analyzed according to the treatment they actually received. All safety analyses will use the Safety Population.

9.5 Analysis of Disposition

The numbers of subjects randomized, completing, or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group and overall for the ITT and safety populations.

9.6 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group and overall for the ITT and safety populations.

9.7 Treatment Compliance and Extent of Exposure

Treatment compliance and extent of exposure will be described by calculating the percentage of planned doses received by the subject and the total number of doses received by the subject and summarized by treatment group for the ITT and safety populations.

9.8 Analysis of Primary and Secondary Efficacy Endpoints

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint, number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182), will be compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in

days each subject was observed during the efficacy evaluation period will be used as an offset variable in the model.

From this model, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group will be estimated. These estimates will be reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \lambda_{DX\text{-}2930} / \lambda_{placebo} = 1 \text{ versus } H_1: \lambda_{DX\text{-}2930} / \lambda_{placebo} \neq 1$$

$\lambda_{DX\text{-}2930}$ refers to the mean Investigator-confirmed HAE attack rate in the DX-2930 group and $\lambda_{placebo}$ refers to the mean Investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean Investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of Investigator-confirmed HAE attacks during the efficacy evaluation period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage change in mean Investigator-confirmed HAE attack rate of each active treatment group from the attack rate of placebo will be calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

All efficacy analyses will be conducted using the ITT population.

In order to maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure will be used for the comparisons of each of the active treatment groups with the placebo group with equal weights for each test set at 1.67% significance level ($\alpha/3$).

9.8.2 Secondary Efficacy Endpoints

The rank-ordered secondary efficacy endpoints are as follows:

1. Number of Investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation period (Day 0 through Day 182).
2. Number of moderate or severe Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182).
3. Number of Investigator confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182).

The secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint.

To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant. The testing procedure is detailed in Section 9.12.5.

9.8.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

The exploratory efficacy endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment effect.

9.9 Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

9.9.1 Pharmacokinetic Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3 and 182±3. Additional samples will be collected on Days 210±3, and 238±3 during the follow-up period for any subjects not entering OLE.

Plasma concentrations of DX-2930 will be summarized with descriptive statistics by nominal PK sampling time.

9.9.2 Pharmacodynamic Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3, and 238±3 during the follow-up period for any subjects not entering OLE.

Plasma kallikrein activity will be summarized with descriptive statistics by nominal PD sampling time.

9.9.3 Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE

9.9.4 C1-INH and C4 Assessments:

Samples will be obtained for C1-INH, C4 and C1q assays at screening for eligibility assessment.

9.10 Safety Analysis

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The number and percentage of subjects with TEAEs will be displayed for each treatment group by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Serious AEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs and AESI will be produced.

AESI will be analyzed according to primary system Organ Classes (SOCs) and Preferred Terms (PTs) determined by the search of relevant Standardized MedDRA Queries (SMQs). Summary tables with SOCs and PTs, from the SMQ searches, will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications (other than rescue medications) will be summarized descriptively for each of the treatment groups and the combined active treatment group.

Actual values and change from screening in vital signs and clinical laboratory tests will be summarized for each treatment group with descriptive statistics at each assessment obtained. For all laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice-versa.

Abnormal physical examination findings will be listed.

The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed for each of the treatment groups.

Additional analyses of AEs, SAEs, severe AEs, AESI, and abnormal findings will be based on the timing (Study Day) and number of prior doses of study medication. The incidence of AEs by

month from the start of study medication will be examined and the incidence among the four treatment arms will be compared. The rate of study discontinuation among the four treatment arms will also be compared.

9.11 Analysis of Quality of Life Assessments

Quality of life data will be obtained using the EQ5D Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the AE-QoL Questionnaire at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional QoL assessment will be conducted on Day 238±3 for subjects not entering OLE.

9.12 Statistical/Analytic Issues

9.12.1 Adjustment for Covariates

The analysis of the primary and secondary efficacy adjusts for the normalized baseline HAE attack rate. No additional covariate adjustment is planned.

9.12.2 Handling of Dropouts or Missing Data

All available data will be included in the analysis. The length of time a subject was observed during the efficacy evaluation period will be included as a variable in the generalized linear model to adjust for differences in follow-up time.

9.12.3 Interim Analysis and Data Monitoring

No interim analyses are planned. However, an independent DSMB will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DSMB review will be conducted according to the DSMB Charter and DSMB SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

9.12.4 Multicenter Studies

Data from all study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

9.12.5 Multiple Comparisons/Multiplicity

The global family-wise Type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 6.4.1) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach with branches for each active treatment group to placebo group comparison will be utilized in which each family of statistical tests will be conducted in a sequential manner. Specifically, a three-branch general gatekeeping procedure with four families of hypotheses will be defined as follows:

- Family 1 (F_1): Hypothesis tests for the primary efficacy endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{11}, H_{12}, and H_{13}).
- Family 2 (F_2): Hypothesis tests for the first ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{21}, H_{22}, and H_{23}).
- Family 3 (F_3): Hypothesis tests for the second ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{31}, H_{32}, and H_{33}).
- Family 4 (F_4): Hypothesis tests for the third ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{41}, H_{42}, and H_{43}).

The 4 sets of hypotheses in F1, F2, F3, and F4 will be tested in a fixed sequence within each active treatment group to placebo group comparison or branch. Testing within a branch will continue in sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests within the branch.

Within a family, hypotheses will be tested using a conservative Bonferroni-based procedure with equal weights for each test set at 1.67% significance level ($\alpha/3$). If the null hypothesis for a test is rejected, α will be propagated entirely to the next test in the sequence, which will then be tested at the 1.67% significance level.

To further illustrate this approach, the test for the primary endpoint will be conducted first at the 1.67% significance level for each active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 1.67% significance level. The testing sequence will continue in order through the remaining secondary endpoints for each active treatment group to placebo comparison or branch as long as the null hypothesis is rejected at the 1.67% significance level.

Testing within the last family (F4) will utilize the remaining α by applying the Holm-Bonferroni procedure.

9.12.6 Sensitivity Analyses

Sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results from the primary analysis method. These analyses will be described in the statistical analysis plan.

10 STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 3.

Table 3. Study Administrative Structure

Sponsor Contact/Sponsor Medical Director:	Jennifer Schranz, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD
Medical Monitor (US, Canada):	PPD, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD Email: PPD
Medical Monitor (Jordan, Europe):	PPD, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD Email: PPD
Study Monitoring (US):	Rho, Inc. PPD, PPD, PPD Phone: PPD
Study Monitoring (Jordan)	Triumpharma PPD, PPD PPD, PPD PPD, Jordan Phone: PPD
Study Monitoring (Canada)	Red Maple Trials Incorporated PPD, PPD PPD, PPD, Canada, PPD Phone: PPD
Study Monitoring (Europe)	Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc. 55 Network Drive, Burlington, MA 01803 Phone: PPD

10.1 Institutional Review Board/Research Ethics Board/Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the Investigator and approved in writing by the IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent and assent forms, any consent or assent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects prior to implementation. The Investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The Investigator must

provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

10.2 Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the International Conference on Harmonisation (ICH) guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements [in accordance with United States Investigational New Drug (IND) regulations (21 CFR 56)].

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The Investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the study.

10.4 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number and birth date (if allowed based on local data protection regulations), not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the Investigator.

The Investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

10.5 Study Monitoring

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an

ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator.

10.6 Case Report Forms and Study Records

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the clinical sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, source data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving randomized study dug.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

A Trial Master File will be maintained by the Sponsor (or designee). All documents and other materials that pertain to the conduct of the trial, quality of the data, and compliance with GCPs will be collected in the Trial Master File.

10.7 Data Safety Monitoring Board

An independent DSMB will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study.

The DSMB will adhere to a prospectively determined Charter, which will be written by the Sponsor and approved by the DSMB. The Charter will define the responsibilities of the DSMB and Sponsor, the number and timing of the DSMB meetings, the conduct of the meetings, and the data sets to be reviewed by the DSMB. Further details regarding the DSMB can be found in the DSMB charter.

10.8 Protocol Violations/Deviations

The Investigator will be instructed not to deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the Investigator should contact their Sponsor representative to discuss the appropriate course of action.

The Investigator should document all protocol deviations/violations in the subject's eCRF and source documents or the Investigator Site File if appropriate. In the event of a significant deviation/violation, the Investigator should notify the Sponsor representative. Significant deviations/violations include, but are not limited to those that increase the health risk to the subject, or confound interpretation of primary study assessments. The Investigator will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects or others to his or her IRB/REB/IEC.

10.9 Premature Closure of the Study

If the Sponsor, Investigator, DSMB, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated overall or at a specific site after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to, the following:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

10.10 Access to Source Documentation and On-Site Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The Investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study.

The Investigator will be responsible for the accuracy of the data entered in the eCRF. The Investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

10.11 Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitors will meet with the Investigators and staff shortly before the start of the trial to review the procedures for study conduct and documentation. During the study, the monitors will visit the sites to verify record keeping and adherence to the protocol. For this study, eCRFs will be used. The monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure accuracy and consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.12 Data Handling Considerations

Data that may potentially unblind the treatment assignment (i.e., investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

10.13 Retention of Data

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and IMP dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the responsible Investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible Investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

10.14 Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the Investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.15 Publication and Disclosure Policy

All information concerning DX-2930, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's advanced written consent. A description of this clinical study may also be available on other externally facing public websites and registries. A summary of the study results may be potentially disclosed as per local and country specific requirements.

The information developed in this study will be used by the Sponsor in connection with the continued development of DX-2930 and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

11 REFERENCE LIST

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12 APPENDICES

Appendix 1 Protocol History

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	14 September 2015	Global
Amendment 1.0	14 December 2015	Global
Amendment 2.0	21 April 2016	Global
Amendment 3.0	09 January 2017	Global

The Protocol Amendment 2.0 includes changes to the Protocol Amendment 1.0, summarized as follows:

- An exclusion criterion was added to exclude subjects who may have participated in a prior DX-2930 study to eliminate non-naïve from the study analysis; consequently, stratification by naïve versus non-naïve subjects was removed from the randomization plan for the study.
- Since no data on embryo-fetal development toxicity are available, per the clinical trial facilitation group's (CTFG) recommendations related to contraception and pregnancy testing in clinical trials, the highest risk is assumed. Therefore, the inclusion criterion for contraception requirements was modified to emphasize the use of highly effective contraceptive measures during treatment and until the end of relevant systemic exposure for women of childbearing potential. It was also clarified that the use of a male condom with or without spermicide or cervical cap, diaphragm, or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective.
- Four additional pregnancy tests (urine or serum) were scheduled on Days 28, 56, 126, and 154 for monitoring of pregnancy during treatment.
- Per Footnote #7 in the "Study Activities Schedule," a correction was made in Section 7 (Study Activities) that a serum- or urine-based pregnancy test will be performed at the Final Follow-up Visit (Subjects Not Continuing in Open-Label Extension Study): Visit 16, Day 238 ± Days.
- It was clarified that no interim analysis is planned.
- An independent Data Safety Monitoring Board (DSMB) replaced the internal study safety committee (SSC), and its procedures were clarified.
- The period for reporting HAE attacks after the final follow-up visit was clarified.
- For the management of acute HAE attacks, it was clarified that administration of the investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the patient receives any treatment for an HAE attack.
- For collection of HAE attack data, it was clarified that weekly communication between the patients and the site, including reports of HAE attacks, must be documented in the eCRF.
- A tertiary objective to evaluate the effect of DX-2930 on health-related quality of life (QoL) was rephrased for clarity.
- Four additional QoL assessments using the Angioedema-Quality of Life (AE-QoL) Questionnaire were added at Day 28 ±3, Day 56 ±3, Day 126 ±3, Day 154 ±3 in text

and in the Study Activities Schedule for a better measure and comparison of the data available from the study.

- It was specified in Section 7.1 (Study Activities-Screening) that the washout after the long-term prophylactic (LTP) therapy is permitted as long as the Investigator determined that doing so would not place the subject at any undue safety risk and would be applicable to subjects who are at least 18 years of age.
- A safety assessment, 12-lead electrocardiogram (ECG), was added at Visit 16/Day 238 in the tables for "study activities schedules" to be consistent with Section 7.17, Final Follow-up Visit (subjects not continuing in Open-Label Extension Study).
- The efficacy evaluation period was updated to begin at Day 0 instead of Day 14 to be consistent with the intent-to-treat analysis principle.
- The description of the primary endpoint was modified for assessment during the efficacy evaluation period rather than per week for consistency with the statistical model. The unit of measurement is irrelevant for the statistical model as the hypothesis test is based on the rate ratio. Results from the statistical model will be reported in both weeks and months to facilitate clinical interpretation.
- The secondary endpoint "Time to first attack, i.e., duration that a subject is attack free until their first attack" was removed from the rank order and will be considered an exploratory endpoint. It was modified to "Time to first HAE attack after Day 14, ie, duration that a subject is attack free after Day 14" to allow enough time to first attack for this endpoint assessment.
- The secondary endpoint "Number of high-morbidity HAE attacks" removed from the rank order and will be considered an exploratory endpoint.
- The description of the secondary endpoints was modified for assessment during the efficacy evaluation period rather than per week to for consistency with the statistical model. The unit of measurement is irrelevant for the statistical model as the hypothesis test is based on the rate ratio. Results from the statistical model will be reported in both weeks and months to facilitate clinical interpretation.
- Statistical methods were updated to use a generalized linear model rather than generalized estimating equation model for the primary analysis. This updated analysis approach also applies to the secondary endpoints.
- Multiplicity procedures were specified in greater detail. Specifically, a general gatekeeping procedure will be used to strongly control the global family-wise Type I error rate (FWER) in the hierarchical testing of the primary and secondary endpoints conducted at the 1.67% significance level for each active treatment group compared with the placebo group.
- In general, the statistical methods were described with additional information regarding the general statistical considerations and statistical/analytical issues (eg, adjustment for covariates, handling of dropouts and data monitoring, handling of dropouts or missing data, interim analysis and data monitoring, multicenter studies, and sensitivity analyses).
- Sample size determination was updated to be consistent with the updated statistical methods.
- Section 10.9, Premature Closure of the Study, was added to include conditions that may warrant termination of the study or site.

- Section 10.12, Data Handling Considerations, was added to include specifics regarding handling of data to prevent potential unblinding.
- In Section 10.14, financial disclosure language was updated to be consistent with 21 CFR 54 2(b) (1998).
- Section 10.15, Study Results/Publication Policy, was updated to include language regarding posting of appropriate study information on applicable websites by the Sponsor.
- Sponsor, Sponsor contact, medical director, and medical monitor information was updated where relevant.
- Minor spelling change was made changing “athough” to “although.”

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **21 April 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Statistical methods were updated to use a generalized linear model rather than generalized estimating equation model for the primary analysis. This updated analysis approach also applies to the secondary endpoints.		Study Synopsis, Statistical Methods
SSC monitoring replaced by DSMB; clarified that no interim analysis is planned for this study.		Study Synopsis, The DSMB replaces the SSC.
Addition to be consistent with the ECG schedule in Section 7.17, Final Follow-up Visit (Subjects not continuing in Open-Label Extension Study) Visit 16, Day 238±3 days		Study Activities Schedule (Synopsis and Appendix 1)
Updated the abbreviation list based on the changes to the protocol.		List of Abbreviations
Rephrased for clarity. “To evaluate the effect of DX-2930 on health related quality of life (QoL)”		Study Synopsis, Section 2.3, Tertiary Objectives
Removed the text around randomization based on naïve versus non-naïve subjects to align with the new exclusion criterion to exclude subjects who may have participated in a prior DX-2930		Study Synopsis; Section 3.1.1.3, Treatment Period; Section 6.13, Randomization
The period for reporting HAE attacks after the final follow-up visit was clarified.		Study Synopsis; Section 3.1.1.5, Follow-up Period
SSC monitoring replaced by DSMB.		Section 3.1.2.1, Interim Analysis and Data Safety Monitoring Board (DSMB)
Text updated to reflect the exclusion of subjects who may have participated in a prior DX-2930 study		Study Synopsis; Section 4.1, Study Population
Text updated to reflect the exclusion of subjects who may have participated in a prior DX-2930 study		Study Synopsis; Section 4.2, Criteria for Inclusion

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **21 April 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Since no data on embryo-fetal development toxicity are available, per the clinical trial facilitation group's (CTFG) recommendations related to contraception and pregnancy testing in clinical trials, highest risk is assumed. Therefore, the inclusion criterion for contraception requirements was modified to emphasize the use of highly effective contraceptive measures during treatment and until the end of relevant systemic exposure for women of child bearing potential; It was also clarified that the use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) is not considered highly effective.		Study Synopsis; Section 4.2, Criteria for Inclusion
Added a new exclusion criterion to exclude subjects who may have participated in a prior DX-2930 study in order to eliminate non-naïve from this study. Also, the other exclusion criteria were renumbered		Study Synopsis; Section 4.3, Exclusion Criteria
Clarifies unblinding procedures.		Section 5.4, Blinding and Unblinding
For the management of acute HAE attacks, it was clarified that administration of the investigational product and study procedures will continue without alteration to the protocol specified study schedule, even if the patient receives any treatment for an HAE attack.		Study Synopsis, HAE Attack Management); Section 5.5.1, Allowed Therapies
Dyax replaced with the general term "Sponsor" throughout the protocol.		Section 5.8, Packaging and Labeling; Section 6.16.1.6, Adverse Events of Special Interest; Section 6.16.3.3, Assessment of Clinical Significance (and wherever relevant except the title page, first row of the Study Synopsis, and Table 2 in Section 10 [Europe monitoring responsibility])

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **21 April 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The efficacy evaluation period updated from Day 0 to Day 14 to be consistent with the intent-to-treat analysis principle. The description of the primary endpoint was modified for assessment during the efficacy evaluation period rather than per week for consistency with the statistical model. The secondary endpoint "Time to first attack, i.e., duration that a subject is attack-free until their first attack" was removed from the rank order and will be considered an exploratory endpoint. It was modified to "Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14" to allow enough time to first attack for this endpoint assessment. The secondary endpoint "Number of high-morbidity HAE attacks" removed from the rank order and will be considered an exploratory endpoint. The description of the secondary endpoints was modified for assessment during the efficacy evaluation period rather than per week for consistency with the statistical model. The unit of measurement is irrelevant for the statistical model as the hypothesis test is based on the rate ratio. Results from the statistical model will be reported in both weeks and months to facilitate clinical interpretation.		Study Synopsis, Criteria for Evaluation; Section 6.4.1, Primary and Secondary Endpoints
For the collection of HAE attack data, it was clarified that weekly communication between the patients and the site, including reports of HAE attacks, must be documented in the eCRF.		Study Synopsis, Collection of HAE Attack Data; Section 6.4.2. HAE Attack Information Collection
Removed time bound of 7 days.		Study Synopsis, Collection of HAE Attack Data; Section 6.4.2, HAE Attack Information Collection
Text updated to reflect the exclusion of subjects who may have participated in a prior DX-2930 study.		Study Synopsis; Study Activities Schedule (Footnote 6); Section 6.8.1.7, C1-INH Functional Assay; Section 6.8.1.8, C4 Assay; Section 6.8.1.9, C1q Assay
Added additional Angioedema-Quality of Life (AE-QoL) Questionnaire assessments on Days 28±3, 56±3, 126±3, and 154±3 for a better measure and comparison of data available from this study.		Synopsis; Study Activities Schedule; Section 6.15, Quality of Life Assessments; Section 9.11, Analysis of Quality of Life Assessments
SSC replaced with DSMB		Section 6.16.3.3, Assessment of Clinical Significance
Updated contacts		Section 6.16.5.5, Safety Contact Information

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **21 April 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Throughout the protocol, as in this section, Dyax was replaced by "the Sponsor."		Section 6.16.1.6, Adverse Events of Special Interest (AESI)
DSMB replaces SSC		Section 6.17, Subject Withdrawal
It was specified that the washout after the LTP therapy is permitted as long as the Investigator determined that doing so would not place the subject at any undue safety risk and would be applicable to subjects who are at least 18 years of age.		Section 7.1, Screening
Four additional pregnancy tests (urine or serum) were scheduled on Days 28, 56, 128, and 154 for monitoring pregnancy during treatment.		Study Activities Schedule, Pregnancy Test (females) and Footnote #7; Sections 7.6, 7.8, 7.11, and 7.14
Specified the instruments (EQ5D and AE-QoL) used for quality of life assessments on Days 0, 98±3, 182±3, and 238±3.		Section 7.3 (Start of Treatment Period); Sections 7.10 and 7.15 (Continuation of Treatment Period); Section 7.17 (Final Follow-up Visit)
Specified the additional assessments for AE-QoL on Days 28±3, 56±3, 126±3, and 154±3 for clear demarcation.		Sections 7.6, 7.8, 7.11. 7.14
DSMB replaces SSC.		Sections 7.9, 7.10, 7.11, 7.12, 7.14
Text added to provide an overview of the general plan for the statistical analyses.		Section 9.1, General Considerations
Text for "sample size determination" was updated to be consistent with the updated statistical methods.		Study Synopsis; Section 9.2, Sample Size Determination
Added consolidated information regarding randomization and stratification in the Statistical Analysis section of the protocol.		Section 9.3, Method of Assigning Study Subjects to Treatment Groups
Text added to clarify that the subjects will be analyzed according to their randomized treatment assignment.		Section 9.4, Analysis Population
Added the populations for clarity.		Section 9.5, Analysis of Disposition
Clarifies the analysis population.		Section 9.6, Demographics and Baseline Characteristics Analyses
Added the method of describing treatment compliance and extent of exposure.		Section 9.7, Treatment Compliance and Extent of Exposure
Efficacy endpoint period beginning on Day 0 instead of Day 14. Results from the statistical model will be reported in both weeks and months to		Section 9.8, Analysis of Primary and Secondary Efficacy Endpoints

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **21 April 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
facilitate clinical interpretation. Statistical methods were updated to use a generalized linear model rather than generalized estimating equation model for the primary analysis. This updated analysis approach also applies to the secondary endpoints. Explains endpoint analyses based on generalized linear model.		
The secondary endpoint "Time to first attack, ie, duration that a subject is attack free until their first attack" was removed from the rank order and will be considered an exploratory endpoint. It was modified to "Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14" to allow enough time to first attack for this endpoint assessment. The secondary endpoint "Number of high-morbidity HAE attacks" removed from the rank order and will be considered an exploratory endpoint.		Section 9.8, Secondary Efficacy Endpoints
Added additional details for the statistical analysis; clarified no plan for interim analysis and plans for DSMB. In general, the statistical methods were described with additional information regarding the general statistical considerations and statistical/analytical issues (eg, adjustment for covariates, handling of dropouts and data monitoring, handling of dropouts or missing data, interim analysis and data monitoring, multicenter studies, and sensitivity analyses).		Section 9.12, Statistical/Analytic Issues
Multiplicity procedures were specified in greater detail. Specifically, a general gatekeeping procedure will be used to strongly control the global FWER in the hierarchical testing of the primary and secondary endpoints conducted at the 1.67% significance level for each active treatment group compared with the placebo group.		Section 9.12, Statistical/Analytic Issues
Added to briefly introduce the plan for sensitivity analysis, which will be described in the statistical analysis plan.		Section 9.12.6, Statistical Analyses
Study contact and Medical Director updated in Table 2.		Section 10, Study Administrative Structure
Clarifies DSMB procedures.		Section 10.7, Data Safety Monitoring
New text		New Section: Section 10.9, Premature Closure of the Study
Clarifies data handling considerations to prevent potential unblinding.		New Section: Section 10.12, Data Handling Considerations

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **21 April 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Added text to be consistent with 21 CFR 54 2(b) (1998).		New Section: Section 10.14, Financial Disclosure
Added text to align with potential disclosure of study results.		Section 10.15, Publication and Disclosure Policy

The Protocol Amendment 1.0 includes changes to the original protocol, summarized as follows:

- The list of inactive ingredients and description of treatments in the synopsis and in Section 5.1 is updated to reflect the use of 150 mg/mL concentration DX-2930 instead of 100 mg/mL concentration DX-2930. Minor updates are made to the components of both DX-2930 and Placebo. The number of injections and the volume of each injection of DX-2930 and Placebo are updated to reflect the change in concentration.
- The 1 month non-human primate data in the Safety Rationale for DX-2930 has been replaced with 6 month non-human primate data as the 6 month data is available and more relevant for this long-term prophylaxis trial. The description of the run-in period is updated to clarify that if a subject's run-in period extended to 8 weeks then in order to be eligible for enrollment they must complete the full 8 weeks prior to entering the treatment period
- Individual study participant stopping rules are updated to clarify that the Investigator has sole discretion to discontinue subject dosing and that the Medical Monitor is available for consultation.
- The expected number of subjects age 12 to 17 to be enrolled in the study is added.
- The blinding and unblinding text is updated to clarify that the Investigator has sole discretion to break the treatment code in an emergency situation through immediate and unrestricted access to the IWRS system. The text is further updated to clarify that the Dyax Pharmacovigilance (PV) Department will be provided with treatment assignments for subjects who experience drug related, serious, unexpected adverse events for the purpose of regulatory reporting.
- The order of the sample collections when multiple sample types are collected at the same time point is updated to correspond to the Laboratory Manual.
- The study day through which treatment emergent AEs are defined is updated so as to be consistent with other sections of the protocol.
- Subject withdrawal text is updated to more clearly distinguish between discontinuation from dosing and discontinuation from the study, as well as to clarify that the use of prohibitive medications may be grounds for withdrawal by the

Investigator. The text is further updated to clarify that the Investigator has sole discretion to withdraw a subject for safety related issues and that the Medical Monitor is available for consultation.

- A minor spelling correction is made changing 'mediations' to 'medications'

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **14 December 2015**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Clarifies the actual ingredients that are referenced in the excipient list.		Page 3 of the Study Synopsis, Inactive Ingredients
Clarifies the nature of the PK and PD measures of evaluation.		Page 13 of the Study Synopsis, Criteria for Evaluation
Data from the 6-month study is available and more relevant for this long-term prophylaxis trial.		Page 28, Section 1.4 Safety Rationale for DX-2930
Neutralizing antibody data from DX-2930-02 is now available.		Page 31, Section 1.6.2 Multiple Ascending Dose Study in HAE Patients (DX-2930-02)
Clarifies the requirements for extended run-in periods.		Pages 4, 10 and 17 of Study Synopsis Page 34, Section 3.1.1, Overall Study Design and Plan (Overview) Page 48, Section 6.4.2, HAE Attack Information Collection Appendix 1 Study Activities Schedule
Clarifies the number of subjects that may be enrolled based on the number of subjects expected to complete.		Page 5 of Study Synopsis Page 34, Section 3.1.1, Overall Study Design and Plan (Overview)
Clarifies the Investigator's role in discontinuing subject dosing.		Page 12 of Study Synopsis Page 38, Section 3.1.2.3 Individual Stopping Rules
Clarifies the number of subjects that may be enrolled based on the number of subjects expected to complete.		Page 40, Section 4.1 Study Population
Per request by European Regulatory Authorities.		Page 5 of Study Synopsis Page 40, Section 4.1 Study Population

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **14 December 2015**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Reflective of changes to the manufacture of IP from 100 mg/ mL to 150 mg/ mL DX2930.		Page 7 of the Study Synopsis Page 42, Section 5.1, Description of Treatments
Clarifies the Investigator's role in breaking the blind and obtaining the treatment assignment in emergency situations. Clarifies that Dyax PV will obtain treatment assignment for regulatory reporting of drug-related, serious, unexpected AEs.		Page 43, Section 5.4 Blinding and Unblinding
Clarifies the timing of the efficacy evaluation period.		Page 12 of the Study Synopsis Page 46, Section 6.4.1 Primary and Secondary Endpoints
Corrects the order of sample draws at time points when multiple samples are drawn.		Page 50, Section 6.8.1 Laboratory Parameters
Clarifies the study day through which TEAEs are captured to be consistent with other sections of the protocol.		Page 55, Section 6.16.1.5 Treatment Emergent Adverse Events (TEAEs)
Clarifies the study day through which TEAEs are captured to be consistent with other sections of the protocol.		Page 56, Section 6.16.2.1 Monitoring of Adverse Events
Clarifies the Investigator's role in withdrawing subjects for safety related reasons. Provides better distinction between discontinuation from dosing and discontinuation from study. Clarifies that use of prohibitive medications may be grounds for withdrawal by Investigator.		Page 61, Section 6.17 Subject Withdrawal
Clarifies the nature of the PK assessments to be evaluated in this study.		Page 75, Section 9.5.1 Pharmacokinetic Assessments
Clarifies the nature of the PD assessments to be evaluated in this study		Page 75, Section 9.5.2 Pharmacodynamic Assessments
Minor spelling correction.		Page 15 of the Study Synopsis Page 78, Section 9.7 Safety Analysis

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	---
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ---	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

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(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microscopic >25		Gross hematuria

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	cells/hpf	cells/hpf		

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(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

4 INVESTIGATOR ATTACK ASSESSMENT

The Principal Investigator for a study site may identify a physician designee to assess patient symptom information and make attack determinations. Sites should be limited to two individuals responsible for assessing attacks, one of them being the Principal Investigator. Assessors must be experienced with HAE and familiar with the study subject's disease history.

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

HAE Attack Assessment and Reporting Procedures (HAARP)

Title:	HAE Attack Assessment and Reporting Procedures (HAARP)
Product Name:	DX-2930
Indication:	Prevention of angioedema attacks in patients with HAE
Sponsor:	Dyax Corp. 55 Network Drive Burlington, MA 01803
Original Date:	14 September 2015
Version:	v1.0

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1 PURPOSE

This document applies to clinical trials that involve investigator adjudication/assessment of angioedema attacks. The purpose of this document is to provide a definition of an HAE attack and to define a standardized set of procedures for the reporting and assessment of events reported by subjects to determine whether those events are true HAE attacks.

2 DEFINITION OF AN ATTACK

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (e.g., urticaria), the reported event persists well beyond the typical time course of an attack (e.g., greater than 7 days), or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

To be counted as a unique attack distinct from their previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Attack resolution is defined as the subject no longer having symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

Patient report of use of acute HAE attack treatment for an attack by itself is not confirmation that an attack occurred.

3 REPORTING AND ASSESSMENT OF ATTACK DATA

At screening for applicable clinical trials, subject HAE attack history will be collected by the site for entry into the clinical database. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant location(s), average duration, acute attack therapy use, and history of long-term prophylaxis.

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects < 18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is

unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

Site personnel will review the information provided by the subject or caregiver and solicit additional information as necessary to document the attack. Information documented by the site will be considered source for the study.

A designated individual at the site (the collector) will contact the subject or caregiver on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject or caregiver.

The Investigator or designee (the assessor) will review the attack information and evaluate if the event represents a confirmed HAE attack. If necessary for the evaluation, the investigator or designee may contact the subject to receive additional information.

3.1 Subject-Reported Symptoms

Subjects and caregivers can use any existing methods by which they track information about their attacks, or, if requested, memory aids can be provided by the study site. However, subjects (or a caregiver) will need to track attacks in such a way as to be able to contact the study site as soon as possible, but not later than 72 hours (3 full days) after the first symptoms appear, to report the information.

3.1.1 Attack Information

The following information should be provided by the subject (or caregiver) at the time they are reporting an attack to the site:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Subjects do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/ or at a scheduled study visit. Subjects should not withhold or delay any treatment they would normally receive to treat their attack in order contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/ or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

During screening, site personnel will train subjects on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The patient will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the subject's compliance with the reporting requirements throughout the study and may retrain the subject if necessary in order to maintain the integrity of the data provided to the site.

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack as stated in Section 2, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Caregiver Report

During screening, site personnel will train subject caregivers (if applicable) on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The caregiver will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the caregiver's compliance with the reporting requirements throughout the study and may retrain the caregiver if necessary in order to maintain the integrity of the data provided to the site.

3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/ or use of back-up contacts, should be established in case the subject is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits. The date and time for check-ins can be modified based on when the last contact with the subject was made, as outlined in the study protocol. When the site is contacted by a subject reporting symptoms of an attack the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be

established in case the subject misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

3.2.1 Review of subject report of symptoms

During contact with the subject, whether subject-initiated or a regular check-in, site personnel should ask the subject to provide them information about new or ongoing HAE attacks experienced.

The site will try to obtain all information necessary to document the attack completely. Missing information may impact the assessment of any attack and should be avoided whenever possible.

3.2.2 Documenting a Reported Attack

Complete and accurate documentation of each reported attack is important to making an Investigator assessment of the attack. The site should document the following information about each attack reported by the subject or caregiver:

- Date and time of contact with the subject
- Date and time the subject first experienced symptoms
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance was required
- If the attack has resolved or is ongoing. If the attack has resolved, the date and time the subject was no longer experiencing any symptoms of the attack
- Names of any medications used to treat the attack including HAE acute therapy or other non-HAE treatments
- If hospitalization occurred
- If a trip to the emergency department occurred

Additional probing questions about what the subject experienced to determine:

- If the subject only experienced prodromal symptoms
- If the subject experienced anything different than their typical attack
- If there were any possible alternative etiologies of the symptoms. For example, a viral gastroenteritis outbreak in the household could explain abdominal symptoms

The overall severity of the subject's attack will be determined by the site using the following definitions:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance needed
- Severe: Marked limitation in activity, assistance required

The site will also document the date and time of investigator or designee review, the official designation of the event as an attack or not, and if applicable, the reason why an event is not considered an attack.

All reported attacks will be entered by site personnel into the electronic case report form (eCRF).

3.2.3 Site Training

Site personnel responsible for collecting attack information about subject HAE attacks will need to pass a "Collector" training assessment covering the following:

- definition of an HAE attack
- requirements of subjects and caretakers for reporting attacks
- reporting worsening symptoms and multiple attacks
- information to be collected from subjects and caregivers as well as the additional probing questions to gather context for the attack information provided
- assessment of attack severity
- entry of the attack data into the eCRF
- reporting HAE attacks as adverse events
- requirements for Investigator assessment of attacks

Trainings will be conducted prior to sites screening subjects. Trainings will be documented in the Trial Master File. Investigators and designees will be trained on these procedures as well and must pass an "Assessor" training in order to officially assess attacks for this study.

All responsible persons involved in the collection of information from subjects or assessing attacks must be listed on FDA Form 1572.

3.3 HAE attacks as Adverse Events

At the time of each contact and scheduled study visit, site personnel will ask if the subject experienced any adverse events or changes to the medications they are taking.

HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF.

Any AE reported to the site meeting criteria for a serious adverse event must be reported to Dyax using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack.

For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional

information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

4 INVESTIGATOR ATTACK ASSESSMENT

The Principal Investigator for a study site may identify a physician designee to assess patient symptom information and make attack determinations. Sites should be limited to two individuals responsible for assessing attacks, one of them being the Principal Investigator. Assessors must be experienced with HAE and familiar with the study subject's disease history.

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

STATISTICAL ANALYSIS PLAN

Protocol Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 for Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Protocol Number:	DX-2930-03
Protocol Version/Date:	Amendment 2.0 21 April 2016
Indication:	Prevention of angioedema attacks in subjects with HAE
Study Phase	III
SAP Author	PPD, MPH (Rho, Inc.)
SAP Analysis Type	Final Analysis
SAP Version/Date	Original SAP 1.0 24 May 2016

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1. LIST OF ABBREVIATIONS

AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1-inhibitor
CI	Confidence interval
CO2	Carbon dioxide
CPK	Creatine phosphokinase
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
EQ5D	EuroQoL Group 5-Dimension
eCRF	Electronic case report form
EDC	Electronic data capture
FWER	Family-wise type I error rate
GEE	Generalized estimating equations
GLM	Generalized linear model
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	Hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web-based randomization system
KM	Kaplan-Meier

LS	Least squares
LTP	Long-term prophylaxis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
PT	Preferred term
QOL	Quality of life
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is being developed after review of DX-2930-03 protocol, but before database lock and unblinding of treatment assignment. This SAP contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be used for analysis, as well as subject characteristics, efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), and quality of life (QoL) parameters. The details of the specific statistical methods as stated in the protocol will be provided and any changes from the protocol-specified analyses will be documented in the SAP prior to database lock. If additional analyses are required to supplement the planned analyses described in this SAP after the database lock, they may be completed and will be described in the CSR. Table, figure, and listing specifications are provided in separate documents.

2.2 Background

DX-2390-03 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the safety and efficacy of DX-2930 as a treatment for the prevention of hereditary angioedema (HAE) attacks. Details of the study design, rationale, and procedures are documented in Protocol DX-2390-03 Amendment 2.0.

2.3 Study Rationale

DX-2930 is a fully human IgG1 recombinant monoclonal antibody that binds specifically to active plasma kallikrein. DX-2930 is being developed for prophylactic treatment of angioedema attacks in patients with HAE, a serious and life-threatening disease.

3. STUDY OBJECTIVES

3.1 Primary Objectives

To evaluate the efficacy of DX-2930 in preventing HAE attacks.

3.2 Secondary Objectives

To evaluate the safety of repeated subcutaneous administrations of DX-2930.

3.3 Tertiary Objectives

- To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930
- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the pharmacokinetics (PK) of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health related quality of life (QoL)

4. STUDY DESIGN

4.1 General Description

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in subjects with Type I and Type II HAE. This double-blind study is planned to be followed by an open-label extension (OLE) that is described in a separate protocol (Protocol DX-2930-04).

A figure showing dosing is in Appendix 10.3. A table showing the Study Activities Schedule for the study is provided in Appendix 10.4.

Long-Term Prophylactic (LTP) Therapy Washout:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm the subject has successfully completed the 2-week washout period before they can enter the run-in period.

Run-In Period:

Screened subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. Only subjects meeting a minimum baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered screen failures. Subjects who fail screening will not be allowed to rescreen into the study.

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through

two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in Appendix 10.3.

Open-Label Extension (OLE) Study:

Subjects who complete the treatment period will be offered the option of enrolling in an open-label extension (OLE) study that will be described in a separate protocol (DX-2930-04).

Follow-up Period:

Subjects who do not participate in the OLE will undergo safety and additional evaluations (i.e., PK and PD) during an 8 week follow-up period. Subjects (or caregivers) will be instructed to inform the site of any HAE attacks they experience for up to 30 days after the final follow-up visit.

4.2 Discussion of Study Design, Including the Choice of Control Group

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in subjects with Type I and Type II HAE. The following is a discussion of the rationale behind the design of the trial.

- **Primary endpoint selection**: The objective of this study is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The number of HAE attacks is a direct way to evaluate efficacy.

- **Dose selection:** The dose rationale is based on the pharmacodynamic bioactivity, PK, safety, and efficacy of DX-2930 from the Phase 1 clinical studies and nonclinical studies. Together, these attributes provide the rationale for the selected doses and regimens to achieve drug levels likely to prevent a majority of HAE attacks. Based on these considerations, 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks were identified as the dosing regimens for evaluation. The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930-treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

- **Control group selection:** This trial incorporates a placebo comparator to evaluate and interpret the efficacy of DX-2930. The use of placebo is justified because 1) placebo does not represent a reduction in current standard of care for subjects due to the availability of acute attack treatments and 2) none of the therapies currently used for the prevention of HAE attacks are suitable for use as an active comparator.

- **Study population:** Subjects 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

- **Baseline symptom severity:** To be eligible to participate in the study, subjects had to meet a minimum baseline HAE attack rate of at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period.

- **Stratified randomization:** Randomization to treatment is stratified by the baseline HAE attack rate observed during the run-in period. The three levels of HAE attack rate strata are 1-<2 attacks per 4 weeks, 2-<3 attacks per 4 weeks and 3 or more attacks per 4 weeks.

- **Safety monitoring:** Adverse events (AE), clinical laboratories and vital signs will be monitored throughout the study.

4.3 Method of Assigning Subjects to Treatment Regimens

Subjects will be randomized after confirmation of study eligibility in a 2:1 ratio to receive repeated SC administrations of DX-2930 or placebo in a double-blind fashion via an Interactive Web-based Randomization System (IWRS). Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

4.4 Blinding

Subjects will be randomized to receive 300 mg DX-2930 every 2 weeks, 300 mg DX-2930 every 4 weeks, 150 mg DX-2930 every 4 weeks or placebo every 2 weeks in a double-blind fashion. The appearance of the placebo will be indistinguishable from DX-2390. Subjects, caregivers for subjects under 18 years of age, Investigators and site personnel will be blinded to the treatment administered until the study is complete. The Sponsor will be blinded to the treatment administered until all subject involvement in the treatment period is complete, the database has locked, and primary statistical analyses have been conducted.

An Unblinded Data Team Charter will be developed to document which roles will have access to which data and their responsibilities. The Unblinded Data Team is independent from the blinded study team and is not involved in the day-to-day conduct of the study.

4.5 Sample Size Determination

Power analysis and sample size estimation was based on 1000 computer simulations using a generalized linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

For a treatment effect of 60% reduction in attacks as compared to placebo, assuming a placebo attack rate of 0.3 attacks per week over a 26 week period for an average total of 7.8 attacks during the treatment period, a sample size of 24 actively treated subjects for the primary active treatment arm and 36 placebo subjects would provide at least 95% power (at alpha=0.025, one-sided). A 60% reduction is well below the smallest expected reduction in attacks, for in the DX-2930-02 study, we observed reductions of attacks of near 100%. These sample sizes will also provide adequately sized safety population for evaluation. Up to 120 subjects (approximately 80 subjects in the 3 active treatment groups and 40 in the placebo group) may be enrolled to account for potential early drop-outs during the study.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

- Number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182).

5.1.2 Secondary Efficacy Endpoints

- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period.
- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period.

5.1.3 Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14.
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period.
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit and/or admission to hospital during the Treatment Period.
- Achievement of a reduction from the baseline in the investigator-confirmed HAE attack rate (i.e., responder analysis).
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location, and medication use.
- Percentage of attack free days.

5.2 Safety Endpoints

The safety and tolerability of DX-2390 will be evaluated through the assessment of adverse events, clinical laboratory testing, vital sign measurements, electrocardiogram (ECG) recordings, concomitant medications and physical examination findings.

5.3 Other Endpoints

Additional endpoints of interest in this study are the plasma concentration of DX-2930, pharmacodynamic biomarker assays, anti-drug antibodies and quality of life data as collected with the EuroQoL Group 5-Dimension (EQ5D) Questionnaire and the Angioedema Quality of Life (AE-QoL) Questionnaire.

6. EFFICACY AND SAFETY VARIABLES

6.1 Study Activities Schedule

Please refer to Appendix 10.4 for details of assessments performed at each visit.

6.2 Efficacy Assessments

The collection, reporting and assessment of attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP). Site personnel will be trained on HAARP prior to screening subjects at their site.

During the study, subjects (or caregivers, in the event the subject is < 18 years old) will be instructed to notify and report details of an attack to the study site within 72 hours of the onset of an HAE attack. In the event that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subjects experience. Weekly communication between the subjects and the site personnel, including reports of HAE attacks must be documented in the electronic case report form (eCRF).

Subjects (or caregivers) will be asked to provide the following information when reporting an attack:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Site personnel will review the information provided and solicit additional information as necessary to document the attack, as described in HAARP.

Sites personal will also record the severity of the attack, if the attack required acute treatment, if the attack resulted in an emergency department visit or hospitalization, if the attack was hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) and whether the attack was peripheral, abdominal or laryngeal.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to the Sponsor using the SAE Reporting Form in the electronic data capture (EDC) system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with

HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and investigator-confirmed HAE attacks will be recorded in the eCRF.

Emergency department visits for HAE attacks and HAE attacks resulting in hospital admissions will be captured.

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region.
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea.
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

6.3 Safety Assessments

6.3.1 Adverse Events

Adverse events will be collected from signing of the informed consent through the last study visit. For a detailed definition on AEs, Serious AEs (SAEs), severity of AEs, and relatedness of AEs and SAEs, please refer to the protocol.

An AE is treatment-emergent if the onset time is after first administration of IMP or, in the event that onset time precedes first IMP administration, the AE increases in severity after first administration of IMP.

In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) and the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

- GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required
- GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Any treatment-emergent ECG abnormality that is considered by the Investigator as clinically significant and requiring intervention/therapy will be assessed as a severe AE.

The causal relationship between the study IMP and the AE will be assessed as Not Related or Related.

6.3.1.1 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be captured and monitored during this study. AESI include hypersensitivity reactions and events of disordered coagulation.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

Events of Disordered Coagulation

Bleeding AESI

Although aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon, as a precautionary measure in evaluating the safety of DX-2930, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (aPTT, PT, INR) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a thrombotic or embolic etiology.

6.3.2 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 10.4). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ±15 minute window for all vital signs.

At study visits in which IMP is administered, vital signs will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

6.3.3 Physical Examination

A physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 10.4). Height and weight will be collected at the screening visit only.

6.3.4 Electrocardiogram (ECG)

A standard 12-lead ECG (single recording) will be performed at screening, baseline prior to Dose 1, Day 56, and Day 144±1 day (to capture the estimated C_{max}), and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site. For subjects that do not rollover into OLE (DX-2930-04), an ECG will be performed on Day 238. The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.3.5 Clinical Laboratories

Laboratory testing will be performed according to the Study Activities Schedule (Appendix 10.4).

Laboratory testing includes general safety parameters (hematology, coagulation, urinalysis, and serum chemistry), serology, pregnancy tests, C1-INH functional assay, C4 assay, C1q assay, PK samples, PD samples, and plasma anti-drug antibody testing. All laboratory tests will be performed using established and validated methods.

6.3.5.1 Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

6.3.5.2 Coagulation

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- International Normalized Ratio (INR)

6.3.5.3 Chemistry

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Blood urea nitrogen (BUN)
- Calcium
- Carbon dioxide (CO2)
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Glucose
- Phosphate
- Magnesium
- Potassium
- Sodium
- Total protein
- Uric acid

6.3.5.4 Urinalysis

- Bilirubin
- Glucose
- Ketones
- Blood

- Nitrite
- pH
- Protein
- Specific gravity
- Microscopy (if indicated by macroscopic findings)

6.3.6 Concomitant Therapies

The Sponsor representatives and Investigator at the site conducting the trial will review and evaluate prior and concomitant medication usage on an ongoing basis. All prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from the time of screening through the duration of the study will be regarded as concomitant medications and must be documented in the source documents and eCRF.

6.4 Other Assessments

6.4.1 Pharmacokinetic Assessment

Blood samples for the measurement of plasma DX-2930 concentration will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.4.2 Pharmacodynamic Assessment

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.4.3 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 238±3 during the follow-up period for any subjects not entering OLE.

6.4.4 Quality of Life Assessments

Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using Angioedema Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28 ±3, 56 ±3, 98±3, 126 ±3, 154 ±3, and 182±3. An additional quality of life assessment will be conducted on Day 238±3 for subjects not entering OLE.

ED-5D-5L

The EQ-5D-5L consists of 2 parts: descriptive questions and a visual analog scale (VAS). The descriptive questions comprise 5 dimensions: Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Each dimension is divided into 5 levels of perceived problems: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the subject's self-rated health on a 20-cm vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine".

AE-QoL

The AE-QoL consists of 4 domains (functioning, fatigue/mood, fears/shame and nutrition) and 17 questions. Details of how to compute scores for the domains and the total score are included in Appendix 10.2.14.

7. STATISTICAL ANALYSIS

7.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, PPD, PPD, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group (DX-2930 300 mg every 2 weeks, DX-2930 300 mg every 4 weeks, DX-2930 150 mg every 4 weeks, and Placebo). All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CI) for least squares mean treatment differences will be provided. Time-to-event data will be summarized using Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI, as well as percentage of censored observations. Plots of the KM curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal statistical hypothesis testing will be performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure as described in Section 9.5.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. P-values will be rounded to 3 decimal places, p-values <0.0005 will be displayed as <0.001.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of subjects for that treatment group within the population of interest, unless otherwise specified.

See Section 10.2 for detailed descriptions of analysis definitions and programming conventions.

7.2 Analysis Populations

The analysis populations will be defined as follows:

7.2.1 Intent-to-treat (ITT) Population

The ITT Population will include all randomized subjects who received any study drug. The primary efficacy analyses will be carried out with the ITT Population. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

7.2.2 Safety Population

The Safety Population will include all subjects who received any study drug. All safety analyses will use the Safety Population. Subjects will be analyzed according to the treatment actually received, regardless of the treatment assigned.

7.3 Subject Disposition

The number of subjects screened, randomized, treated with study drug, completed the study and discontinued prematurely by reason will be summarized overall and by randomized treatment assignment for all subjects. For each analysis population, the number of subjects included in the population, completing the study and those that discontinued prematurely by reason, will be summarized by treatment group, overall DX-2930, and overall. Listings of all disposition data will be provided.

7.4 Protocol Deviations

Protocol deviations will be collected at both the site and subject level.

Deviations at the site level will be applied to all subjects who were enrolled at that site at the time of the deviation. Deviation types for site level deviations are: Use of incorrect equipment, use of incorrect forms, use of expired laboratory samples, use of equipment with expired maintenance, study procedure completed by non-authorized personnel, site personnel did not complete training prior to completing study procedure, amendment implementation without approval/notification or IRB/EC, temperature excursion for IP and other.

Deviation types for subject level deviations are: eligibility criteria, informed consent/assent/HIPAA, concomitant medication, investigational product, study visit (missed/out of window), study procedure (missed/out of window), site personnel/assessor error, randomization, safety reporting, IRB/EC reporting, EQ-5D, Angioedema Quality of Life, lab collection, and other (not otherwise defined).

Summary tables of protocol deviation type by treatment group, overall DX-2930, and overall will be provided for the ITT Population. All protocol deviations will be included in a subject listing.

7.5 Demographic and Other Baseline Characteristics

Baseline and demographic variables will be descriptively summarized by treatment group, overall DX-2930, and overall for each analysis population.

Demographic variables to be presented include age (years), age category (<18, 18 to <40, 40 to <65, ≥65 years), sex (male, female), ethnicity (Hispanic, Non-Hispanic), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other), race group (White, Other) geographical region (US, Canada, Europe and Jordan), height (cm), weight (kg), weight group (<50, 50 to <75, 75 to <100, ≥100 kg), BMI (kg/m^2) and BMI group (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2).

A separate table will be created for baseline characteristics and will include age at onset of angioedema symptoms, HAE type (Type I, Type II, Unspecified), history of laryngeal attacks, primary attack locations, number of attacks in the last 1, 3, and 12 months, baseline HAE attack rate (attacks/4 weeks) and baseline HAE attack rate strata (1 to <2, 2 to <3, ≥3 attacks/4 weeks). All baseline and demographic data will be presented in subject listings.

7.6 Medical History

Medical history will be coded using Medical Dictionary for regulatory Activities (MedDRA) version 18.1 and summarized by system organ class (SOC) and preferred term (PT) by treatment group, overall DX-2930 and overall for each analysis population. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency. All medical history will be presented in subject listings.

7.7 Treatment Compliance and Extent of Exposure

All planned study drug administrations will be recorded in the case report form, including whether a full, partial, or no dose was given; date and time of dose; and location of the injection. Regardless of treatment assignment, all subjects are to receive two injections of blinded study drug given in the same upper arm, with at least 2 cm separation between each injection site.

It is anticipated that all subjects will be compliant with treatment because the study drug will be administered by qualified site personnel. Treatment compliance and the extent of exposure will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects that received at least 80% of planned doses, summarized by treatment group for each analysis population. Listings of study administrations by subject will also be provided.

7.8 Analysis of Efficacy

All efficacy analyses will be performed on the ITT Population.

7.8.1 Primary Efficacy Analysis

The primary efficacy endpoint, number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182), will be compared for each active treatment group

(DX-2930) to the placebo group using a generalized linear model (GLM) for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model. See Section 10.2.9.1 for the calculation of the normalized baseline attack rate.

From this model, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group will be estimated. These estimates will be reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \lambda_{DX\text{-}2930} / \lambda_{placebo} = 1 \text{ versus } H_1: \lambda_{DX\text{-}2930} / \lambda_{placebo} \neq 1$$

$\lambda_{DX\text{-}2930}$ refers to the mean investigator-confirmed HAE attack rate in the DX-2930 group and $\lambda_{Placebo}$ refers to the mean investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of investigator-confirmed HAE attacks during the treatment period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage difference in mean investigator-confirmed HAE attack rate of each active treatment group from the attack rate of placebo will be calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

In order to maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure will be used for the comparisons of each of the active treatment groups with the placebo group with equal weights for each test set at 1.67% significance level ($\alpha/3$). See Section 9.5 for more information.

Unadjusted monthly investigator-confirmed HAE attack rates will be calculated for the pretreatment, run-in and treatment periods. See Section 10.2.9 for details. The pretreatment period, run-in period, treatment period, treatment period change from baseline, and treatment period change from run-in period in the monthly investigator-confirmed HAE attack rate will be summarized by treatment group. This summary will include the total number of investigator-confirmed HAE attacks reported and the subject-time in months each subject contributed to the pretreatment, run-in period, and treatment period. Figures by treatment group (one for each

treatment group) plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to randomization for each subject will be created.

In addition to the data summaries for the primary analysis of the primary efficacy endpoint described above, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized descriptively by month (per 28 day interval) and treatment group. The summary will include the number, change from pretreatment, and percent change from pretreatment of investigator-confirmed HAE attacks. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. The date of the first exposure to study drug will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later. See Section 10.2.6.1 for the definition of the pretreatment period.

All HAE attacks will be presented in listings.

7.8.2 Secondary Efficacy Analyses

The rank ordered secondary efficacy endpoints are as follows:

1. Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period.
2. Number of moderate or severe investigator-confirmed HAE attacks during the treatment period.

The secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

To adjust for the potential of inflated overall type-I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant. See Section 9.5 for more information.

7.8.3 Exploratory Efficacy Analyses

Exploratory analyses will include data summaries for the following:

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack free after Day 14
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period.
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital.
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit.
- Number of investigator-confirmed HAE attacks resulting in admission to the hospital.

- Achievement of a reduction from pretreatment in the investigator-confirmed HAE attack rate (i.e., responder analysis).
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, and rescue mediation use.
- Percentage of attack free days

The exploratory efficacy endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment effect.

Time to first HAE attack after Day 14

The time to first HAE attack (days) will be calculated from the date of Day 14 visit to the date of the first attack after Day 14 visit. Subjects who do not have an attack will be censored at the date of discontinuation or completion of the study (Day 182 for subjects who do not roll-over into the OLE). Time to the first HAE attack after Day 14 will be summarized using Kaplan-Meier methods. A log-rank test comparing each active treatment group to the placebo group will be included.

Number of high-morbidity investigator-confirmed HAE attacks

A high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal. If the length of hospitalization can't be determined due to missing dates and times, then that hospitalization will be conservatively counted as being greater than 24 hours. The number of high-morbidity investigator-confirmed HAE attacks during the treatment period will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital

For each HAE attack, the site records if the attack resulted in a visit to the emergency department or admission to the hospital. The number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed HAE attacks resulting in an emergency department visit

For each HAE attack, the site records if the attack resulted in a visit to the emergency department. The number of investigator-confirmed HAE attacks resulting in an emergency department visit during the treatment period will be analyzed using the same method as for the

primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed HAE attacks resulting in admission to the hospital

For each HAE attack, the site records if the attack resulted in hospitalization. The number of investigator-confirmed HAE attacks resulting in admission to the hospital during the treatment period will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Achievement of reduction from pretreatment in the investigator-confirmed HAE attack rate (i.e., responder analysis)

There will be five classes of responders based on percent reduction in the investigator-confirmed HAE attack rate from the pretreatment attack rate: 50% or more reduction, 60% or more reduction, 70% or more reduction, 80% or more reduction and 90% or more reduction. For each subject, a treatment period HAE attack rate and pretreatment HAE attack rate will be calculated. See Section 10.2.9 for details. The percentage reduction will be calculated as the pretreatment HAE attack rate minus the treatment period HAE attack rate divided by the pretreatment HAE attack rate. Summary statistics will be presented for each of the five classes of responders by treatment. The five classes of responders are nested and not mutually exclusive.

Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location and mediation use

Attack characteristics, as described below, will be summarized by treatment group and overall DX-2930 for the pretreatment period and treatment period.

HAE Attack Duration

For each subject, the mean, minimum and maximum duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. See Section 10.2.7.1 for details. The subject-level average attack duration will be categorized into 12 hour intervals and tabulated by category (<12 hours, 12-24 hours, >24-48 hours, and >48 hours).

HAE Attack Severity

For each subject, the mean and maximum severity of all investigator-confirmed HAE attacks will be calculated using a numerical rating and summarized. See Section 10.2.7.2 for details. The number and percentage of subjects, as well as the number of events, will be tabulated by attack severity (mild, moderate, and severe).

HAE Attack Location

The number and percentage of subjects with attacks, as well as the number of events, will be tabulated by attack location (peripheral, abdominal, and laryngeal).

Rescue Medication Use

The number and percentage of subjects with rescue medication use for an HAE attack, as well as the number of events, will be tabulated by rescue medication by type (ecallantide, icatibant, nano-filtered C1-INH, plasma-derived C1-INH, recombinant C1-INH, fresh frozen plasma, and other).

Supportive Treatment Use

The number and percentage of subjects with supportive treatment use for an HAE attack, as well as the number of events, will be tabulated by supportive treatment by type (IV fluids, pain medication, oxygen, anti-emetic, and other).

Percentage of HAE attack free days

The percentage of HAE attack free days will be calculated by counting the number of days in the treatment period without an HAE attack and dividing by the number of days the subject was in the treatment period. If an HAE attack was 8 hours or less on a particular day that day will be considered attack-free. Summaries of the percentage of HAE attack free days will be provided by treatment group.

7.9 Analysis of Safety

All safety analyses will be performed on the Safety Population. No inferential statistics are planned.

7.9.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary version 18.1.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

The analyses described in this section will be based on treatment-emergent AEs; plainly referred to as AEs in this section for brevity.

Related AEs are AEs classified as related to study drug by the investigator. Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

For this analysis, AEs will be classified to one of three analysis periods:

- *Pretreatment Period AEs* will include AEs starting at or after informed consent to those starting before the first exposure to study drug (AEs starting prior to treatment on Day 0).

- *Treatment Period AEs* will include all AEs starting at or after the first exposure to study drug to those starting before or at the subject's last visit date during the treatment period (AEs starting at or after treatment on Day 0 to the Day 182 visit).

- *Follow-up Period AEs* will include all AEs starting at or after the subject's last visit date of the treatment period (AEs starting after the Day 182 visit).

For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

The number and percentage of subjects with any AE, any related AE, any SAE, any related SAE, any severe AE, and any related severe AE will as well as the total number of events for each category will be summarized by treatment group. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized by treatment group and overall DX-2930. This tabulation will be repeated for each of the analysis periods.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group and overall DX-2930 by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs for treatment period and follow-up period AEs. This tabulation will be repeated for SAEs for pretreatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group and overall DX-2930 by PT for treatment period AEs only. This tabulation will be repeated for related AEs and serious AEs for treatment period AEs. Tabulations will be presented sorted by PT by descending frequency in the overall DX-2930 group and then the placebo group.

All AEs will be provided in subject listings. Listings will be presented separately for each analysis period. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and AEs of special interest (AESIs) will be produced.

Adverse events of special interest (AESI) for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Standardized MedDRA Queries (SMQ) for each AESI will be performed using the study data. The number and percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized for each treatment group and overall DX-2930 by SOC and PT. Separate summary tables will be created for each AESI and for those events with the SMQs classified as related, serious, related serious, severe, and related severe. A listing detailing the PT within the SMQ will be provided.

7.9.2 Clinical Laboratory Evaluation

Laboratory test results will be presented in conventional units.

Baseline is defined as the last non-missing value prior to the first exposure to study drug.

Continuous laboratory test results (serum chemistry, hematology, and urine pH) will be summarized as described below.

Actual values and changes from baseline in clinical laboratory tests for hematology, coagulation, chemistries, and urinalysis will be summarized for each treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis. All laboratory results will be presented in subject listings.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized for each treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Categorical laboratory test results (urinalysis excluding pH) will be summarized for treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the investigator for a subject across study visit to identify any trends.

7.9.3 Vital Signs

Baseline is defined as the last non-missing value prior to the first exposure to study drug.

Actual values and changes from baseline in vital signs will be summarized for each treatment group and DX-2930 overall by study visit and study time point. All vital sign data will be presented in subject listings.

Vital sign values will be classified according to clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a non-clinically significant result and clinically significant result will be summarized for each treatment group and overall DX-2930 by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the result yielding the most severe classification will be selected for analysis. Subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameter that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

7.9.4 Electrocardiography

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG not performed, will be summarized for each treatment group and overall DX-2930 by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

All ECG data will be provided in subject listings.

7.9.5 Physical Examinations

Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant or not performed by the investigator and will be summarized for each treatment group and DX-2930 overall by study visit. Subjects with clinically significant abnormal physical examination findings will be listed. This listing will include all results of the body system that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

All physical examination findings will be provided in subject listings.

7.9.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version 2015 Q3.

Prior medications are defined as medications with start and stop times at or prior to the time of study drug administration.

Concomitant medications are defined as medications with a start times after the time of study drug administration or medications with a start times prior to study drug administration but continuing after treatment.

For medications with partial onset times, non-missing date parts will be used to determine if the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to study drug administration then the medication will be classified as concomitant medication.

The number and percentage of subjects with prior or concomitant medications will be summarized for each treatment group and overall DX-2930 by therapeutic class and preferred term. Therapeutic class will be based on the Therapeutic Subgroup corresponding to level 2 of the Anatomic Therapeutic Chemical (ATC) classification system. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency in the overall DX-2930 group and then the placebo group. A separate similar table will be provided for rescue medications. All medications will be presented in subject listings.

7.10 Other Analyses

Additional analyses of pharmacokinetic (PK) and pharmacodynamic (PD) data will be described in a separate PK/PD report.

Additional analysis of quality of life (QoL) data will be described in a separate QoL report.

7.10.1 Analysis of Pharmacokinetic Data

Plasma concentrations of DX-2930 will be summarized for each treatment group by nominal PK sampling time and listed by subject using the Safety Population.

Plasma concentrations reported as BLQ (below the limit of quantification) of the assay will be reported as zero in the data listings, and BLQ concentrations are treated as zero in the calculation of summary statistics.

7.10.2 Analysis of Pharmacodynamic Data

Plasma kallikrein activity will be summarized for each treatment group by nominal PD sampling time and listed by subject using the Safety Population.

7.10.3 Analysis of Immunogenicity Data

The number and percentage of positive antibodies will be summarized for each treatment group and DX-2930 overall by study visit and overall and listed by subject using the Safety Population.

7.10.4 Analysis of Quality of Life Data

The number and percentage of subjects at each level of the EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) for each treatment group and DX-2930 overall by study visit using the Safety Population. In addition, the VAS score for the subject's self-rated health will be summarized for each treatment group and DX-2930 overall by study visit using the Safety Population.

The responses to the AE-QoL for each item will be tabulated for each treatment group and DX-2930 overall by study visit using the Safety Population. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized for each treatment group and DX-2930 overall by study visit using the Safety Population.

All QoL data will be provided in subject listings.

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

8.1 Changes in the Conduct of the Study

There was no change in the conduct of the study.

8.2 Change from the Analyses Planned in the Protocol

8.2.1 Efficacy Evaluation Period

The phase "Efficacy Evaluation Period" was used in the protocol to describe the time interval for which efficacy would be evaluated and was defined as Day 0 through Day 182. This phase was changed to treatment period for consistency with the Study Activities Schedule. The definition of the duration of the interval remains Day 0 through Day 182.

8.2.2 ITT and Safety Population Definitions

The definition of the ITT Population specified in the protocol stated that the population will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. The definition in the SAP was modified from "at least 1 dose of active IMP or placebo" to "any exposure to study drug". This change was made to clarify that a subject did not need to receive the full dose to be included in this analysis population, but that subjects receiving partial doses would be included.

A similar modification was applied to the definition of the Safety Population.

8.2.3 Adverse Events

The protocol stated that incidence of AEs and rate of study discontinuation among the four treatments arms would be compared, the SAP clarified that this comparison would be based on descriptive statistics.

Additionally, the analysis of the incidence of AEs by month from start of study drug was omitted. Because subjects are repeatedly exposed to study drug on at least a monthly basis, it is not expected that the type or frequency of AE would vary by month.

8.2.4 Laboratory Parameters

The protocol specified that for laboratory parameters the change from screening would be summarized. Instead, a change from baseline will be summarized and a definition of baseline was included in the SAP.

The protocol specified that laboratory parameters would be summarized using shift tables. This summary was omitted and replaced with a summary of results based on reference ranges and clinical significance as determined by the investigator.

8.2.5 Vital Sign Parameters

The protocol specified that for vital sign parameters the change from screening would be summarized. Instead, a change from baseline will be summarized and a definition of baseline was included in the SAP.

9. STATISTICAL/ANALYTIC ISSUES

9.1 Adjustment for covariates

The analysis of the primary and secondary efficacy adjusts for the normalized pretreatment HAE attack rate. No additional covariate adjustment is planned.

9.2 Handling of Dropouts or Missing Data

All available data will be included in the analysis. The length of time a subject was observed during the treatment period will be included as a variable in the generalized linear model to adjust for differences in follow-up time.

9.3 Interim Analysis and Data Monitoring

No interim analyses are planned. However, an independent Data Safety Monitoring Board (DSMB) will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DSMB review will be conducted according to the DSMB Charter and DSMB SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

9.4 Multicenter Studies

Data from all study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

9.5 Multiple Comparisons/Multiplicity

The global family-wise type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 7.8.2) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach with branches for each active treatment group to placebo group comparison will be utilized in which each family of statistical tests will be conducted in a sequential manner. Specifically, a three-branch general gatekeeping procedure with three families of hypotheses will be defined as follows:

Family 1 (F_1): Hypothesis tests for the primary efficacy endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{11}, H_{12}, and H_{13}).

Family 2 (F_2): Hypothesis tests for the first ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{21}, H_{22}, and H_{23}).

Family 3 (F_3): Hypothesis tests for the second ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{31}, H_{32}, and H_{33}).

The 3 sets of hypotheses in F1, F2, and F3 will be tested in a fixed sequence within each active treatment group to placebo group comparison or branch. Testing within a branch will continue in

sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests within the branch.

Within a family, hypotheses will be tested using a conservative Bonferroni-based procedure with equal weights for each test set at 1.67% significance level (α/3). If the null hypothesis for a test is rejected, α will be propagated entirely to the next test in the sequence, which will then be tested at the 1.67% significance level.

To further illustrate this approach, the test for the primary endpoint will be conducted first at the 1.67% significance level for each active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 1.67% significance level. The testing sequence will continue in order through the remaining secondary endpoints for each active treatment group to placebo comparison or branch as long as the null hypothesis is rejected at the 1.67% significance level.

Testing within the last family (F3) will utilize the remaining α by applying the Holm-Bonferroni procedure.

9.6 Examination of Subgroups

Subgroup analyses are planned for the primary efficacy endpoint and adverse events. Any p-values that are presented will be descriptive.

The following subgroups will be used:

- Age Group (<18, 18 to <40, 40 to <65, ≥65 years)
- Sex (Male, Female)
- Race Group (White, Other)
- Weight Group (<50, 50 to <75, 75 to <100, ≥100 kg)
- BMI Group (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m2)
- Run-in Period HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- Pretreatment Period HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- Type of Long-term Prophylactic Therapy Prior to Study Randomization (C1-INH, Androgens, Anti-fibrinolytics, Not on LTP)

The subgroups will be analyzed using the same method as described for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint and the primary analysis of the adverse events.

9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

1. The primary analysis will be repeated using the Safety Population. Subjects will be analyzed according to the treatment actually received. This analysis will only be presented if the Safety Population is different from the ITT Population or if subjects did not receive treatment as randomized.

2. The primary analysis will be repeated counting HAE attacks occurring on Day 14 after administration of study drug through Day 182, instead of Day 0 to Day 182.

3. The primary analysis will be repeated counting HAE attacks occurring on Day 7 after administration of study drug through Day 182, instead of Day 0 to Day 182.

4. The primary analysis will be repeated using all subject reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed.

5. The primary analysis will be repeated using a generalized estimating equations (GEE) analysis method counting HAE attacks occurring on Day 14 after administration of study drug through Day 182 in order to descriptively compare the results from this study with those from DX-2930-02 study. The methods for this analysis are listed below.

   HAE attack rates for each active treatment group will be compared to the placebo group using a mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) for count data (assuming a Poisson distribution with log link function) using GEE. The model will include a fixed effect for treatment (categorical), pretreatment period attack rate (continuous), and a random effect for subject.

   Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. Subject weeks for which completed observation is less than the full 168 hours within a week will be treated as a full week if at least 3 or more days of data were recorded during the week. Weeks with fewer than 3 days will not be included.

   In the event that there are 0 events in one of the treatment groups, a small value of 0.000001 will be added in order to calculate event rates.

Additionally, as applicable, the following sensitivity analyses will be performed on secondary and exploratory efficacy endpoints as detailed in Table 1. Data summaries will parallel those described for the each of the endpoints.

Table 1: Sensitivity Analysis for Secondary and Exploratory Efficacy Endpoints

Secondary and Exploratory Efficacy Endpoint	Sensitivity Analysis Item				
	1	**2**	**3**	**4**	**5**
Number of HAE attacks requiring acute treatment	x	x	x	x	
Number of moderate or severe HAE attacks	x	x	x	x	
Time to first HAE attack	x		x	x	
Number of high-morbidity HAE attacks	x	x	x	x	
Number of HAE attacks resulting in visit to emergency department or admission to the hospital	x	x	x	x	
Number of HAE attacks resulting in visit to emergency department	x	x	x	x	
Number of HAE attacks resulting in admission to the hospital	x	x	x	x	
Responder Analysis	x	x	x	x	
Characteristics of HAE attacks	x	x	x	x	
Percentage of attack-free days	x	x	x	x	

10. APPENDICIES

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10.1.3 List of Planned Listings

Listing No.	Title
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16.2.2	Protocol Deviations
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16.2.8.6	ECGs
16.2.8.7	Immunogenicity
16.2.8.8	Physical Examinations

10.2 Definitions and Programming Conventions

10.2.1 Age

Age will be calculated as the date of birth minus the date of informed consent, truncated to years.

10.2.2 BMI

BMI will be calculated as:

$$BMI = \frac{mass\ (kg)}{height(m)^2}$$

10.2.3 Study Day

The study day is calculated as start or stop date – date of randomization + 1 for dates on or after randomization, or start or stop date – date of randomization for dates prior to randomization.

10.2.4 Durations of Events

The duration of an event is calculated as stop date/time – start date/time if time is not missing, and stop date – start date + 1 if either the start or stop time is missing.

10.2.5 Baseline

Baseline is defined as the last non-missing value prior to first exposure to study drug.

10.2.6 Analysis Periods

10.2.6.1 Pretreatment Period

The pretreatment period is defined as the interval of time that starts at the date/time informed consent is signed and ends prior to the date/time of first exposure to study drug (Day 0 visit).

[*date/time of informed consent*, *date/time of first exposure to study drug*)

10.2.6.2 Run-in Period

The run-in period is defined as the interval of time that starts at the start date for the run-in period and ends on the end date for the run-in period.

[*start date of run-in period*, *end date of run-in period*)

10.2.6.3 Treatment Period

The treatment period is defined as the interval of time that starts on the date/time of first exposure to study drug (Day 0 visit) and ends on the date of Day 182 visit.

[*date/time of first exposure to study drug*, *date of Day 182 visit*]

10.2.6.4 Follow-up Period

The follow-up period is defined as the interval of time that starts on the date of the Day 182 visit + 1 and ends on the date of the subject's last date of contact for the study.

[*date of Day 182 visit + 1*, *date of last study contact*]

10.2.7 HAE Attack Characteristics

10.2.7.1 HAE Attack Duration

The duration of an HAE attack is calculated as stop date/time – start date/time if time is not missing, and stop date – start date + 1 if both the start and stop time is missing. If the attack stop time is not missing but the start time is missing, start time will be imputed as 0:00. If start time is not missing but the end time is missing it will be imputed as 23:59.

10.2.7.2 HAE Attack Severity

The overall severity of the subject's attack will be determined by the site using the following definitions:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance needed
- Severe: Marked limitation in activity, assistance required

To calculate the average attack severity per subject, a numeric value will be attributed to each severity as follows: 1=Mild, 2=Moderate, and 3=Severe. Higher values will indicate more severe attacks, while lower values will indicate less severe attacks.

10.2.8 Unique HAE Attacks

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

That is there must be at least 24 hours between the stop date/ time of the first event and the start date/time of the next event, for attacks to be considered distinct from the previous attack. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be counted as one attack.

10.2.9 HAE Attack Rate

10.2.9.1 Pretreatment HAE Attack Rate

The pretreatment HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of HAE attacks occurring during the pretreatment period divided by the number of days the subject contributed to the pretreatment period multiplied by 28 days.

10.2.9.2 Run-in Period HAE Attack Rate

The run-in period HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as number of HAE attacks occurring during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days.

10.2.9.3 Treatment Period HAE Attack Rate

The treatment period HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of HAE attacks occurring during the treatment period divided by number of days the subject contributed to the treatment period multiplied by 28 days.

10.2.10 Time to First HAE Attack

The time to first HAE attack (days) will be calculated as the earliest of the date of the HAE attack after the Day 14, date of study discontinuation or completion, or date of Day 182 visit for subjects who do not roll-over into the OLE visit minus the date of Day 14 visit plus 1.

Subjects with attacks occurring first will be events. Subjects who discontinue/complete the study or roll-over into the OLE prior to having a post-Day 14 visit HAE attack will be censored.

10.2.11 Adverse Events

10.2.11.1 Treatment-emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

10.2.11.2 Related Adverse Events

Related AEs are AEs classified as related to study drug by the investigator.

10.2.11.3 Severe Adverse Events

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

10.2.12 GLM Model Sample SAS Code

Sample code for the primary efficacy analysis of the primary endpoint.

```
PROC GENMOD DATA=eff_data;
  CLASS trtgrp;
  MODEL no_attks = trtgrp bl_rate / DIST=poisson LINK=log OFFSET=logdays PSCALE;
  LSMEANS trt / DIFF CL EXP ILINK;
  ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1 0 0 -1 / EXP;
  ESTIMATE '300mg every 4 wk vs pbo' trtgrp 0 1 0 -1 / EXP;
  ESTIMATE '150mg every 4 wk vs pbo' trtgrp 0 0 1 -1 / EXP;
RUN;
```

Where:
eff_data = efficacy analysis dataset
trtgrp = treatment group (categorical)
no_attks = number of HAE attacks during the analysis period
bl_rate = normalized pretreatment HAE attack rate (continuous)
logdays = logarithm of time in days each subject was observed during the analysis period

10.2.13 GEE Model Sample SAS Code

Sample code for a sensitivity analysis of the primary endpoint.

```
PROC GENMOD DATA=eff_data;
  CLASS trtgrp subject;
  MODEL no_attks = trtgrp bl_rate / DIST=poisson LINK=log;
  REPEATED SUBJECT=subject / CORR=IND;
  LSMEANS trtgrp / DIFF CL EXP ILINK;
  ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1 0 0 -1 / EXP;
  ESTIMATE '300mg every 4 wk vs pbo' trtgrp 0 1 0 -1 / EXP;
  ESTIMATE '150mg every 4 wk vs pbo' trtgrp 0 0 1 -1 / EXP;
RUN;
```

Where:
eff_data = efficacy analysis dataset
trtgrp = treatment group (categorical)
no_attks = number of HAE attacks per week
bl_rate = normalized pretreatment HAE attack rate (continuous)

10.2.14 Angioedema Quality of Life

Below are instructions for how to calculate AE-QoL domain scores and total score.

AE-QoL is meant to be evaluated by determining its four individual domain scores (profile instrument), but it may also be used to determine a total score (index instrument).

Each item answered by the subject scores between 0 and 4 points depending on the answer option chosen by the subject. The first answer option gets 0 points, the second option 1 point, the

third option 2 points, etc. The AE-QoL domain scores and total score are calculated by using the following formula:

(Sum of all completed items) / (maximum sum of all possible items)*100

Computation of AE-QoL Total Score
Example 1: All items were completed (maximum possible sum: 68 points)
Sum of all 17 completed items: 41 points.
Total score = 100*(41/68) = 60 (out of a possible 100 points)

Example 2: 2 items were not completed (maximum possible sum: 60 points).
Sum of all 15 completed items: 41 points.
Total score = 100*(41/60) = 68 (out of a possible 100 points)

Computation of Domain Scores (Example: Fears/Shame)
Example: Sum of all 6 completed items: 14 points
Maximum possible sum: 24 points
Domain Score = 100*(14/24) = 58 (out of a possible 100 points)

Remarks
Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0-to-100 scale), the calculated scores are not or only little influenced by missing items.

An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.

The minimal and highest possible domain and total scores are 0 and 100, respectively.

References
Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, Metz M, Staubach P, Maurer M. Development and construct validation of the angioedema quality of life questionnaire. Allergy. 2012; 67(10): 1289-98.

10.3 Treatment Period Dosing Schedule

Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/ Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/ Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/ Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/ Week 4	DX-2930	DX-2930	DX-2930	Placebo
4	Day 42/ Week 6	DX-2930	Placebo	Placebo	Placebo
5	Day 56/ Week 8	DX-2930	DX-2930	DX-2930	Placebo
6	Day 70/ Week 10	DX-2930	Placebo	Placebo	Placebo
7	Day 84/ Week 12	DX-2930	DX-2930	DX-2930	Placebo
8	Day 98/ Week 14	DX-2930	Placebo	Placebo	Placebo
9	Day 112/ Week 16	DX-2930	DX-2930	DX-2930	Placebo
10	Day 126/ Week 18	DX-2930	Placebo	Placebo	Placebo
11	Day 140/ Week 20	DX-2930	DX-2930	DX-2930	Placebo
12	Day 154/ Week 22	DX-2930	Placebo	Placebo	Placebo
13	Day 168/ Week 24	DX-2930	DX-2930	DX-2930	Placebo
--	Day 182/ Week 26	No Dose	No Dose	No Dose	No Dose

10.4 Study Activity Schedule

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
Informed Consent	X																
Eligibility Review	X		X														
Long-term prophylactic therapy washout[5]	X																
Randomization			X														
Blinded IMP Treatment			X		X	X	X	X	X	X	X	X		X			
Demographic and Medical History	X																
C1-INH, C1q and C4 Testing[6]	X																
Pregnancy Test[7] (females)	X		X			X		X		X	X			X	X		X
Vital Signs[8]	X		X		X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination[9]	X		X			X		X		X		X			X		X
12-Lead ECG[10]	X		X					X					X		X		
Clinical Laboratory Testing[11]	X		X			X		X		X		X			X		X
Serologies: HBsAg, HCV, and HIV	X																
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

Study Activities Schedule

	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
HAE Attack Data[12]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Quality of Life Assessments[13]			X			X		X		X	X			X	X		X
PK Blood Sampling			X					X		X		X			X	X	X
PD Sample Collection			X					X		X		X			X	X	X
Plasma Anti-Drug Antibody Testing			X					X		X		X			X		X
Discharge from Study[14,15]															X		X

ECG = Electrocardiogram; PK = Pharmacokinetic; PD = Pharmacodynamic; IMP = Investigational Medicinal Product

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum or urine-based.
8. There is a ± 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema-Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28 ±3, 56 ±3, 98±3, 126 ±3, 154 ±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

STATISTICAL ANALYSIS PLAN

Protocol Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 for Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Protocol Number:	DX-2930-03
Protocol Version/Date:	Amendment 3.0 09 January 2017
Indication:	Prevention of angioedema attacks in subjects with HAE
Study Phase	III
SAP Analysis Type	Final Analysis
SAP Version/Date	Original SAP 24 May 2016 Amendment 1.0 03 May 2017

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1. LIST OF ABBREVIATIONS

AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1-inhibitor
CI	Confidence interval
cHMWK	Cleaved High Molecular Weight Kininnogen
CO2	Carbon dioxide
CPK	Creatine phosphokinase
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EQ5D	EuroQoL Group 5-Dimension
eCRF	Electronic case report form
EDC	Electronic data capture
FWER	Family-wise type I error rate
GEE	Generalized estimating equations
GLM	Generalized linear model
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	Hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web-based randomization system
KM	Kaplan-Meier

LS	Least squares
LTP	Long-term prophylaxis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
PT	Preferred term
QOL	Quality of life
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is being developed after review of DX-2930-03 protocol, but before database lock and unblinding of treatment assignment. This SAP contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be used for analysis, as well as subject characteristics, efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), and quality of life (QoL) parameters. The details of the specific statistical methods as stated in the protocol will be provided and any changes from the protocol-specified analyses will be documented in the SAP prior to database lock. If additional analyses are required to supplement the planned analyses described in this SAP after the database lock, they may be completed and will be described in the CSR. Table, figure, and listing specifications are provided in separate documents.

2.2 Background

DX-2390-03 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the safety and efficacy of DX-2930 as a treatment for the prevention of hereditary angioedema (HAE) attacks. Details of the study design, rationale, and procedures are documented in Protocol DX-2390-03 Amendment 3.0.

2.3 Study Rationale

DX-2930 is a fully human IgG1 recombinant monoclonal antibody that binds specifically to active plasma kallikrein. DX-2930 is being developed for prophylactic treatment of angioedema attacks in patients with HAE, a serious and life-threatening disease.

3. STUDY OBJECTIVES

3.1 Primary Objectives

To evaluate the efficacy of DX-2930 in preventing HAE attacks.

3.2 Secondary Objectives

To evaluate the safety of repeated subcutaneous administrations of DX-2930.

3.3 Tertiary Objectives

- To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930
- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the pharmacokinetics (PK) of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health related quality of life (QoL)

4. STUDY DESIGN

4.1 General Description

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in subjects with Type I and Type II HAE. This double-blind study is planned to be followed by an open-label extension (OLE) that is described in a separate protocol (Protocol DX-2930-04).

A table showing dosing is in Appendix 10.4. A table showing the Study Activities Schedule for the study is provided in Appendix 10.5.

Long-Term Prophylactic (LTP) Therapy Washout:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm the subject has successfully completed the 2-week washout period before they can enter the run-in period.

Run-In Period:

Screened subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. Only subjects meeting a minimum baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered screen failures. Subjects who fail screening will not be allowed to rescreen into the study.

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through

two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in Appendix 10.4.

Open-Label Extension (OLE) Study:

Subjects who complete the treatment period will be offered the option of enrolling in an open-label extension (OLE) study that will be described in a separate protocol (DX-2930-04).

Follow-up Period:

Subjects who do not participate in the OLE will undergo safety and additional evaluations (i.e., PK and PD) during an 8 week follow-up period. Subjects (or caregivers) will be instructed to inform the site of any HAE attacks they experience for up to 30 days after the final follow-up visit.

4.2 Discussion of Study Design, Including the Choice of Control Group

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in subjects with Type I and Type II HAE. The following is a discussion of the rationale behind the design of the trial.

- **Primary endpoint selection**: The objective of this study is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The number of HAE attacks is a direct way to evaluate efficacy.

- **Dose selection:** The dose rationale is based on the pharmacodynamic bioactivity, PK, safety, and efficacy of DX-2930 from the Phase 1 clinical studies and nonclinical studies. Together, these attributes provide the rationale for the selected doses and regimens to achieve drug levels likely to prevent a majority of HAE attacks. Based on these considerations, 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks were identified as the dosing regimens for evaluation. The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930-treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

- **Control group selection:** This trial incorporates a placebo comparator to evaluate and interpret the efficacy of DX-2930. The use of placebo is justified because 1) placebo does not represent a reduction in current standard of care for subjects due to the availability of acute attack treatments and 2) none of the therapies currently used for the prevention of HAE attacks are suitable for use as an active comparator.

- **Study population:** Subjects 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

- **Baseline symptom severity:** To be eligible to participate in the study, subjects had to meet a minimum baseline HAE attack rate of at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period.

- **Stratified randomization:** Randomization to treatment is stratified by the baseline HAE attack rate observed during the run-in period. The three levels of HAE attack rate strata are 1-<2 attacks per 4 weeks, 2-<3 attacks per 4 weeks and 3 or more attacks per 4 weeks.

- **Safety monitoring:** Adverse events (AE), clinical laboratories and vital signs will be monitored throughout the study.

4.3 Method of Assigning Subjects to Treatment Regimens

Subjects will be randomized after confirmation of study eligibility in a 2:1 ratio to receive repeated SC administrations of DX-2930 or placebo in a double-blind fashion via an Interactive Web-based Randomization System (IWRS). Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

4.4 Blinding

Subjects will be randomized to receive 300 mg DX-2930 every 2 weeks, 300 mg DX-2930 every 4 weeks, 150 mg DX-2930 every 4 weeks or placebo every 2 weeks in a double-blind fashion. The appearance of the placebo will be indistinguishable from DX-2390. Subjects, caregivers for subjects under 18 years of age, Investigators and site personnel will be blinded to the treatment administered until the study is complete. The Sponsor will be blinded to the treatment administered until all subject involvement in the treatment period is complete, the database has locked, and primary statistical analyses have been conducted.

An Unblinded Data Team Charter will be developed to document which roles will have access to which data and their responsibilities. The Unblinded Data Team is independent from the blinded study team and is not involved in the day-to-day conduct of the study.

4.5 Sample Size Determination

Power analysis and sample size estimation was based on 1000 computer simulations using a generalized linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

For a treatment effect of 60% reduction in attacks as compared to placebo, assuming a placebo attack rate of 0.3 attacks per week over a 26 week period for an average total of 7.8 attacks during the treatment period, a sample size of 24 actively treated subjects for the primary active treatment arm and 36 placebo subjects would provide at least 95% power (at alpha=0.025, one-sided). A 60% reduction is well below the smallest expected reduction in attacks, for in the DX-2930-02 study, we observed reductions of attacks of near 100%. These sample sizes will also provide adequately sized safety population for evaluation. Up to 120 subjects (approximately 80 subjects in the 3 active treatment groups and 40 in the placebo group) may be enrolled to account for potential early drop-outs during the study.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

Primary and secondary efficacy endpoints will be based on the treatment period spanning Day 0 (after study drug administration) through Day 182, unless otherwise specified.

5.1.1 Primary Efficacy Endpoint

- Number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)

5.1.2 Secondary Efficacy Endpoints

- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182)
- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)
- Number of Investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

5.1.3 Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit and/or admission to hospital during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 through Day 182)
- Achievement of a pre-specified reduction from the run-in period in the investigator-confirmed HAE attack rate (i.e., responder analysis) during the treatment period (Day 0 through Day 182).
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location, and medication use during the run-in period and treatment period (Day 0 through Day 182)
- Percentage of attack free days during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 visit during the treatment period (Day 0 through Day 182)

- Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 visit after Day 14 (Day 14 through Day 182)

5.2 Safety Endpoints

The safety and tolerability of DX-2390 will be evaluated through the assessment of adverse events, clinical laboratory testing, vital sign measurements, electrocardiogram (ECG) recordings, concomitant medications and physical examination findings.

5.3 Other Endpoints

Additional endpoints of interest in this study are the plasma concentration of DX-2930, pharmacodynamic biomarker assays, anti-drug antibodies and quality of life data as collected with the EuroQoL Group 5-Dimension (EQ5D) Questionnaire and the Angioedema Quality of Life (AE-QoL) Questionnaire.

6. EFFICACY AND SAFETY VARIABLES

6.1 Study Activities Schedule

Please refer to Appendix 10.5 for details of assessments performed at each visit.

6.2 Efficacy Assessments

The collection, reporting and assessment of attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP). Site personnel will be trained on HAARP prior to screening subjects at their site.

During the study, subjects (or caregivers, in the event the subject is < 18 years old) will be instructed to notify and report details of an attack to the study site within 72 hours of the onset of an HAE attack. In the event that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subjects experience. Weekly communication between the subjects and the site personnel, including reports of HAE attacks must be documented in the electronic case report form (eCRF).

Subjects (or caregivers) will be asked to provide the following information when reporting an attack:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Site personnel will review the information provided and solicit additional information as necessary to document the attack, as described in HAARP.

Sites personal will also record the severity of the attack, if the attack required acute treatment, if the attack resulted in an emergency department visit or hospitalization, if the attack was hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) and whether the attack was peripheral, abdominal or laryngeal.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to the Sponsor using the SAE Reporting Form in the electronic data capture (EDC) system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with

HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and investigator-confirmed HAE attacks will be recorded in the eCRF.

Emergency department visits for HAE attacks and HAE attacks resulting in hospital admissions will be captured.

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region.
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea.
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

6.3 Safety Assessments

6.3.1 Adverse Events

Adverse events will be collected from signing of the informed consent through the last study visit. For a detailed definition on AEs, Serious AEs (SAEs), severity of AEs, and relatedness of AEs and SAEs, please refer to the protocol.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.
In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) and the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases). For

abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

- GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required
- GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Any treatment-emergent ECG abnormality that is considered by the Investigator as clinically significant and requiring intervention/therapy will be assessed as a severe AE.

The causal relationship between the study IMP and the AE will be assessed as Not Related or Related.

6.3.1.1 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be captured and monitored during this study. AESI include hypersensitivity reactions and events of disordered coagulation.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

Events of Disordered Coagulation

Bleeding AESI

Although aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon, as a precautionary measure in evaluating the safety of DX-2930, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (aPTT, PT, INR) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a thrombotic or embolic etiology.

6.3.2 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 10.5). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ±15 minute window for all vital signs.

At study visits in which IMP is administered, vital signs will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

6.3.3 Physical Examination

A physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 10.5). Height and weight will be collected at the screening visit only.

6.3.4 Electrocardiogram (ECG)

A standard 12-lead ECG (single recording) will be performed at screening, baseline prior to Dose 1, Day 56, and Day 144±1 day (to capture the estimated C_{max}), and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site. For subjects that do not rollover into OLE (DX-2930-04), an ECG will be performed on Day 238. The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.3.5 Clinical Laboratories

Laboratory testing will be performed according to the Study Activities Schedule (Appendix 10.5).

Laboratory testing includes general safety parameters (hematology, coagulation, urinalysis, and serum chemistry), serology, pregnancy tests, C1-INH functional assay, C4 assay, C1q assay, PK samples, PD samples, and plasma anti-drug antibody testing. All laboratory tests will be performed using established and validated methods.

6.3.5.1 Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

6.3.5.2 Coagulation

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- International Normalized Ratio (INR)

6.3.5.3 Chemistry

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Blood urea nitrogen (BUN)
- Calcium
- Carbon dioxide (CO2)
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Glucose
- Phosphate
- Magnesium
- Potassium
- Sodium
- Total protein
- Uric acid

6.3.5.4 Urinalysis

- Bilirubin
- Glucose
- Ketones
- Blood

- Nitrite
- pH
- Protein
- Specific gravity
- Microscopy (if indicated by macroscopic findings)

6.3.6 Concomitant Therapies

The Sponsor representatives and Investigator at the site conducting the trial will review and evaluate prior and concomitant medication usage on an ongoing basis. All prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from the time of screening through the duration of the study will be regarded as concomitant medications and must be documented in the source documents and eCRF.

6.4 Other Assessments

6.4.1 Pharmacokinetic Assessment

Blood samples for the measurement of plasma DX-2930 concentration will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.4.2 Pharmacodynamic Assessment

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.4.3 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 238±3 during the follow-up period for any subjects not entering OLE.

6.4.4 Quality of Life Assessments

Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using Angioedema Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28 ±3, 56 ±3, 98±3, 126 ±3, 154 ±3, and 182±3. An additional quality of life assessment will be conducted on Day 238±3 for subjects not entering OLE.

ED-5D-5L

The EQ-5D-5L consists of 2 parts: descriptive questions and a visual analog scale (VAS). The descriptive questions comprise 5 dimensions: Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Each dimension is divided into 5 levels of perceived problems: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the subject's self-rated health on a 20-cm vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine".

AE-QoL

The AE-QoL consists of 4 domains (functioning, fatigue/mood, fears/shame and nutrition) and 17 questions. Details of how to compute scores for the domains and the total score are included in Section 10.3.21.

7. STATISTICAL ANALYSIS

7.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, PPD, PPD, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group (DX-2930 300 mg every 2 weeks, DX-2930 300 mg every 4 weeks, DX-2930 150 mg every 4 weeks, and Placebo). All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, treatment differences, standard errors, p-values, and 95% confidence intervals (CI) for least squares mean treatment differences will be provided. Time-to-event data will be summarized using Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI, as well as percentage of censored observations. Plots of the KM curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal statistical hypothesis testing will be performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure as described in Section 9.5.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. P-values will be rounded to 3 decimal places, p-values <0.0005 will be displayed as <0.001.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of subjects for that treatment group within the population of interest, unless otherwise specified.

See Section 10.3 for detailed descriptions of analysis definitions and programming conventions.

7.2 Analysis Populations

The analysis populations will be defined as follows:

7.2.1 Intent-to-treat (ITT) Population

The ITT population will include all randomized subjects who received any study drug. The primary efficacy analyses will be carried out with the ITT population. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

7.2.2 Safety Population

The Safety population will include all subjects who received any study drug. All safety analyses will use the Safety population. Subjects will be analyzed according to the treatment actually received, regardless of the treatment assigned.

7.3 Subject Disposition

The number of subjects screened, randomized, treated with study drug, treated as randomized, and included in each analysis population will be summarized by randomized treatment assignment, overall DX-2930, and overall for all subjects. This summary will be provided by study site as well. See Section 10.2 for a list of study sites.

For each analysis population, the number of subjects included in the population, completing the study, completing the treatment period (by roll-over status to the long term extension DX-2930-04 study), completing the follow-up period, and those that discontinued prematurely by reason, will be summarized by treatment group, overall DX-2930, and overall for all subjects.

Listings of all disposition data will be provided. A Kaplan-Meier (KM) plot showing the time to withdrawal will be presented by treatment group for the ITT population.

7.4 Protocol Deviations

Protocol deviations will be collected at both the site and subject level.

Deviations at the site level will be applied to all subjects who were enrolled at that site at the time of the deviation. Deviation types for site level deviations are: Use of incorrect equipment, use of incorrect forms, use of expired laboratory samples, use of equipment with expired maintenance, study procedure completed by non-authorized personnel, site personnel did not complete training prior to completing study procedure, amendment implementation without approval/notification or IRB/EC, temperature excursion for IP and other.

Deviation types for subject level deviations are: eligibility criteria, informed consent/assent/HIPAA, concomitant medication, investigational product (IP), study visit (missed/out of window), study procedure (missed/out of window), site personnel/assessor error, randomization, safety reporting, IRB/EC reporting, EQ-5D, Angioedema Quality of Life, lab collection, and other (not otherwise defined).

Summary tables of protocol deviation type by treatment group, overall DX-2930, and overall will be provided for the ITT Population. All protocol deviations will be included in a subject listing.

7.5 Demographic and Other Baseline Characteristics

Baseline and demographic variables will be descriptively summarized by treatment group, overall DX-2930, and overall for each analysis population.

Demographic and baseline characteristic variables to be presented include age (years), age category (<18, 18 to <40, 40 to <65, ≥65 years), sex (male, female), ethnicity (Hispanic, Non-Hispanic), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other), race group (White, Other), geographical region (US, Canada, Europe and Jordan), height (cm), weight (kg), weight group (<50, 50 to <75, 75 to <100, ≥100 kg), BMI (kg/m^2), BMI group for subjects ≥ 18 years of age (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), BMI percentile group for subjects < 18 years of age (Underweight: <5th percentile, Healthy or Overweight: 5th to <95th percentile, Obese: >=95th percentile), long term prophylactic (LTP) therapy use prior to study randomization (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP), and type of LTP therapy prior to study randomization (C1-INH, Oral Therapy, C1-INH and Oral Therapy, Not on LTP).

A separate table will be created for baseline HAE characteristics and will include age at onset of angioedema symptoms, HAE type (Type I, Type II, Unspecified), history of laryngeal attacks, primary attack locations, number of attacks in the last 1, 3, and 12 months, run-in period HAE attack rate (attacks/4 weeks), run-in period HAE attack rate group (1 to <2, 2 to <3, ≥3 attacks/4 weeks) and run-in period HAE attack rate strata (1 to <2, 2 to <3, ≥3 attacks/4 weeks).

All baseline and demographic data will be presented in subject listings.

7.6 Medical History

Medical history will be coded using Medical Dictionary for regulatory Activities (MedDRA) version 20.0 and summarized by system organ class (SOC) and preferred term (PT) by treatment group, overall DX-2930 and overall for each analysis population. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

All medical history will be presented in subject listings.

7.7 Treatment Compliance and Extent of Exposure

All planned study drug administrations will be recorded in the case report form, including whether a full, partial, or no dose was given; date and time of dose; and location of the injection. Regardless of treatment assignment, all subjects are to receive two injections of blinded study drug given in the same upper arm, with at least 2 cm separation between each injection site.

It is anticipated that all subjects will be compliant with treatment because the study drug will be administered by qualified site personnel. Treatment compliance and the extent of exposure will be described by the percentage of planned doses received by the subject, total number of doses

received by the subject, and the number and percentage of subjects that received at least 80% of planned doses, summarized by treatment group for each analysis population. Listings of study administrations by subject will also be provided.

7.8 Analysis of Efficacy

All efficacy analyses will be performed on the ITT population.

7.8.1 Primary Efficacy Analysis

The primary efficacy endpoint, number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182), will be compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model (GLM) for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model. See Section 10.3.10.1 for the calculation of the normalized run-in period attack rate.

From this model, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group will be estimated. These estimates will be reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

$$H_0: \lambda_{DX\text{-}2930} / \lambda_{placebo} = 1 \text{ versus } H_1: \lambda_{DX\text{-}2930} / \lambda_{placebo} \neq 1$$

$\lambda_{DX\text{-}2930}$ refers to the mean investigator-confirmed HAE attack rate in the DX-2930 group and $\lambda_{Placebo}$ refers to the mean investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of investigator-confirmed HAE attacks during the treatment period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage difference in mean investigator-confirmed HAE attack rate of each active treatment group from the attack rate of placebo will be calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

In order to maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure will be used for the comparisons of each of the active treatment groups with the placebo group

with equal weights for each test set at 1.67% significance level (α/3). See Section 9.5 for more information.

Unadjusted monthly investigator-confirmed HAE attack rates will be calculated for the run-in and treatment periods. See Section 10.3.10 for details. The run-in period, treatment period, and treatment period change from run-in period in the monthly investigator-confirmed HAE attack rate will be summarized by treatment group. This summary will include the total number of investigator-confirmed HAE attacks reported and the subject-time in months each subject contributed to the run-in and treatment periods. Figures by treatment group plotting the on-study investigator-confirmed HAE attacks reported during the treatment period with timing relative to randomization for each subject will be created (i.e., "birds on a wire" plots).

In addition to the data summaries for the primary analysis of the primary efficacy endpoint described above, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized descriptively by month (per 28 day interval) and treatment group. The summary will include the monthly investigator-confirmed HAE attack rate, change from run-in period, and percent change from run-in period of investigator-confirmed HAE attack rate. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. The date of the first exposure to study drug will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later. See Section 10.3.7.2 for the definition of the run-in period.

All HAE attacks will be presented in listings.

7.8.2 Secondary Efficacy Analyses

The rank ordered secondary efficacy endpoints are as follows:

1. Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182)
2. Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)
3. Number of Investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

The secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

To adjust for the potential of inflated overall type-I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant. A summary table will be provided to tabulate the statistical testing results for the primary and secondary endpoints, including the rate ratio and its 95% CI,

unadjusted p-value estimated from the Poisson GLM model, and adjusted p-value corrected for multiple comparisons, for each endpoint and each comparison between a DX-2930 treatment group and the placebo group in the multiple testing hierarchy. See Section 9.5 for more information on the multiple testing strategy.

7.8.3 Exploratory Efficacy Analyses

Exploratory analyses will include data summaries for the following:

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack free after Day 14
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in admission to the hospital during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 through Day 182)
- Achievement of a pre-specified reduction from the run-in period in the investigator-confirmed HAE attack rate (i.e., responder analysis) during the treatment period (Day 0 through Day 182)
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, and rescue mediation use during the run-in period and treatment period (Day 0 through Day 182)
- Percentage of attack free days during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed HAE attack-free period of 1 month , 3 months, or until the Day 182 visit during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed HAE attack-free period of 1 month, 3 months, or until the Day 182 visit after Day 14 (Day 14 through Day 182)

The exploratory efficacy endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment effect.

Time to first HAE attack after Day 14

The time to first HAE attack (days) will be calculated from the date of Day 14 visit to the date of the first attack after Day 14 visit. Subjects who do not have an attack will be censored at the date of discontinuation (if prior to completion of the treatment period) or the date of the Day 182 visit. Time to the first HAE attack after Day 14 will be summarized using Kaplan-Meier methods. A log-rank test comparing each active treatment group to the placebo group will be included.

Number of high-morbidity investigator-confirmed HAE attacks during the treatment period

A high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal. If the length of hospitalization can't be determined due to missing dates and times, then that hospitalization will be conservatively counted as being greater than 24 hours. The number of high-morbidity investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period

For each HAE attack, the site records if the attack resulted in a visit to the emergency department or admission to the hospital. The number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed HAE attacks resulting in an emergency department visit during the treatment period

For each HAE attack, the site records if the attack resulted in a visit to the emergency department. The number of investigator-confirmed HAE attacks resulting in an emergency department visit during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed HAE attacks resulting in admission to the hospital during the treatment period

For each HAE attack, the site records if the attack resulted in hospitalization. The number of investigator-confirmed HAE attacks resulting in admission to the hospital during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed laryngeal HAE attacks during the treatment period

For each HAE attack, the investigator records a primary location and up to 3 secondary location(s). In this analysis, a laryngeal HAE attack will be defined as an attack with either the primary or secondary location indicated as laryngeal.

The number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint,

with an addition of the history of laryngeal HAE attacks (categorical) as a fixed effect in the model. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Achievement of a pre-specified reduction from run-in period in the investigator-confirmed HAE attack rate (i.e., responder analysis)

There will be five classes of responders based on pre-specified percentage reduction in the investigator-confirmed HAE attack rate from the run-in period attack rate: 50% or more reduction, 60% or more reduction, 70% or more reduction, 80% or more reduction and 90% or more reduction. For each subject, a treatment period HAE attack rate and run-in period HAE attack rate will be calculated. See Section 10.3.10 for details. The percentage reduction will be calculated as the run-in period HAE attack rate minus the treatment period HAE attack rate divided by the run-in period HAE attack rate. Summary statistics will be presented for each of the five classes of responders by treatment. The five classes of responders are nested within each other and not mutually exclusive.

Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location and mediation use during the run-in and treatment periods

Attack characteristics at subject level and event level, as described below, will be summarized by treatment group and overall DX-2930 for the run-in period and treatment period.

Subject level HAE attack characteristics

HAE Attack Duration

For each subject, the mean duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. See Section 10.3.9 for details on handling HAE attack data. The subject-level average attack duration will be categorized into 12 hour intervals and tabulated by category (<12 hours, 12-24 hours, >24-48 hours, and >48 hours).

HAE Attack Severity

For each subject, the mean and maximum severity of all investigator-confirmed HAE attacks will be calculated using a numerical rating and summarized. See Section 10.3.9.6 for details. The number and percentage of subjects will be tabulated by maximum attack severity (no attacks, mild, moderate, and severe).

Event level HAE attack characteristics

HAE Attack Location

The number and percentage of subjects with attacks, as well as the number of events, will be tabulated by the primary attack location (peripheral, abdominal, and laryngeal) as determined by the investigator. Additionally, the attack location will be re-classified and summarized with an emphasis on the laryngeal attack. In this summary, an attack with either the primary or secondary location(s) identified as laryngeal will be considered as a laryngeal attack; otherwise attacks will be classified by their reported primary attack location.

Rescue Medication Use

The number and percentage of subjects with rescue medication use for an HAE attack, as well as the number of events, will be tabulated by rescue medication by type (ecallantide, icatibant, nano-filtered C1-INH, plasma-derived C1-INH, recombinant C1-INH, fresh frozen plasma, and other) as reported in the AE CRF.

Supportive Treatment Use

The number and percentage of subjects with supportive treatment use for an HAE attack, as well as the number of events, will be tabulated by supportive treatment by type (IV fluids, pain medication, oxygen, anti-emetic, and other) as reported in the AE CRF.

Percentage of HAE attack free days during the treatment period

The percentage of HAE attack free days during the treatment period (Day 0 through Day 182) will be calculated by counting the number of days in the treatment period without an HAE attack and dividing by the number of days the subject was in the treatment period. An attack-free day is defined as a calendar day with no investigator-confirmed HAE attack.

Descriptive statistics for the percentage of HAE attack free days will be summarized by treatment group.

Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 Visit during the treatment period

A subject is considered as attack free during a time period if the subject has no investigator-confirmed HAE attacks during that time period. Subjects who discontinued during a time period are considered as non-responders for that time period.

The number and percentage of subjects who achieve investigator-confirmed HAE attack free intervals of 1 month (4 weeks; 'Day 0 to one day before Day 28 visit'), 3 months (12 weeks; 'Day 0 to one day before Day 70 visit'), or until the Day 182 visit (approximately 6 months or 24 weeks; 'Day 0 to Day 182 visit') during the treatment period will be tabulated by treatment group. Risk difference comparing each active DX-2930 treatment group to the placebo treatment group, and corresponding exact 95% confidence interval (Santner, 1980) will be provided.

Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 Visit after Day 14 during the treatment period

A subject is considered as attack free during a time period if this subject has no investigator-confirmed HAE attacks during that time period. Subjects who discontinued during a time period are considered as a non-responder for that time period.

The number and percentage of subjects who achieve investigator-confirmed HAE attack free intervals of 1 month (4 weeks; 'Day 14 visit to one day before Day 42 visit'), 3 months (12 weeks; 'Day 14 visit to one day before Day 84 visit'), or until the Day 182 visit (approximately 6 months or 24 weeks; 'Day 14 visit to Day 182 visit') after Day 14 during the treatment period will be tabulated by treatment group. Risk differences comparing each active DX-2930 treatment

group to the placebo treatment group, and corresponding exact 95% confidence intervals (Santner, 1980) will be provided.

7.9 Analysis of Safety

All safety analyses will be performed on the safety population. No inferential statistics are planned.

7.9.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary version 20.0.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

The analyses described in this section will be based on treatment-emergent AEs; plainly referred to as AEs in this section for brevity.

Related AEs are AEs classified as related to study drug by the investigator. Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

In this study, the primary endpoint is based on an AE. If DX2930 is efficacious, it will result in a systematic difference in the incidence of AEs by treatment group which will complicate the interpretation of the safety. Thus, the collection of tabulations described in this section (with the exception of the analyses of AEs of special interest (AESI) and injection site reaction (ISR)) will be produced for 2 mutually exclusive subgroups of AEs based on if the AE was identified in EDC as a subject-reported HAE attack or not, and defined as follows:

- Non-HAE Attack Reported AEs will include the subset of AEs identified in EDC as not a reported HAE attack. Essentially, this will be all AEs excluding HAE attack reported events.

- HAE Attack Reported AEs will include the subset of AEs identified in EDC as a reported HAE attack. Note that this includes investigator-confirmed HAE attacks; all investigator-confirmed HAE attacks will be coded to the PT of HAE.

For this analysis, AEs will be classified to one of three analysis periods:

- *Pretreatment Period AEs* will include AEs starting at or after informed consent to those starting before the first exposure to study drug (AEs starting prior to treatment on Day 0).

- *Treatment Period AEs* will include all AEs starting at or after the first exposure to study drug to those starting before or at the subject's last visit date during the treatment period (AEs starting at or after treatment on Day 0 to the Day 182 visit).

- *Follow-up Period AEs* will include all AEs starting at or after the subject's last visit date of the treatment period (AEs starting after the Day 182 visit).

For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

The number and percentage of subjects with any AE, any related AE, any severe AE, any related severe AE, any SAE, and any related SAE, as well as the total number of events for each category, will be summarized by treatment group. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized by treatment group and overall DX-2930. This tabulation will be repeated for each of the analysis periods. For serious AEs and investigator-reported AESI during the treatment period and follow-up period, relative risks and risk differences, and their associated exact 95% CI (Santner, 1980) will be provided for the comparison between each active DX-2930 dose group and the placebo group, and overall DX-2930 group and the placebo group.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group and overall DX-2930 by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, severe AEs, related severe AEs, SAEs, and related SAEs, for treatment period and follow-up period AEs. This tabulation will be repeated for SAEs for pretreatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group. For serious AEs during the treatment period and follow-up period, risk difference and corresponding exact 95% CI (Santner, 1980) will be provided for the comparison between each active DX-2930 dose group and the placebo group, and overall DX-2930 group and the placebo group, by SOC and PT.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group and overall DX-2930 by PT for treatment period AEs only. This tabulation will be repeated for related AEs and severe AEs, for treatment period AEs. Tabulations will be presented sorted by PT by descending frequency in the overall DX-2930 group and then the placebo group.

All AEs will be provided in subject listings. Listings will be presented separately for each analysis period. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, and severe AEs will be produced.

Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Investigators are required to document any potential AESI AEs on the CRF page, and notify the sponsor within 24 hours. These AESI AEs are collectively referred to as investigator-reported AESI.

In addition to investigator-reported AESI, standardized MedDRA Queries (SMQ) for each AESI will be performed using the study data. The algorithm to define SMQ-defined AESI is provided

in Section 10.3.13.5. For SMQ-defined AESI, separate summary tables will be created for AESI categories of hypersensitivity events, hypercoagulable events, and bleeding events.

Investigator-reported AESI and SMQ-defined AESI will be summarized separately, as shown below:

- Summary of AESI: The number and percentage of subjects with any AESI AE, any related AESI AE, any severe AESI AE, any related severe AESI AE, any AESI SAE, and any related AESI SAE, as well as the total number of events for each category, will be summarized by treatment group. The number of deaths due to an AESI AE, hospitalization due to an AESI AE and study discontinuation due to an AESI AE will be summarized by treatment group and overall DX-2930 for each analysis period.

- AESI by SOC and PT: The number and percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized for each treatment group and overall DX-2930 by SOC and PT for each analysis period. Risk difference and corresponding exact 95% CI (Santner, 1980) will be provided for the comparisons between each active DX-2930 dose group and the placebo group, and overall DX-2930 group and the placebo group. This tabulation will be repeated for related AESI for the treatment period and follow-up period AEs. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

- Related AESI by SOC and PT: The number and percentage of subjects with a related AESI, as well as the total number of related AESIs, will be summarized for each treatment group and overall DX-2930 by SOC and PT for the treatment period and follow-up period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

SMQ-defined hypersensitivity AESI during the treatment period include some terms of injection site reactions. It was considered by the Data Safety Monitoring Board (DSMB) that including these terms in the tabulation would take away focus on systemic AESIs. Therefore, tables on SMQ-defined hypersensitivity AESI during the treatment period will be summarized in two ways: a display with all injection site reaction terms (PTs containing ‘Injection site’, ‘Administration site’, or ‘Application site’) included, and a display with all injection site reaction terms excluded.

A listing of investigator-reported AESI will be provided.

Injection Site Reactions (ISR)

ISR AEs were not predefined in the protocol, but instead are identified using the algorithm detailed in Section 10.3.13.6 based on the spontaneous reporting of adverse events.

The number and percentage of subjects with any ISR AE, any related ISR AE, any severe ISR AE, any related severe ISR AE, any ISR SAE, and any related ISR SAE, as well as the total

number of events for each category, will be summarized by treatment group. The number of deaths due to an ISR AE, hospitalization due to an ISR AE and study discontinuation due to an ISR AE will be summarized by treatment group and overall DX-2930. This tabulation will be performed for the treatment period only.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs, will be summarized for each treatment group and overall DX-2930 by SOC, and PT for the treatment period. The number and percentage of subjects with an ISR AE will be summarized for each treatment group and overall DX-2930 by SOC, PT, and maximum severity for the treatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

The duration of ISR AEs overall and by PT will be summarized numerically (summary statistics) and categorically (0 - 0.5 hour, >0.5 - 1 hour, >1- 12 hours, >12 – 24 hours, ≤1 day - unclear, >1 – 14 days, and >14 days). The definition of the duration of ISR is provided in Section 10.3.13.7.

A Listing of ISR AEs during the treatment period will be provided.

Table 1 provides a summary of the AE tabulations by analysis period as described in this section.

Table 1: Adverse Event Tabulations by Analysis Period

	Pretreatment Period	Treatment Period	Follow-up Period
AE summary	x	x	x
AE by SOC and PT	x	x	x
AE by PT		x	
Related AE by SOC and PT		x	x
Related AE by PT		x	
Severe AE by SOC and PT	x	x	x
Related Severe AE by SOC and PT		x	x
SAE by SOC and PT	x	x	x
SAE by PT		x	
Related SAE by SOC and PT		x	x
Summary of Investigator-reported AESI	x	x	x
Investigator-reported AESI by SOC and PT	x	x	x
Related Investigator-reported AESI by SOC and PT		x	x
Summary of SMQ-defined AESI	x	x[a]	x
SMQ-defined AESI by SOC and PT	x	x[a]	x
Related SMQ-defined AESI by SOC and PT		x[a]	x
Summary of ISR AEs		x	
ISR AEs by SOC and PT		x	
ISR AEs by SOC, PT, and Severity		x	
Number and duration of ISR AEs		x	

[a]For SMQ-defined hypersensitivity AESI during the treatment period, two sets of summary tables will be provided for the AEs including or excluding injection site reactions (PTs start with 'Injection site')

7.9.2 Clinical Laboratory Evaluation

Laboratory test results will be presented in conventional units.

Baseline is defined as the last non-missing value prior to the first exposure to study drug.

Continuous laboratory test results (serum chemistry, hematology, and urine pH) will be summarized as described below.

Actual values and changes from baseline in clinical laboratory tests for hematology, coagulation, chemistries, and urinalysis will be summarized for each treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis. All laboratory results will be presented in subject listings.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. See Section 10.3.20 for details on handling clinical significance attribution for lab values. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized for each treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Categorical laboratory test results (urinalysis excluding pH) will be summarized for treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the investigator for a subject across study visit to identify any trends.

7.9.3 Vital Signs

Baseline is defined as the last non-missing value prior to the first exposure to study drug.

Actual values and changes from baseline in vital signs will be summarized for each treatment group and DX-2930 overall by study visit and study time point. All vital sign data will be presented in subject listings.

Vital sign values will be classified according to clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a non-clinically significant result and clinically significant result will be summarized for each treatment group and overall DX-2930 by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the result yielding the most severe classification will be selected for analysis. Subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameter that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

7.9.4 Electrocardiography

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG not performed, will be summarized for each treatment group and overall DX-2930 by study visit. Subjects with abnormal ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

All ECG data will be provided in subject listings.

7.9.5 Physical Examinations

Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant or not performed by the investigator and will be summarized for each treatment group and DX-2930 overall by study visit. Subjects with clinically significant abnormal physical examination findings will be listed. This listing will include all results of the body system that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

All physical examination findings will be provided in subject listings.

7.9.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version 2017 Q1.

Prior medications are defined as medications with start and stop times at or prior to the time of study drug administration.

Concomitant medications are defined as medications with a start times after the time of study drug administration or medications with a start times prior to study drug administration but continuing after treatment.

For medications with partial onset times, non-missing date parts will be used to determine if the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to study drug administration then the medication will be classified as concomitant medication.

The number and percentage of subjects with prior or concomitant medications excluding medications taken for an HAE attack will be summarized for each treatment group and overall DX-2930 by therapeutic class and preferred term. Therapeutic class will be based on the Therapeutic Subgroup corresponding to level 2 of the Anatomic Therapeutic Chemical (ATC) classification system. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency in the overall DX-2930 group and then the placebo group. A separate, similar table will be provided for concomitant medications taken for an HAE attack. All medications will be presented in subject listings.

7.10 Other Analyses

Additional analyses of pharmacokinetic (PK) and pharmacodynamic (PD) data will be described in a separate PK/PD report.

Additional analysis of quality of life (QoL) data will be described in a separate QoL report.

7.10.1 Analysis of Pharmacokinetic Data

Plasma concentrations of DX-2930 will be summarized for each treatment group by nominal PK sampling time and listed by subject using the safety population.

Plasma concentrations reported as BLQ (below the limit of quantification) of the assay will be reported as zero in the data listings, and BLQ concentrations are treated as zero in the calculation of summary statistics.

7.10.2 Analysis of Pharmacodynamic Data

Plasma kallikrein activity measured by percentage of cleaved high molecular weight kininnogen (%cHMWK) will be summarized for each treatment group by nominal PD sampling time and listed by subject using the safety population.

7.10.3 Analysis of Immunogenicity Data

The number and percentage of subjects with neutralizing antibody, positive, negative, or not evaluable antibody results will be summarized for each treatment group and DX-2930 overall by study visit and overall and all immunogenicity data for subjects with any positive immunogenicity result will be listed by subject using the safety population.

7.10.4 Analysis of Quality of Life Data

The number and percentage of subjects at each level of the EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) for each treatment group and DX-2930 overall by study visit using the safety population. In addition, the VAS score for the subject's self-rated health will be summarized for each treatment group and DX-2930 overall by study visit using the safety population.

The responses to the AE-QoL for each item will be tabulated for each treatment group and DX-2930 overall by study visit using the safety population. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized for each treatment group and DX-2930 overall by study visit using the safety population.

All QoL data will be provided in subject listings.

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

8.1 Changes in the Conduct of the Study

There was no change in the conduct of the study.

8.2 Change from the Analyses Planned in the Protocol

8.2.1 Efficacy Evaluation Period

The phase "Efficacy Evaluation Period" was used in the protocol to describe the time interval for which efficacy would be evaluated and was defined as Day 0 through Day 182. This phase was changed to treatment period for consistency with the Study Activities Schedule. The definition of the duration of the interval remains Day 0 through Day 182.

8.2.2 ITT and Safety Population Definitions

The definition of the ITT population specified in the protocol stated that the population will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. The definition in the SAP was modified from "at least 1 dose of active IMP or placebo" to "any exposure to study drug". This change was made to clarify that a subject did not need to receive the full dose to be included in this analysis population, but that subjects receiving partial doses would be included.

A similar modification was applied to the definition of the safety population.

8.2.3 Adverse Events

The protocol stated that incidence of AEs and rate of study discontinuation among the four treatments arms would be compared, the SAP clarified that this comparison would be based on descriptive statistics.

Additionally, the analysis of the incidence of AEs by month from start of study drug was omitted. Because subjects are repeatedly exposed to study drug on at least a monthly basis, it is not expected that the type or frequency of AE would vary by month.

The protocol stated that an AE is treatment-emergent if the onset time is after first administration of IMP; the SAP clarified that an AE is treatment-emergent if the onset time is on or after first administration of study drug.

8.2.4 Laboratory Parameters

The protocol specified that for laboratory parameters the change from screening would be summarized. Instead, a change from baseline will be summarized and a definition of baseline was included in the SAP.

The protocol specified that laboratory parameters would be summarized using shift tables. This summary was omitted and replaced with a summary of results based on reference ranges and clinical significance as determined by the investigator.

8.2.5 Vital Sign Parameters

The protocol specified that for vital sign parameters the change from screening would be summarized. Instead, a change from baseline will be summarized and a definition of baseline was included in the SAP.

9. STATISTICAL/ANALYTIC ISSUES

9.1 Adjustment for covariates

The analysis of the primary and secondary efficacy adjusts for the normalized pretreatment HAE attack rate. No additional covariate adjustment is planned.

9.2 Handling of Dropouts or Missing Data

All available data will be included in the analysis. The length of time a subject was observed during the treatment period will be included as a variable in the generalized linear model to adjust for differences in follow-up time.

9.3 Interim Analysis and Data Monitoring

No interim analyses are planned. However, an independent Data Safety Monitoring Board (DSMB) will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DSMB review will be conducted according to the DSMB Charter and DSMB SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

9.4 Multicenter Studies

Data from all study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

9.5 Multiple Comparisons/Multiplicity

The global family-wise type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 7.8.2) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach with branches for each active treatment group to placebo group comparison will be utilized in which each family of statistical tests will be conducted in a sequential manner. Specifically, a three-branch general gatekeeping procedure with three families of hypotheses will be defined as follows:

Family 1 (F_1): Hypothesis tests for the primary efficacy endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{11}, H_{12}, and H_{13}).

Family 2 (F_2): Hypothesis tests for the first ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{21}, H_{22}, and H_{23}).

Family 3 (F_3): Hypothesis tests for the second ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{31}, H_{32}, and H_{33}).

Family 4 (F_4): Hypothesis tests for the third ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{41}, H_{42}, and H_{43}).

The 4 sets of hypotheses in F1, F2, F3, and F4 will be tested in a fixed sequence within each active treatment group to placebo group comparison or branch. Testing within a branch will continue in sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests within the branch.

Within a family, hypotheses will be tested using a conservative Bonferroni-based procedure with equal weights for each test set at 1.67% significance level (α/3). If the null hypothesis for a test is rejected, α will be propagated entirely to the next test in the sequence, which will then be tested at the 1.67% significance level.

To further illustrate this approach, the test for the primary endpoint will be conducted first at the 1.67% significance level for each active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 1.67% significance level. The testing sequence will continue in order through the remaining secondary endpoints for each active treatment group to placebo comparison or branch as long as the null hypothesis is rejected at the 1.67% significance level.

Testing within the last family (F4) will utilize the remaining α by applying the Holm-Bonferroni procedure.

9.6 Examination of Subgroups

Subgroup analyses are planned to be conducted for the primary efficacy endpoint and adverse events (non-HAE attack treatment period AEs, related AEs, and severe AEs). In addition, a subgroup analysis by history of laryngeal attacks will be performed for the exploratory efficacy endpoint, number of investigator-confirmed laryngeal HAE attacks during the treatment period. Any p-values that are presented will be descriptive.

The following subgroups will be used:

- Age Group (<18, 18 to <40, 40 to <65, ≥65 years)
- Sex (Male, Female)
- Race Group (White, Other)
- Weight Group (<50, 50 to <75, 75 to <100, ≥100 kg)
- BMI Group (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m2)
- Run-in Period HAE Attack Rate Group (1 to <2, 2 to <3, ≥3 attacks/4 weeks)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- Type of Long-term Prophylactic Therapy Prior to Study Randomization (C1-INH, Oral Therapy, C1-INH and Oral Therapy, Not on LTP)
- History of laryngeal HAE attack (history laryngeal attack, no history of laryngeal attack)

The subgroups will be analyzed using the same method as described for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint and the primary analysis of the adverse events. For the subgroup analyses

conducted for the primary efficacy endpoint, a forest plot depicting the rate ratio and corresponding 95% CI estimated from the Poisson generalized linear model will be provided for each active treatment group versus placebo group comparison within each subgroup.

9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary efficacy endpoint and/or secondary and exploratory endpoints to evaluate the robustness of the results. See Table 2 for details.

1. The primary analysis will be repeated using the safety population. Subjects will be analyzed according to the treatment actually received. This analysis will only be presented if the safety population is different from the ITT population or if subjects did not receive treatment as randomized.

2. The primary analysis will be repeated counting HAE attacks occurring on Day 7 after administration of study drug through Day 182, instead of Day 0 to Day 182.

3. The primary analysis will be repeated using all subject reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed.

4. The primary analysis will be repeated using a generalized estimating equations (GEE) analysis method counting HAE attacks occurring on Day 14 after administration of study drug through Day 182 in order to descriptively compare the results from this study with those from DX-2930-02 study. The methods for this analysis are listed below.

   HAE attack rates for each active treatment group will be compared to the placebo group using a mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) for count data (assuming a Poisson distribution with log link function) using GEE. The model will include a fixed effect for treatment (categorical), pretreatment period attack rate (continuous), and a random effect for subject.

   Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. Subject weeks for which completed observation is less than the full 168 hours within a week will be treated as a full week if at least 3 or more days of data were recorded during the week. Weeks with fewer than 3 days will not be included.

   In the event that there are 0 events in one of the treatment groups, a small value of 0.000001 will be added in order to calculate event rates.

5. The impact of missing data on the primary analysis will be explored using a tipping point analysis.

   Subjects who do not complete the treatment period (Day 0 through Day 182) but who were dosed and have contributed any amount of time to the treatment period will be included in the primary analysis. These subjects will have some portion of the treatment period observed

and the remainder of the treatment period, after study discontinuation, will be unobserved. The model used for the primary analysis assumes that events occur at a constant rate within an individual, and uses only the number of events in the observed portion of the treatment period with an offset parameter to account for the length of time in which those events were observed to derive the event rate for that individual.

To better understand the impact of unobserved portion of the treatment period generated by subjects who discontinue early on the results of our primary analysis, a tipping point analysis will be conducted. In this analysis, a range of progressively more conservative assumptions about the number of events occurring in the unobserved portion of the treatment period will be explored in order to find the assumption which will reverse the conclusion (i.e., yield a non-significant p-value) of the primary analysis. The assumption that will reverse the conclusion is referred to as the tipping point. Once the tipping point is identified, the clinical plausibility of the assumption can be assessed.

The tipping point analysis will employ the same model as specified for the primary analysis including progressively conservative assumptions about the unobserved portion of time generated by subjects who discontinue early. The exact range of assumptions will be determined after treatment unblinding to ensure an appropriate range is explored based on the magnitude of treatment effect and pattern of missing data. The results of the various assumptions will be summarized with attack rate ratios, corresponding 95% confidence intervals and p-values in both tabular and graphical presentations. The details of this method are described in Section 10.3.12.

6. The primary analysis will be repeated counting HAE attacks occurring on Day 14 after administration of study drug through Day 182, instead of Day 0 to Day 182.

Table 2 details which sensitivity analyses will be performed for each efficacy endpoint. Data summaries will parallel those described for the each of the endpoints.

Table 2: Sensitivity Analysis for Efficacy Endpoints

	Sensitivity Analysis Item					
Efficacy Endpoint	**1**	**2**	**3**	**4**	**5**	**6**
Number of HAE attacks	x	x	x	x	x	x
Number of HAE attacks requiring acute treatment	x	x	x			x
Number of moderate or severe HAE attacks	x	x	x			x
Number of Investigator confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182	x	-	x			-
Time to first HAE attack after Day 14	x	x	x			-
Number of high-morbidity HAE attacks	x	x	x			x
Number of HAE attacks resulting in visit to emergency department or admission to the hospital	x	x	x			x
Number of HAE attacks resulting in visit to emergency department	x	x	x			x
Number of HAE attacks resulting in admission to the hospital	x	x	x			x
Number of investigator-confirmed laryngeal HAE attacks	x	x	x			x
Responder Analysis	x	x	x			x
Characteristics of HAE attacks	x	x	x			x
Percentage of attack-free days	x	x	x			x
Achievement of attack-free during treatment period or after Day 14	x					-

10. APPENDICIES

10.1 Appendix I List of Statistical Outputs

10.1.1 List of Planned Tables

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14.1.1.1	Analysis Population by Treatment Group – All Subjects
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14.2.2.1	Investigator-confirmed HAE Attacks Requiring Acute Treatment during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.3.1	Moderate and Severe Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.4.1	Time to First HAE Attack After Day 14 by Treatment Group – ITT Population
14.2.5.1	High-morbidity Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.6.1	Investigator-confirmed HAE Attacks Requiring an Emergency Department Visit or Admission to the Hospital during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.7.1	Investigator-confirmed HAE Attacks Requiring an Emergency Department Visit during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population

14.2.8.1	Investigator-confirmed HAE Attacks Requiring Admission to the Hospital during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population

10.1.3 List of Planned Listings

Listing No.	Title
16.2.1	Disposition
16.2.2	Protocol Deviations
16.2.3.1	Analysis Populations
16.2.3.2	Inclusion and Exclusion Criteria
16.2.4.1	Demographics
16.2.4.2	Baseline Disease Characteristics
16.2.4.3	Medical History
16.2.4.4	Prior and Concomitant Medications
16.2.5.1	Study Drug Administration
16.2.5.2	Treatment Compliance and Exposure
16.2.6.1	HAE Attacks
16.2.6.2	Plasma Concentration of DX-2930
16.2.6.3	Kallikrein Activity
16.2.6.4	EQ5D
16.2.6.5	Angioedema Quality of Life
16.2.7	Adverse Events
16.2.8.1	Hematology Values
16.2.8.2	Coagulation Values
16.2.8.3	Chemistry Values
16.2.8.4	Urinalysis Values
16.2.8.5	Vital Signs
16.2.8.6	ECGs
16.2.8.7	Immunogenicity
16.2.8.8	Physical Examinations

10.2 List of Clinical Study Sites

Site #	State/Province	Country	PI Last Name
PPD	AL	US	Anderson
	MA	US	Banerji
	OH	US	Bernstein
	NY	US	Busse
	PA	US	Craig
	NY	US	Davis-Lorton
	WA	US	Gower
	CA	US	Jacobs
	MD	US	Li
	FL	US	Lockey
	TX	US	Lumry
	OH	US	McNeil
	MO	US	Wedner
	KS	US	Gierer
	NC	US	Johnston
	AR	US	Manning
	OH	US	Radojicic
	CO	US	Soteres
	MN	US	Shapiro
	NJ	US	Weinstein
	TX	US	Otto
	MI	US	Baptist
	CO	US	Melamed
	PA	US	Petrov
	OH	US	Rehman
		Puerto Rico	Zaragoza
	CA	US	Riedl
	LA	US	Boggs
	VA	US	Schwartz
	UT	US	Harris
	NC	US	Lugar
	NJ	US	Sher
	CA	US	Tachdijian
	OK	US	Nickel
	WI	US	Zafra
	MA	US	Hong
	UT	US	Smith

PPD

UK	US	Longhurst
	Germany	Magerl
	Germany	Staubach
	Italy	Cicardi
	Germany	Martinez-Saguer
Ontario	Canada	Sussman
Quebec	Canada	Hébert
Alberta	Canada	Ritchie
Ontario	Canada	Yang
Québec	Canada	Chapdelaine
	Jordan	Shennak

10.3 Definitions and Programming Conventions

10.3.1 Age

Age will be calculated as the date of birth minus the date of informed consent, divided by 365.25, and truncated to years.

10.3.2 BMI

BMI will be calculated as:

$$BMI = \frac{mass\ (kg)}{height(m)^2}$$

The mass and height collected at the screening visit will be used to calculate baseline BMI.

10.3.3 LTP Prior to Study Randomization

The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to study randomization will be determined by applying the algorithm presented in Table 3 to prior medications (i.e., medications with start and stop date prior to study enrollment) reported for that subject that lasted for ≥4 days.

Table 3 LTP Prior to Study Randomization

LTP	Algorithm to Identify Medications
C1-INH	ATC level 4 in ('B06AC') and preferred drug term not in ('icatibant', 'ecallantide', 'icatibant acetate')
Androgens	ATC level 4 in ('G03BA', 'G03BB', 'A14AA') or preferred drug term in ('danazol', 'oxandrolone')
Anti-fibrinolytics	ATC level 4 in ('B02AA', 'B02AB')

Subjects will be further classified into four LTP subgroup, based on the LTP use prior to study randomization. Table 4 provides the algorithm to classify subjects by type of LTP use prior to study randomization.

Table 4 LTP Subgroup

LTP Subgroup	Subject
C1-INH	Subjects who took only C1-INH as LTP
Oral Therapy	Subjects who took either Androgens and/or Anti-fibrinolytics as LTP but not C1-INH
C1-INH and Oral Therapy	Subjects who took C1-INH and androgens and/or anti-fibrinolytics as LTP
Not on LTP	Subjects who didn't take any LTP medications prior to study randomization

10.3.4 Study Day

The study day is calculated as start or stop date – date of randomization + 1 for dates on or after randomization, or start or stop date – date of randomization for dates prior to randomization.

10.3.5 Durations of Events

The duration of an event is calculated as stop date/time – start date/time if time is not missing, and stop date – start date + 1 if either the start or stop time is missing.

10.3.6 Baseline

Baseline is defined as the last non-missing value prior to first exposure to study drug.

10.3.7 Analysis Periods

10.3.7.1 Pretreatment Period

The pretreatment period is defined as the interval of time that starts at the date/time informed consent is signed and ends prior to the date/time of first exposure to study drug (Day 0 visit).

[*date/time of informed consent*, *date/time of first exposure to study drug*)

10.3.7.2 Run-in Period

The run-in period is defined as the interval of time that starts at the start date for the run-in period and ends on the end date for the run-in period.

[*start date of run-in period*, *end date of run-in period*]

10.3.7.3 Treatment Period

The treatment period is defined as the interval of time that starts on the date/time of first exposure to study drug (Day 0 visit) and ends on the date of Day 182 visit.

[*date/time of first exposure to study drug*, *date of Day 182 visit*]

10.3.7.4 Follow-up Period

The follow-up period is defined as the interval of time that starts on the date of the Day 182 visit + 1 and ends on the date of the subject's last date of contact for the study.

[*date of Day 182 visit + 1*, *date of last study contact*]

10.3.8 Handling of Data for Subjects who Rolled-Over to the DX-2930-04 Early

Two subjects (subject ID 107007 and 108001) rolled-over to DX-2930-04 (long-term extension study) prior to the Day 182 visit due to study site error. These two subjects were considered to have completed the DX-2930-03 study as the early discontinuation of the treatment period was in error. For these two subjects, the following data handling conventions were employed:

- The planned number of doses used in the compliance and extent of exposure calculations will be based on the planned number of doses at their last visit instead of the Day 182 visit.

- For the tipping point analysis these subjects will be treated as study completers. No imputation will be performed for these subjects. The shorten duration of observation will be accounted for in the model with the use of the offset parameter.

10.3.9 Handling of HAE Attack Data

The following rules apply to the handling of HAE attack data for efficacy analyses only. HAE attacks starting prior to the run-in period are not processed by these rules. For safety analyses, HAE attacks will be analyzed as reported.

10.3.9.1 Imputing Missing Start or End Date and Time for HAE Attacks

In general, missing start time will be imputed as 0:00 and missing end time will be imputed as 23:59. However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in-between:

- For HAE attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous HAE attack to ensure there are 24 hours in between the two attacks.

- For HAE attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack (see Section 10.3.9.2 for details on combining HAE attacks)

- For HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next HAE attack to ensure there are 24 hours in between the two attacks.

- For HAE attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack (see Section 10.3.9.2 for details on combining HAE attacks)

For HAE attacks with a non-missing start date and time and a missing stop date and time:

- If the event is not indicated as ongoing, the stop date and time will be imputed as start date and time + 48 hours or 24 hours before the start date and time of the next attack, whichever is earlier.

- If the event is indicated as ongoing, the stop date and time will be imputed as the earlier of the following two date and time:

    - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.

    - 24 hours before the start date and time of the next attack.

10.3.9.2 Unique HAE Attacks

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Specifically, there must be at least 24 hours between the stop date/ time of the first event and the start date/time of the next event, for the attacks to be considered distinct. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be counted as one attack.

When two or more attacks are combined for efficacy analysis, the parameters of the attacks will be conservatively chosen. The start date and time of the combined attack will take the earliest start date and time from the individual attacks; and the end date and time of the combined attack will take the latest end date and time of the individual attacks. The severity of the combined attack will take the highest severity from the individual attacks. The primary location of the combined attack will be determined by the primary location of the individual attacks, and by following the hierarchy of laryngeal attack, abdominal attack, and peripheral attack. One primary location will be taken; and all the other primary location(s) and secondary locations will be considered as secondary location for the combined attack. The rescue medications and supportive treatment for the combined attack will include all the records from individual attacks. Also, the combined attack will be considered as an investigator-confirmed attack if any of the individual attack being combined is an investigator-confirmed attack.

10.3.9.3 HAE Attack Duration

The duration of an HAE attack is calculated as stop date/time – start date/time.

10.3.9.4 Investigator-confirmed HAE Attacks Requiring Acute Therapy

Investigator-confirmed HAE attacks requiring acute therapy are those attacks identified as 'treated for HAE attack with acute therapy' on the CRF.

10.3.9.5 Moderate and Severe Investigator-confirmed HAE Attacks

Moderate and severe investigator-confirmed HAE attacks are those attacks that were classified as of moderate or severe according to the HARRP defined severity and reported as such on the CRF.

10.3.9.6 HAE Attack Severity

The overall severity of the subject's attack was to be determined by the investigator using the following definitions provided as part of HARRP:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance needed
- Severe: Marked limitation in activity, assistance required

The average attack severity will be calculated per subject by attributing a numeric value to each severity as follows: 1=Mild, 2=Moderate, and 3=Severe. Higher values will indicate more severe attacks, while lower values will indicate less severe attacks.

10.3.10 HAE Attack Rate

10.3.10.1 Run-in Period HAE Attack Rate

The run-in period HAE attack rate will be presented as the normalized number of attacks per month (4 weeks) and calculated for each subject as number of HAE attacks occurring during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days.

Due to a slightly longer than planned run-in period, four of the randomized subjects had a calculated run-in period HAE attack rate that is lower than 1 (0.97). The actual value of the calculated run-in period attack rate will be used as the run-in period attack rate for these subjects. However, these subjects will be included in the 1-2 attacks/month group in the run-in period HAE attack rate group categorization.

10.3.10.2 Treatment Period HAE Attack Rate

The treatment period HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of HAE attacks occurring during the treatment period divided by number of days the subject contributed to the treatment period multiplied by 28 days.

10.3.11 Time to First HAE Attack

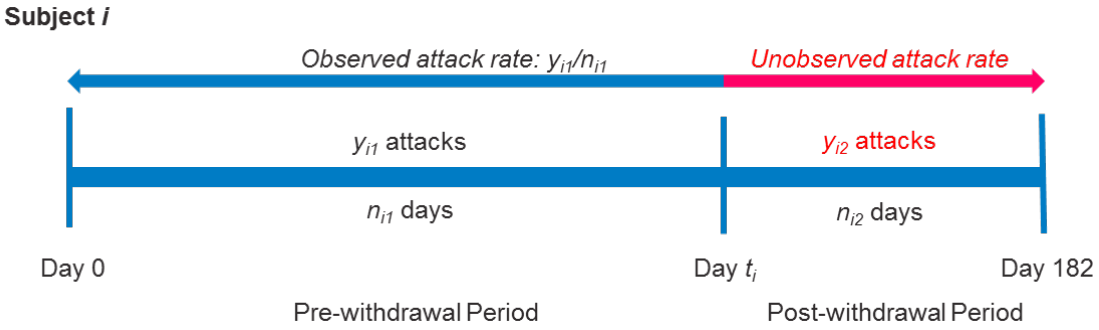
The time to first HAE attack (days) will be calculated as the earliest of the date of the HAE attack after the Day 14, date of study discontinuation or completion, or date of Day 182 visit for subjects who do not roll-over into the OLE visit minus the date of Day 14 visit plus 1.

Subjects with attacks occurring first will be events. Subjects who discontinue/complete the study or roll-over into the OLE prior to having a post-Day 14 visit HAE attack will be censored.

10.3.12 Details of the Tipping Point Analyses

Figure 1 illustrates the missing data pattern generated from subjects who discontinue early from the treatment period of the DX-2930-03 study. Subject i receives first dose of the study drug at Day 0 and discontinues the study at Day t_i prior to the end of the treatment period at Day 182. The pre-withdrawal period for Subject i is defined as Day 0 through Day t_i and the post-withdrawal period is defined as Day $t_i + 1$ through Day 182. In the pre-withdrawal period, we know both the length of the period (n_{i1}) and the number of investigator-confirmed HAE attacks during the period (y_{i1}), and can calculate the observed attack rate (y_{i1}/n_{i1}) for the period. In the post-withdrawal period, we know only the length of the period (n_{i2}), however, both the number of investigator-confirmed HAE attacks during the period (y_{i2}) and the unobserved attack rate (y_{i2}/n_{i2}) for the period are unknown.

Figure 1 Missing Data Pattern for Subjects who Discontinue Early from the Treatment Period of Study DX-2930-03



To assess the impact of the unobserved portion of the treatment period generated by subjects who discontinue the study prior to completing the treatment period on the results of our primary analysis, a tipping point analysis will be conducted. In this analysis, a range of progressively more conservative assumptions about the number of events occurring in the post-withdrawal period will be explored in order to find the assumption which will reverse the conclusion (i.e., yield a non-significant p-value) of the primary analysis. The assumption that will reverse the conclusion is referred to as the tipping point. Once the tipping point is identified, the clinical plausibility of the assumption can be assessed.

The tipping point analysis will employ the same model as specified for the primary analysis including progressively conservative assumptions about the unobserved attack rate during the post-withdrawal period. This is achieved by assuming that subjects in the active treatment arm who discontinue the study prior to completing the treatment period would have, on average, their unobserved attack rate worse by some amount (δ) compared with the observed attack rates of subjects that completed the study. Subjects who discontinue the study prior to completing the treatment period from the placebo arm would have the same unobserved attack rate as those who completed the study. In contrast, the model used for the primary analysis assumes that events occur at a constant rate within an individual, and uses only the number of events in the observed portion of the treatment period with an offset parameter to account for the length of time in which those events were observed to derive the event rate for that individual (i.e., the observed attack rate).

The tipping point analysis will be conducted as follows:

Step 1: Multiple Imputation (MI)

MI will be used to impute 1000 samples of the unobserved attack rate (y_{i2}/n_{i2}) for each subject who discontinued the study prior to completing the treatment period conditional on the observed data. Multiple imputation is used to incorporate variance that accounts for the uncertainty associated with the imputed values (Rubin, 1976) (Rubin, 1987). The imputed unobserved attack rate will be used to generate 1000 imputed values of the total number of attacks over the entire treatment period for each subject who discontinued the study prior to completing the treatment period.

Steps 1a – 1c detail the multiple imputation approach to generate complete data for subjects who discontinued the study prior to completing the treatment period:

Step 1a: 1000 independent samples are drawn from the posterior distribution of model parameters fit using a Bayesian analysis of the model defined for the primary analysis. The sampled set of values of the model parameters are then used to generate a set of values for the expected unobserved attack rate (y_{i2}/n_{i2}) for each subject who discontinued the study prior to completing the treatment period using each subjects covariate values. This will result in 1000 imputed values for the unobserved attack rate for each discontinued subject.

Step 1b: The expected unobserved attack rate (y_{i2}/n_{i2}) for each subject who discontinued the study prior to completing the treatment period is then multiplied by the length of the post-withdrawal period (n_{i2}) for that subject to get the expected number of attacks for the post-withdrawal period (y_{i2}).

Step 1c: The expected number of attacks for the post-withdrawal period (y_{i2}) is added to the observed number of attacks in the pre-withdrawal period (y_{i1}) to get the total number of attacks over the entire treatment period ($y_{i1} + y_{i2}$) for subjects who discontinued the study prior to completing the treatment period.

Step 2: Analyze the MI Datasets with Primary Analysis Model

The primary regression model will be run using each of the 1000 multiply imputed complete data sets. The primary regression model is the Poisson regression generalized linear model with covariates for run-in period attack rate, treatment group, and an offset variable for the log number of days observed.

Step 3: Combine Estimates using Rubin's Rules

From each of 1000 runs of the primary analysis model, the estimates will be combined using Rubin's rules (Rubin, 1987) to get one estimate for each of the rate ratios comparing the active treatment groups to placebo and corresponding 95% confidence intervals and p-values. These values will be summarized in both a tabular and graphical form.

Step 4: Pattern Imputation with Delta Adjustment

Steps 1 through 3 will be repeated with a slight modification at Step 1b to explore the impact of progressively worse assumptions (defined by δ) on the unobserved attack rate for subjects who discontinue early from the active treatment arms. In this study, δ represents a rate ratio comparing the rate of investigator-confirmed HAE attacks in the treatment group to the rate of investigator-confirmed HAE attacks in the placebo.

Modified Step 1b: For subjects that discontinue the study prior to completing the treatment period from the active treatment arms, the expected unobserved attack rate (y_{i2}/n_{i2}) for each discontinued subject is first multiplied by a specific rate ratio δ, then multiplied by the length of post-withdrawal period (n_{i2}) for that subject to get the expected number of attacks for the post-withdrawal period (y_{i2}). For subjects that discontinue the study prior to completing the treatment period from the placebo arm, Step 1b is followed without modification.

Steps 1 through 4 are repeated for values of δ that represent progressively worse assumptions on the unobserved attack rate for subjects who discontinue the study prior to completing the treatment period from the active treatment arms until the tipping point is identified (value of δ that yields a non-significant p-value). As the value of δ increases, the overall attack rate imputed for subjects in the active treatment arm increases. Values of $\delta > 1$ will be determined post-hoc in order to define reasonable increments for which to increase δ given the magnitude of treatment effect and the pattern of missing data.

Note that the imputed results generated following Steps 1 through 3 without modification represent the case when $\delta=1$, corresponding to missing at random (MAR) imputation. The estimates generated from the case when $\delta=1$, should be very similar if not exactly the same as the estimates generated from the primary analysis model.

If the value of δ which causes the study results to be reversed is plausible, then the missing data assumptions used are questionable. However, if the value of δ is not plausible, then the missing data assumptions are reasonable.

In the DX-2930-03 study, the protocol specifies that there must be 24 hours in between each investigator-confirmed HAE attack. Therefore, the total number of attacks during the treatment period is restricted to about 1 attack per day. If δ allows for more attacks than 1 per day, then the value of δ is not plausible under the study specifications and the missing data assumptions will be declared reasonable.

10.3.13 Adverse Events

10.3.13.1 Treatment-emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

10.3.13.2 Related Adverse Events

Related AEs are AEs classified as related to study drug by the investigator.

10.3.13.3 Severe Adverse Events

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

10.3.13.4 Investigator-reported AESI

An investigator-reported AESI is an adverse event identified by the investigator on the CRF as an adverse event of special interest.

10.3.13.5 SMQ-Defined AESI

The broad terms from MedDRA 20.0 SMQ will be used to identify an SMQ-defined AESI. Table 5 shows the SMQ's used to identify AESI of hypersensitivity, hypercoagulable, and bleeding.

Table 5 SMQs Used to Identify AESI

AESI	SMQ
Hypersensitivity	Hypersensitivity
Hypercoagulable	Embolic and thrombotic events, arterial Embolic and thrombotic events, venous Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
Bleeding	Haemorrhage laboratory terms Haemorrhage terms (excl laboratory terms)

10.3.13.6 Injection Site Reaction AEs

Injection site reaction (ISR) AEs will be identified by adverse events with the preferred terms starting with 'Injection site', 'Application site', or 'Administration site'.

10.3.13.7 Duration of Injection Site Reaction AEs

Duration of ISR AEs is calculated as 'stop date/time – start date/time' for the ISR AEs with non-missing start and stop date/time.

The missing start or stop date/time for ISR AEs will not be imputed. ISR AEs with missing start or stop date/time will be excluded from the summary statistics analysis and reported as number missing in the continuous analysis of ISR AE duration. For the categorical analyses on ISR AE duration, the following rules will be applied:

- ISR AE with non-missing start and stop date/time: duration of the AE will be calculated as 'stop date/time – start date/time' and mapped to a duration category.
- ISR AE with non-missing start and stop dates and missing time: duration of the AE will be calculated as 'stop date – start date +1'. If the calculated duration is 1 day, then the duration category for this AE is ≤ 1 day - unclear. If the calculated duration is greater than 1 day, then it will be mapped to a >1 Day category.
- ISR AE with missing start or stop date: The ISR AE will be excluded from the categorical analyses on duration.

10.3.14 Non-standard Laboratory Results

The non-standard laboratory results will be converted to numeric values using the rules shown in Table 6.

Table 6 Convention for Converting Non-Standard Laboratory Results

Non-Standard Lab Values	Standardized Numeric Values
<0.1	Deduct 0.01 from the reference value. i.e., 0.09
>1.045	Add 0.001 to the reference value. i.e. 1.046

10.3.15 GLM Model Sample SAS Code

Sample code for the primary efficacy analysis of the primary endpoint.

```
PROC GENMOD DATA=eff_data;
CLASS trtgrp;
MODEL no_attks = trtgrp bl_rate / DIST=poisson LINK=log OFFSET=logdays PSCALE;
LSMEANS trt / DIFF CL EXP ILINK;
ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1 0 0 -1 / EXP;
ESTIMATE '300mg every 4 wk vs pbo' trtgrp 0 1 0 -1 / EXP;
ESTIMATE '150mg every 4 wk vs pbo' trtgrp 0 0 1 -1 / EXP;
RUN;
```

Where:
eff_data = efficacy analysis dataset
trtgrp = treatment group (categorical)
no_attks = number of HAE attacks during the analysis period
bl_rate = normalized pretreatment HAE attack rate (continuous)
logdays = logarithm of time in days each subject was observed during the analysis period

10.3.16 GEE Model Sample SAS Code

Sample code for a sensitivity analysis of the primary endpoint.

```
PROC GENMOD DATA=eff_data;
   CLASS trtgrp subject;
  MODEL no_attks = trtgrp bl_rate / DIST=poisson LINK=log;
   REPEATED SUBJECT=subject / CORR=IND;
   LSMEANS trtgrp / DIFF CL EXP ILINK;
   ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1 0 0 -1 / EXP;
   ESTIMATE '300mg every 4 wk vs pbo' trtgrp 0 1 0 -1 / EXP;
   ESTIMATE '150mg every 4 wk vs pbo' trtgrp 0 0 1 -1 / EXP;
RUN;
```

Where:
eff_data = efficacy analysis dataset
trtgrp = treatment group (categorical)
no_attks = number of HAE attacks per week
bl_rate = normalized pretreatment HAE attack rate (continuous)

10.3.17 Tipping Point Analysis Sample SAS Code

Step 1: Use multiple imputation to impute the unobserved rate of attacks by completing the following process:

1a. Sample code that draws 1000 independent samples from the posterior distribution of model parameters which are fit using a Bayesian analysis.

```
proc genmod data = prim_eff_all order = data;
  class trtpn; *treatment group;
  model NUM_ATTKS = trtpn runbase /DIST= poisson LINK = log OFFSET =
LNUMDAYS ;
  bayes outpost=bayes_prim thin=1 nmc=1000 nbi=200;
 run;
```

Sample code for the sampled set of values being used to generate values for the unobserved attack rate for subjects who discontinued the study prior to completing the treatment period. The values are generated using the model parameter estimates from Step 1a and each subjects covariate values. There should be 1000 imputed values for each discontinued subject.

The variable miss_treat is an indicator for not completing the treatment period and attk_rate is the unobserved attack rate for the post-withdrawal period.

```
%macro mi_data;
%do i = 1 %to 1000;
*estimate lambda for poisson distribution;
data prim_eff_all&i;
  set prim_eff_all;

  *calculate the rate for each sample of coefficients from the model in Step 1a using each
subjects covariate values;
  if TRTPN = 1 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN1&i);
  if TRTPN = 2 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN2&i);
  if TRTPN = 3 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN3&i);
  if TRTPN = 4 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN4&i);
*calculate the attack rate;
 if miss_treat = 1 then attk_rate = RAND('POISSON', lambda);
run;
%end;
%mend mi_data;
```

1b. The expected unobserved attack rate (from step 1b) for each subject who discontinued early is then multiplied by the length of the post-withdrawal period for that subject to get the expected number of attacks for the post-withdrawal period.

1c. The expected number of attacks for the post-withdrawal period is added to the observed number of attacks in the pre-withdrawal period to get the total number of attacks over the entire treatment period.

Step 2: The sample code shows the for primary regression model being run using each of the 1000 multiply imputed complete data sets. The imputation variable is the indicator for the which imputation dataset is being analyzed and prim_ efficacy is the dataset that includes the 1000 datasets that have been imputed using step 1.

```
proc genmod data = prim_efficacy order = data;
  by imputation;
  class trtpn; *treatment group;
 model num_attks_final = trtpn runbase /DIST= poisson LINK = log PSCALE; *model;
 lsmeans trtpn/ diff cl exp ilink;
run;
```

Step 3: Combine the results from the multiply imputed datasets using Rubin's rules (then exponentiate the estimate and the 95% confidence interval for the estimate of the rate ratios). Below is the code used to combine the results across imputations (note: the estimates and the 95% CI of the estimates need to be exponentiated).

```
proc mianalyze data = Diffs;
  by trtpn;
  where _trtpn = 1;
  modeleffects estimate;
  stderr stderr;
run;
```

10.3.18 Sample Code to Derive Relative Risk and Risk Difference

```
proc freq data=adae;
  tables trt*SAE / riskdiff relrisk;
  exact relrisk riskdiff;
run;
```

10.3.19 Sample Code on Time-to-Event Analyses

```
proc lifetest data = time_attk;
  time attk14*cnsr(0);
  strata trt01p/ diff = control('Placebo')  test = (logrank);
run;
```

where attk14 is the time to the first attack after day 14
cnsor is the indicator for being an event

10.3.20 Clinical Significance Attributions for Laboratory Results

The EDC system design permitted attribution of clinical significance for all laboratory values, not just those that are outside of the reference range. Therefore, many data points have an attribution of clinical significance when none is expected.

The laboratory results will be programmatically classified for analysis due to the database limitation using the following algorithm:

1. Lab results within the reference range will be classified as Normal.
2. Lab results outside of the reference range will be classified as a) CS Low, b) NCS Low, c) NCS High, or d) CS High using a combination of the CS/NCS classification by the investigator and the Low/High classification based on the central lab reference range.

10.3.21 Angioedema Quality of Life

Below are instructions for how to calculate AE-QoL domain scores and total score.

AE-QoL is meant to be evaluated by determining its four individual domain scores (profile instrument), but it may also be used to determine a total score (index instrument).

Each item answered by the subject scores between 0 and 4 points depending on the answer option chosen by the subject. The first answer option gets 0 points, the second option 1 point, the third option 2 points, etc. The AE-QoL domain scores and total score are calculated by using the following formula:

(Sum of all completed items) / (maximum sum of all possible items)*100

<u>Computation of AE-QoL Total Score</u>
Example 1: All items were completed (maximum possible sum: 68 points)
Sum of all 17 completed items: 41 points.
Total score = 100*(41/68) = 60 (out of a possible 100 points)

Example 2: 2 items were not completed (maximum possible sum: 60 points).
Sum of all 15 completed items: 41 points.
Total score = 100*(41/60) = 68 (out of a possible 100 points)

<u>Computation of Domain Scores (Example: Fears/Shame)</u>
Example: Sum of all 6 completed items: 14 points
Maximum possible sum: 24 points
Domain Score = 100*(14/24) = 58 (out of a possible 100 points)

<u>Remarks</u>
Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0-to-100 scale), the calculated scores are not or only little influenced by missing items.

An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.

The minimal and highest possible domain and total scores are 0 and 100, respectively.

10.4 Treatment Period Dosing Schedule

Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/ Week/Visit**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/ Week 0/Visit 1	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/ Week 2/Visit 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/ Week 4/Visit 3	DX-2930	DX-2930	DX-2930	Placebo
4	Day 42/ Week 6/Visit 4	DX-2930	Placebo	Placebo	Placebo
5	Day 56/ Week 8/Visit 5	DX-2930	DX-2930	DX-2930	Placebo
6	Day 70/ Week 10/Visit 6	DX-2930	Placebo	Placebo	Placebo
7	Day 84/ Week 12/Visit 7	DX-2930	DX-2930	DX-2930	Placebo
8	Day 98/ Week 14/Visit 8	DX-2930	Placebo	Placebo	Placebo
9	Day 112/ Week 16/Visit 9	DX-2930	DX-2930	DX-2930	Placebo
10	Day 126/ Week 18/Visit 10	DX-2930	Placebo	Placebo	Placebo
11	Day 140/ Week 20/Visit 11	DX-2930	DX-2930	DX-2930	Placebo
12	Day 154/ Week 22/Visit 12	DX-2930	Placebo	Placebo	Placebo
13	Day 168/ Week 24/Visit 13	DX-2930	DX-2930	DX-2930	Placebo
--	Day 182/ Week 26/Visit 14	No Dose	No Dose	No Dose	No Dose

10.5 Study Activity Schedule

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
Informed Consent	X																
Eligibility Review	X		X														
Long-term Prophylactic Therapy Washout[5]	X																
Randomization			X														
Blinded IMP Treatment			X		X	X	X	X	X	X	X	X		X			
Demographic and Medical History	X																
C1-INH, C1q and C4 Testing[6]	X																
Pregnancy Test[7] (females)	X		X			X		X		X	X			X	X		X
Vital Signs[8]	X		X		X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination[9]	X		X			X		X		X		X			X		X
12-Lead ECG[10]	X		X					X					X		X		X
Clinical Laboratory Testing[11]	X		X			X		X		X		X			X		X
Serologies: HBsAg, HCV, and HIV	X																
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

Study Activities Schedule

	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
HAE Attack Data[12]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Quality of Life Assessments[13]			X			X		X		X	X			X	X		X
PK Blood Sampling			X					X		X		X			X	X	X
PD Sample Collection			X					X		X		X			X	X	X
Plasma Anti-Drug Antibody Testing			X					X		X		X			X		X
Discharge from Study[14,15]															X		X

BP = blood Pressure; C1-INH = C1 Inhibitor; C_{max} = Maximum plasma drug concentration; ECG = Electrocardiogram; HAE = hereditary Angioedema; HbsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency virus; HR = Heart Rate; IMP = Investigational Medicinal Product; LTP = Long-term Prophylactic; OLe = Open-label Extension; PD = Pharmacodynamic; PK = Pharmacokinetic; RR = Resting Rate

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window.
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			Visit 1 Dose 1 Day 0	Site Check-in[4]	Visit 2 Dose 2 Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visits 6 and 7 Doses 6 and 7 Days 70 and 84	Visit 8 Dose 8 Day 98	Visits 9 and 10 Doses 9 and 10 Days 112 and 126	Visit 11 Dose 11 Day 140	Day 144±1	Visits 12 and 13 Doses 12 and 13 Days 154 and 168	Visit 14 Day 182	Visit 15 Day 210	Visit 16 Day 238

enter the run-in period.

6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum- or urine-based.
8. There is a ±15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.
9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Self-Report Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema Quality of Life Questionnaire (AE-QoL) at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks

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Abstract

Background: Lanadelumab demonstrated efficacy in preventing hereditary angioedema (HAE) attacks in the phase 3 HELP Study.

Objective: To assess time to onset of effect and long-term efficacy of lanadelumab, based on exploratory findings from the HELP Study.

Methods: Eligible patients with HAE type I/II received lanadelumab 150 mg every 4 weeks (q4wks), 300 mg q4wks, 300 mg q2wks, or placebo. Ad hoc analyses evaluated day 0-69 findings using a Poisson regression model accounting for overdispersion. Least-squares mean monthly HAE attack rate for lanadelumab was compared with placebo. Intrapatient comparisons for days 0-69 versus steady state (days 70-182) used a paired *t* test for continuous endpoints or Kappa statistics for categorical endpoints.

Results: One hundred twenty-five patients were randomized and treated. During days 0-69, mean monthly attack rate was significantly lower with lanadelumab (0.41-0.76) vs placebo (2.04), including attacks requiring acute treatment (0.33-0.61 vs 1.66) and moderate/severe attacks (0.31-0.48 vs 1.33, all $P \leq .001$). More patients receiving lanadelumab vs placebo were attack free (37.9%-48.1% vs 7.3%) and responders (85.7%-100% vs 26.8%). During steady state, the efficacy of lanadelumab vs placebo was similar or improved vs days 0-69. Intrapatient differences were significant with lanadelumab 300 mg q4wks for select outcomes. Lanadelumab efficacy was durable—HAE attack rate was consistently lower vs placebo, from the first 2 weeks of treatment through study end. Treatment emergent adverse events were comparable during days 0-69 and 70-182.

Conclusion: Protection with lanadelumab started from the first dose and continued throughout the entire study period.

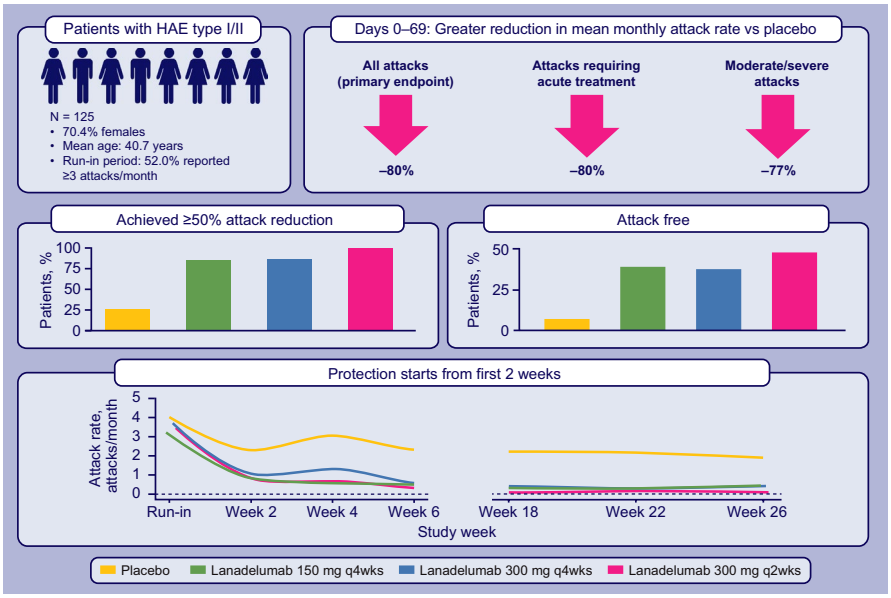
KEYWORDS

durable efficacy, hereditary angioedema, long-term prophylaxis, onset of action

Abbreviations: C1-INH, C1-inhibitor; CI, confidence interval; D0-69, days 0-69; HAE, hereditary angioedema; max, maximum; min, minimum; q2wks, every 2 weeks; q4wks, every 4 weeks; SD, standard deviation; SS, steady-state; κs, Kappa statistic.

Peng Lu was a full-time employee of Shire, a Takeda company, at the time of this analysis.

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GRAPHICAL ABSTRACT

During days 0-69, lanadelumab-treated patients had a significantly lower mean monthly hereditary angioedema (HAE) attack rate vs placebo and were more likely to be responders and attack free. Protection starts early and is sustained; during steady state, lanadelumab efficacy was similar or improved vs days 0-69. Prophylactic agents with rapid onset, sustained effect, and convenient dosing frequency can improve HAE management plans.

Abbreviations: HAE, hereditary angioedema; q2wks, every 2 weeks.

1 | INTRODUCTION

Hereditary angioedema (HAE) with C1-inhibitor (C1-INH) deficiency, a rare autosomal dominant disease caused by *SERPING1* gene mutations, is characterized by diminished levels (type I, ~85% of cases) or dysfunctional activity (type II) of the serine protease inhibitor C1-INH.[1,2] Symptoms manifest as painful, recurring swelling episodes affecting subcutaneous and/or submucosal tissues throughout the body.[1,3] HAE attacks may be debilitating and/or disfiguring, profoundly disrupting school or work productivity, restricting participation in social events, and negatively impacting emotional well-being.[4] Attacks affecting the larynx can be fatal[5]; worries about risk of suffocation contribute to the continual patient burden.[6]

Hereditary angioedema symptoms recur with unpredictable frequency and severity throughout patients' lives.[4] Given the heavy burden of disease, effective and reliable prevention of attacks is an integral aspect of care for many patients. Long-term prophylaxis aims to reduce pain and disability associated with recurrent attacks. Treatment recommendations emphasize the importance of individualizing prophylactic therapy for all patients with severe HAE symptoms.[2] The need to start or continue prophylactic therapy should be continually reassessed.[2,7]

The armamentarium of prophylactic treatment options against HAE attacks continues to grow; however, unmet needs remain. For some patients, effectiveness, safety/tolerability, or convenience of licensed agents is suboptimal. For instance, androgens have undesirable anabolic and androgenic adverse effects and several contraindications,[2,8,9] whereas C1-INH replacement requires frequent administration, the intravenous formulation may be difficult to administer, and some patients require dose escalation to achieve control.[10,11]

Excess production of the potent vasodilator bradykinin, as a result of C1-INH deficiency, is a key underlying defect in HAE type I/II.[12] Endogenous C1-INH is an important inhibitor of key plasma proteins within the contact system, including factor XIIa and plasma kallikrein. Unopposed activity of plasma kallikrein as a result of C1-INH deficiency results in overproduction of bradykinin, leading to increased vascular permeability and resultant swelling episodes characteristic of HAE attacks.[12-14]

Lanadelumab is a highly potent and specific, fully human monoclonal antibody inhibitor of plasma kallikrein with a long half-life (~2 weeks)[15,16]; steady state is expected to be reached by ~70 days[17] (~5 times the half-life). This agent is currently approved as prophylactic therapy in several countries/regions, including the United States, European Union, Canada, Australia, Switzerland, and Brazil.[18-23] In the United States, lanadelumab is indicated as prophylaxis to prevent HAE attacks in patients ≥12 years of age, at a recommended dose of 300 mg every 2 weeks (q2wks); dosing every 4 weeks (q4wks) may be considered for some patients who are well controlled for >6 months.[18]

The pivotal HELP Study (NCT02586805) demonstrated efficacy of lanadelumab vs placebo in preventing HAE attacks over a 26-week treatment period (days 0-182), as well as during the steady-state period (days 70-182).[17] Herein, we report exploratory findings from ad hoc analyses from the HELP Study demonstrating a rapid onset of action and a sustained effect of lanadelumab vs placebo.

2 | PATIENTS AND METHODS

2.1 | Study design

A detailed description of the study design and methodology of the HELP Study have been previously reported.[17] Briefly, the HELP Study was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 study evaluating safety and efficacy of subcutaneously administered lanadelumab vs placebo over a 26-week treatment period. This study was conducted per International Conference on Harmonization Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local ethical and legal guidance. At screening, written informed consent (or assent, if applicable) was obtained from all patients.

Eligible patients were ≥12 years of age with a confirmed diagnosis of HAE type I/II and a baseline of ≥1 confirmed attack/4 weeks during a 4-week run-in period.[17] The run-in period could be shortened if the patient experienced ≥3 attacks before the end of the 4-week period, or could be extended to 8 weeks if the patient did not experience any attacks during the initial 4 weeks, in which case ≥2 attacks were required within the extended interval in order to proceed to enrollment and randomization. Prior to the start of the run-in period, patients were required to complete a ≥2-week washout period from any long-term prophylactic therapy, if applicable.

2.2 | Treatment groups

Eligible patients were randomized in a 2:1 ratio to receive lanadelumab (one of three dose regimens—150 mg q4wks, 300 mg q4wks, 300 mg q2wks) or placebo for a treatment period of 26 weeks (from the first dose on day 0 through 2 weeks after the final dose), for a total of 13 doses. Patients, caregivers, investigators, site personnel, and the sponsor were blinded to treatment. To maintain the blind, treatments were administered as two separate 1 mL subcutaneous injections q2wks in the upper arm. All patients had access to acute treatment if required for an attack. Patients who completed the HELP Study were able to enter into the open-label extension.

2.3 | Outcome measures

The number of HAE attacks during 26 weeks of treatment (days 0-182) was the primary efficacy endpoint in the HELP Study. Number of attacks requiring acute treatment and number of moderate or severe attacks during days 0-182, as well as the number of HAE attacks occurring from days 14 to 182, were secondary efficacy endpoints. Various exploratory endpoints were assessed, including number of high-morbidity attacks, percentage of patients who were responders, and maximum severity of attacks. Efficacy of lanadelumab during the steady-state period (days 70-182) was evaluated via post hoc analysis. Adverse events over the entire treatment period were also captured.[17]

2.4 | Ad hoc analyses for treatment days 0-69

Efficacy findings from the HELP Study, during both the full treatment period (days 0-182) and the steady-state period (days 70-182), have been previously reported.[17] In order to assess onset of action with lanadelumab, ad hoc analyses evaluated efficacy findings during days 0-69 of treatment. As with the primary study, these analyses were conducted using a Poisson regression model accounting for overdispersion. The least-squares mean monthly HAE attack rate for each lanadelumab treatment group was compared with placebo for the primary endpoint (number of confirmed HAE attacks) and selected secondary endpoints (eg, rate of attacks requiring acute treatment, rate of moderate or severe attacks). Exploratory endpoints (eg, responder analysis, maximum attack severity) were also evaluated. The model included fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous). Exploratory efficacy endpoints were compared between treatment groups without adjustment for multiplicity. *P* values were provided for exploratory purposes.

Intrapatient comparison of findings during days 0-69 vs the steady-state period was performed on select endpoints for patients with available data in both time periods, including the primary endpoint (number of confirmed HAE attacks), secondary endpoints (rate of attacks requiring acute treatment, rate of moderate or severe attacks), and exploratory endpoints (rate of high-morbidity attacks, maximum attack severity). For these analyses, a paired *t* test was used for continuous endpoints. *P*-values were provided for exploratory purposes. For categorical endpoints (eg, maximum attack severity), Kappa statistics were used to assess the magnitude of agreement in findings between the two treatment periods. Kappa statistics can be interpreted using the following scale: 1 = perfect agreement (precision/reliability); 0 = agreement fully by chance; 0.01-0.20 = slight agreement; 0.21-0.40 = fair agreement; 0.41-0.60 = moderate agreement; 0.61-0.80 = substantial agreement; and 0.81-0.99 = almost perfect agreement.[24]

Additionally, attack rates in 2- or 4-week intervals throughout the study period were evaluated.

3 | RESULTS

A total of 125 eligible patients were randomized and treated. All patients were included in the day 0-69 analysis (lanadelumab 150 mg q4wks, n = 28; 300 mg q4wks, n = 29; 300 mg q2wks, n = 27; and placebo, n = 41), whereas 120 patients were included in the day 70-182 (steady state) analysis (lanadelumab 150 mg q4wks, n = 28; 300 mg q4wks, n = 29; 300 mg q2wks, n = 26; and placebo, n = 37). Patients who discontinued prior to day 70 (4 patients in the placebo group and 1 patient in the 300 mg q2wks group) were not included.

Baseline demographics and clinical characteristics were generally balanced between treatment arms. The mean patient age was 40.7 years, 70.4% were female, and the majority (90.4%) had HAE type I. During the run-in period, patients experienced a mean (standard deviation) of 3.66 (2.61) HAE attacks per month; over half of

the patients (52.0%) reported ≥3 attacks per month. Most patients (64.8%) had a history of laryngeal attacks.

3.1 | Lanadelumab demonstrates rapid onset of action vs placebo

The mean monthly rate of HAE attacks was significantly lower with lanadelumab compared with placebo from the start of treatment (Figure 1A), including attacks requiring acute treatment (Figure 1B) and moderate/severe attacks (Figure 1C); $P \leq .001$ for all. Importantly, the lower rate of HAE attacks in lanadelumab-treated patients was evident starting from the first 2 weeks of treatment and continued throughout the study (Figure 2). At weeks 1 to 2, attack rate per 2 weeks vs baseline was reduced by 61.9% with lanadelumab 150 mg q4wks, 74.3% with 300 mg q4wks, and 80.8% with 300 mg q2wks, compared with 37.6% with placebo. Similarly, at month 1, attack rate per month vs baseline was reduced by 67.4% with lanadelumab 150 mg q4wks, 70.0% with 300 mg q4wks, and 83.5% with 300 mg q2wks, compared with 21.5% for placebo. At month 6, attack rate per month vs baseline was reduced by 83.1% with lanadelumab 150 mg q4wks, 96.6% with 300 mg q4wks, and 97.2% with 300 mg q2wks, compared with 20.8% for placebo.

The maximum attack severity was lower in patients receiving lanadelumab than in those receiving placebo during days 0-69. As shown in Figure 3, 37.9%-48.1% of patients in the lanadelumab-treated groups were attack free through day 69 of treatment, compared with 7.3% of placebo-treated patients. Additionally, a higher proportion of patients treated with lanadelumab during days 0-69 were responders (achieved ≥50% reduction in the number of attacks relative to the run-in period) compared with patients receiving placebo (Figure 4).

3.2 | Lanadelumab demonstrates sustained efficacy

The efficacy of lanadelumab vs placebo during the steady-state period was similar or improved compared with days 0-69 of treatment. Intrapatient differences during these time periods were significant with lanadelumab 300 mg q4wks for select outcomes (Table 1).

As shown in Figure 5, a numerically larger percentage of lanadelumab-treated patients were attack free during the steady-state period compared with days 0-69; a lower intrapatient agreement

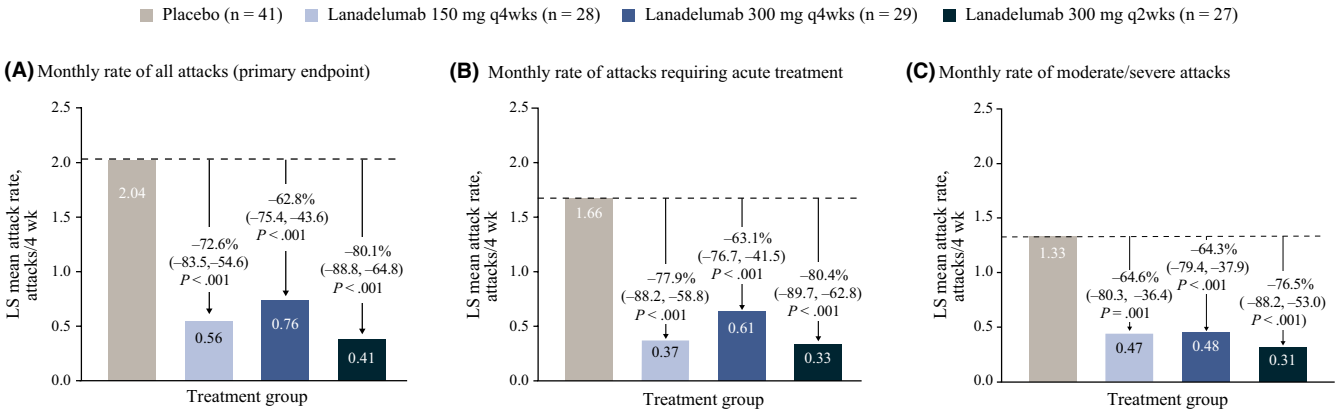


FIGURE 1 Investigator-confirmed hereditary angioedema attack rate during days 0-69 of treatment. A, Monthly rate of all attacks (primary endpoint). B, Monthly rate of attacks requiring acute treatment. C, Monthly rate of moderate/severe attacks

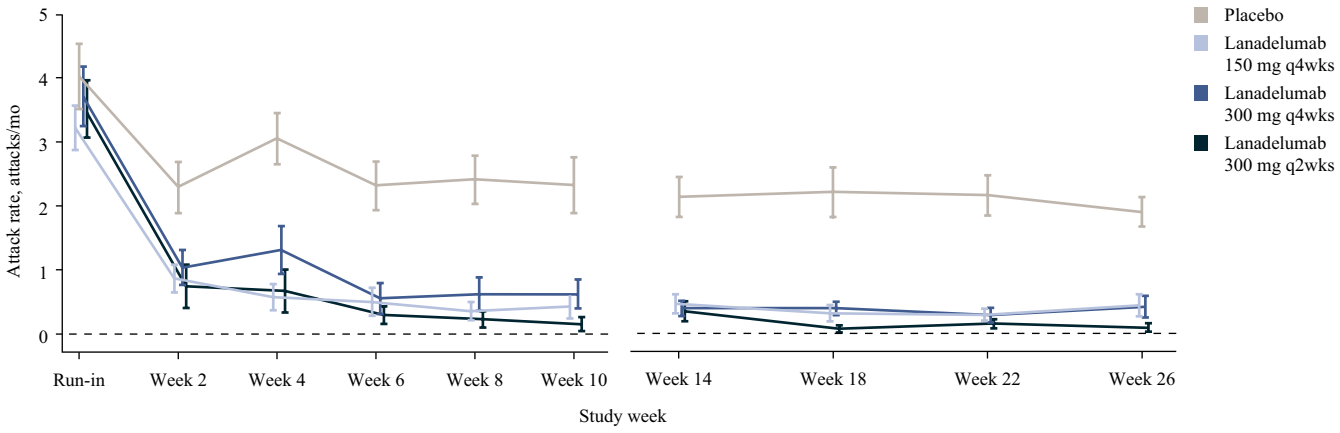


FIGURE 2 Rate of hereditary angioedema attacks during days 0-69 of treatment and during the steady-state period. Attack rates were based on attacks occurring within 2 wk prior to each time point. A month is defined as 28 d. Error bars indicate the standard error of the mean

(lower Kappa statistic) was shown for maximum attack severity with the 300 mg q2wks dosing arm.

3.3 | Safety

Treatment emergent adverse events (TEAEs) were reported by 82.1% and 75.6% of lanadelumab-treated patients during days 0-69 and days 70-182 of treatment, respectively. No treatment-related serious TEAEs nor deaths due to TEAEs occurred during either treatment period. One patient experienced a treatment-related severe TEAE during days 70-182, and one patient discontinued lanadelumab use during this time due to TEAE (Table 2). Injection-site pain, headache, viral upper respiratory tract infection, and injection site erythema were the most commonly occurring TEAEs with lanadelumab treatment during days 0-69 and days 70-182 (Table 3).

4 | DISCUSSION

Hereditary angioedema is associated with a heavy burden of illness. Symptoms recur in an unpredictable manner, and severity of attacks does not correlate with attack frequency.[4,25] Emphasis is increasingly being placed on long-term prevention of HAE attacks to reduce pain and disability associated with severe symptoms and to help mitigate the heavy physical and psychological burden patients face throughout life.[25]

The current ad hoc analyses from the HELP Study were focused on describing attack reduction rates prior to reaching steady state in order to address questions related to when attack rates can be expected to improve. Findings showed that efficacy of lanadelumab in preventing HAE attacks is evident within the first 2 weeks of treatment, and continues over time, including in patients with a high frequency of attacks at baseline (52% of patients reported ≥3 attacks per month during the run-in period). This early onset of effect is consistent with findings reported in a post hoc analysis of the COMPACT study, which evaluated prophylactic therapy with 60 IU/kg of plasma-derived C1-INH administered subcutaneously twice weekly.[26] In that analysis, a preventive effect vs placebo was seen within the first 2 weeks of treatment with plasma-derived C1-INH.

In our study of patients with relatively severe HAE, at weeks 1-2, attack rate per 2 weeks vs baseline was reduced by 80.8% in the lanadelumab 300 mg q2wks treatment group. It should be noted, however, that given the heterogeneous nature of HAE and its highly unpredictable and fluctuating disease course,[27] caution is required when interpreting data over short time periods, such as 2-week intervals.

Our study also showed statistically significant improvements with lanadelumab vs placebo in HAE attack rate during days 0-69 of treatment (prior to reaching steady state). The goal for this analysis was to demonstrate a trend for rapid onset and consistent improvement vs placebo across the three active doses during this time period; comparisons among the active doses were not the main focus. Importantly, lanadelumab is a long-term treatment for prevention of HAE attacks; the data summary for its efficacy during days 0-69 of treatment should not be considered a basis for long-term dose selection. The recommended starting dosage of lanadelumab (300 mg every 2 weeks),[18] as approved by regulatory bodies, was determined based on efficacy results from the full 182 days of treatment in the HELP Study. As demonstrated previously,[17] the 300 mg q2wks treatment arm was at least numerically more effective compared with the

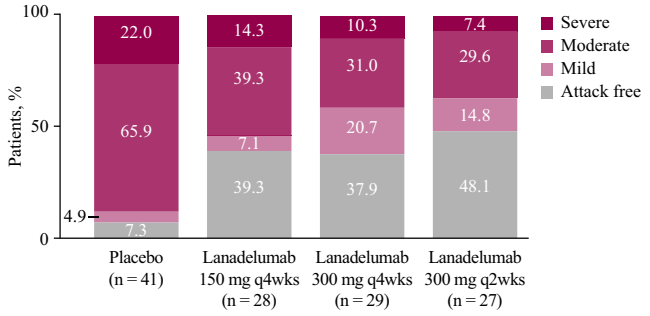


FIGURE 3 Attacks by maximum severity, days 0-69 of treatment. Due to rounding, some bars may not total 100%

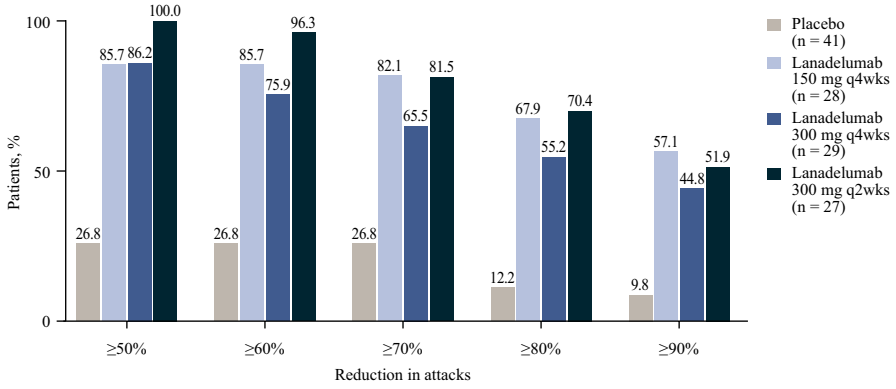


FIGURE 4 Proportion of patients achieving ≥50% to ≥90% reduction in attack rate during days 0-69 relative to the run-in period. Responders were defined as patients who achieved ≥50% reduction in number of attacks relative to the run-in period. For each patient, the percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. The percentage reduction groups are not mutually exclusive; patients may appear in more than one group, as applicable, based on their percentage reduction

TABLE 1 Intrapatient comparison of monthly attack rates during the steady-state period (days 70-182) vs days 0-69

	Mean difference in attack rate (SD)[a]	95% CI of the mean difference	Median difference (min, max)	*P*-value[b]
Difference in monthly attack rate (primary endpoint)				
Placebo	−0.19 (0.881)	−0.487, 0.101	−0.21 (−1.7, 1.3)	.191
Lanadelumab 150 mg q4wks	−0.11 (0.465)	−0.291, 0.069	0.00 (−1.2, 0.9)	.217
Lanadelumab 300 mg q4wks	−0.44 (0.757)	−0.726, −0.151	−0.40 (−2.7, 1.0)	.004
Lanadelumab 300 mg q2wks	−0.23 (0.671)	−0.499, 0.043	0.00 (−3.2, 0.4)	.095
Difference in monthly rate of moderate/severe attacks				
Placebo	−0.24 (0.967)	−0.565, 0.080	−0.16 (−2.5, 1.6)	.136
Lanadelumab 150 mg q4wks	−0.16 (0.470)	−0.338, 0.027	0.00 (−1.6, 0.6)	.091
Lanadelumab 300 mg q4wks	−0.27 (0.667)	−0.528, −0.021	0.00 (−2.4, 1.0)	.035
Lanadelumab 300 mg q2wks	−0.16 (0.690)	−0.437, 0.120	0.00 (−3.2, 0.8)	.253
Difference in monthly rate of attacks requiring acute treatment				
Placebo	−0.12 (0.714)	−0.360, 0.116	−0.16 (−1.6, 1.3)	.306
Lanadelumab 150 mg q4wks	−0.06 (0.397)	−0.219, 0.089	0.00 (−1.1, 0.9)	.395
Lanadelumab 300 mg q4wks	−0.37 (0.746)	−0.653, −0.085	0.00 (−2.5, 0.8)	.013
Lanadelumab 300 mg q2wks	−0.18 (0.688)	−0.457, 0.098	0.00 (−3.2, 0.7)	.195
Difference in rate of high-morbidity attacks[c]				
Placebo	0.01 (0.396)	−0.125, 0.139	0.00 (−1.2, 1.0)	.912
Lanadelumab 150 mg q4wks	−0.04 (0.245)	−0.140, 0.050	0.00 (−0.8, 0.7)	.340
Lanadelumab 300 mg q4wks	−0.02 (0.128)	−0.064, 0.033	0.00 (−0.4, 0.3)	.518
Lanadelumab 300 mg q2wks	−0.03 (0.096)	−0.066, 0.012	0.00 (−0.4, 0.0)	.166

Note: Lanadelumab 150 mg q4wks, n = 28; Lanadelumab 300 mg q4wks, n = 29; Lanadelumab 300 mg q2wks, n = 26; placebo, n = 37.

Abbreviations: CI, confidence interval; max, maximum; min, minimum; q2wks, every 2 weeks; q4wks, every 4 weeks; SD, standard deviation.

[a]Difference in attack rate was calculated as days 70-182 attack rate minus days 0-69 attack rate.

[b]*P* values were derived from a paired *t* test comparing findings during days 0-69 vs the steady-state period.

[c]Defined as any attack that had at least one of the following characteristics: severe, resulted in hospitalization (except hospitalization for observation <24 h), hemodynamically significant (systolic blood pressure <90 mm Hg, requires intravenous hydration, or associated with syncope or near-syncope), or laryngeal.

other lanadelumab dosage arms vs placebo across all primary and secondary efficacy analyses during the full treatment period.

Findings also showed that maximum attack severity was lower in lanadelumab-treated patients during this time period; 48.1% of patients receiving lanadelumab 300 mg q2wks (the recommended starting dose)[18] were attack free. This percentage increases to 76.9% during the steady-state period, per previously reported findings.[17]

Our findings demonstrated that the efficacy of lanadelumab in preventing HAE attacks is sustained and durable; a trend for similar or improved efficacy during the steady-state period compared with days 0-69 of treatment was shown.

The lower Kappa statistic for maximum attack severity with the 300 mg q2wks dosing arm during the steady-state period vs days 0-69 reflects a lower intrapatient agreement (ie, a greater difference in

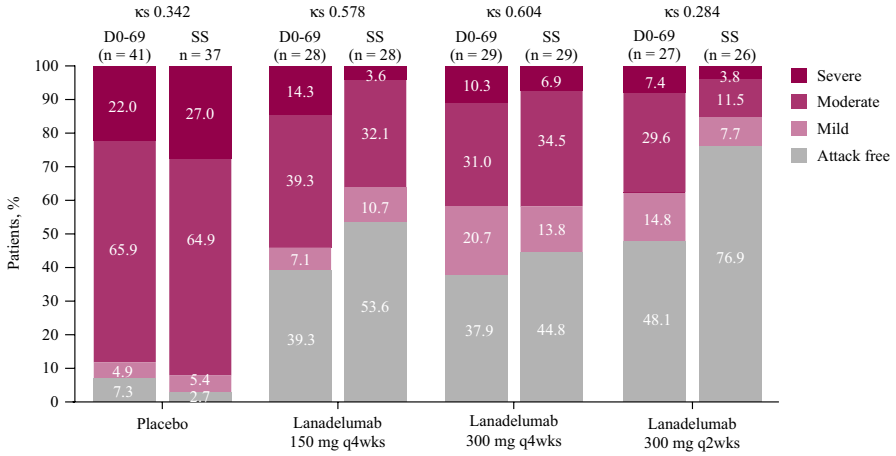


FIGURE 5 Agreement in findings for maximum attack severity during days 0-69 (D0-69) vs the steady-state (SS) period. The Kappa statistic (κs) was used to assess the magnitude of agreement in findings between the two treatment periods. Kappa statistics are interpreted using the following scale: 1=perfect agreement (precision/reliability); 0=agreement fully by chance; 0.01-0.20=slight agreement; 0.21-0.40=fair agreement; 0.41-0.60=moderate agreement; 0.61-0.80=substantial agreement; 0.81-0.99=almost perfect agreement.[24] Due to rounding, some bars may not total 100%. Subjects were included if they had both Day 0-69 and Day 70-182 results

TABLE 2 Summary of TEAEs[a]

	Days 0-69					Steady state (days 70-182)				
		Lanadelumab					Lanadelumab			
	Placebo	150 mg q4wks	300 mg q4wks	300 mg q2wks	Total	Placebo	150 mg q4wks	300 mg q4wks	300 mg q2wks	Total
N	41	28	29	27	84	37	28	28	26	82
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	26 (63.4)	21 (75.0)	23 (79.3)	25 (92.6)	69 (82.1)	24 (64.9)	22 (78.6)	18 (64.3)	22 (84.6)	62 (75.6)
Any related TEAE	14 (34.1)	14 (50.0)	14 (48.3)	17 (63.0)	45 (53.6)	7 (18.9)	13 (46.4)	10 (35.7)	11 (42.3)	34 (41.5)
Any serious TEAE	0	0	2 (6.9)	0	2 (2.4)	0	0	1 (3.6)	1 (3.8)	2 (2.4)
Any related serious TEAE	0	0	0	0	0	0	0	0	0	0
Any related severe TEAE	1 (2.4)	0	0	0	0	0	0	1 (3.6)	0	1 (1.2)
Hospitalization due to TEAEs	0	0	2 (6.9)	0	2 (2.4)	0	0	1 (3.6)	1 (3.8)	2 (2.4)
Discontinuation due to TEAE	1 (2.4)	0	0	0	0	0	0	1 (3.6)	0	1 (1.2)
Deaths due to TEAEs	0	0	0	0	0	0	0	0	0	0

[a]Excluding hereditary angioedema attack-reported events.

results) between these two time periods. These results suggest a trend toward a higher likelihood of achieving optimal efficacy (eg, being attack free) with this dose than with the other lanadelumab doses (for which a higher Kappa statistic was shown, indicating a smaller degree of difference in findings between steady state and days 0-69).

The safety profile of lanadelumab was generally comparable during days 0-69 and days 70-182 of treatment. No notable differences in percentage of patients experiencing TEAEs or treatment-related TEAEs were found, and the most commonly occurring TEAEs were similar during both treatment periods (primarily injection site pain).

Findings from these exploratory analyses are highly relevant from the perspective of both patients and healthcare providers. For patients, prophylactic agents with a rapid onset of action, sustained effect, and convenient dosing frequency and route of administration can help reduce the treatment burden of this chronic disease and improve HAE management plans, helping to normalize daily life (including participation in social activities, achievement of educational goals, and improved work productivity). Such agents can also help alleviate the emotional burden associated with the unpredictable nature of the disease. For healthcare providers, the decision to initiate and continue long-term preventative HAE therapy is based on

TABLE 3 TEAEs occurring in ≥5% of patients (by preferred term) in the total lanadelumab group (excluding hereditary angioedema attacks)

	Placebo	Lanadelumab			
		150 mg q4wks	300 mg q4wks	300 mg q2wks	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Days 0-69					
Injection site pain	12 (29.3)	12 (42.9)	9 (31.0)	13 (48.1)	34 (40.5)
Headache	8 (19.5)	1 (3.6)	4 (13.8)	6 (22.2)	11 (13.1)
Viral upper respiratory tract infection	4 (9.8)	2 (7.1)	3 (10.3)	2 (7.4)	7 (8.3)
Injection site erythema	1 (2.4)	2 (7.1)	2 (6.9)	2 (7.4)	6 (7.1)
Days 70-182					
Injection site pain	8 (21.6)	9 (32.1)	7 (25.0)	7 (26.9)	23 (28.0)
Viral upper respiratory tract infection	9 (24.3)	3 (10.7)	5 (17.9)	9 (34.6)	17 (20.7)
Headache	1 (2.7)	3 (10.7)	3 (10.7)	7 (26.9)	13 (15.9)
Injection site erythema	0	4 (14.3)	1 (3.6)	1 (3.8)	6 (7.3)

multiple factors related to disease activity and control, including the frequency, severity, and location of attacks; access to emergency care facilities; impact of attacks on patients' daily life; and patient preference.[2,10,25] The likelihood of adherence to long-term therapy is another important consideration.

An understanding of what to expect from therapy (including how quickly a protective effect against attacks is likely to begin and how long it is expected to continue) can assist with deciding whether to initiate and how long to continue prophylactic treatment, and may help encourage patients to adhere to treatment. In the authors' clinical experience, knowledge of the durable protection from attacks provided by lanadelumab may help patients feel less concerned about the continual need to avoid possible triggering factors.

In conclusion, findings from these ad hoc analyses demonstrate a rapid onset of action and sustained prevention of attacks with lanadelumab in patients with HAE. Patients can expect to achieve a favorable early response, and a comparable or improved response over time.

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CONFLICTS OF INTEREST

MAR has received research grants from BioCryst, CSL Behring, Pharming, and Shire*; consulting fees from Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Shire*; and speaker honoraria from CSL Behring, Pharming, and Shire; and is a medical advisory board member of the US Hereditary Angioedema Association. MM has received research grant support and/or speaker/consultancy fees from Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Shire.* JAB has been a clinical investigator for BioCryst, CSL Behring, Pharming, and Shire*; a speaker for CSL Behring, Pharming, and Shire*; and a consultant for BioCryst, CSL Behring, Kabi, KalVista, Pharming, and Shire*; and is a medical advisory board member of the US Hereditary Angioedema Association. AB has received institutional research/study support from BioCryst and Shire* and/or honoraria for consulting from BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Shire.* HJL has received research grant support and/or speaker/consultancy fees

from Adverum, BioCryst, CSL Behring, Octapharma, Pharming, and Shire.* HHL has been a clinical investigator and received grants and/or honoraria from BioCryst, CSL Behring, Pharming, and Shire.* PL was a full-time employee of Shire* at the time of this analysis and holds stock/stock options in Takeda. Her current affiliation is Pharvaris B.V. JH and SJ are full-time employees of Shire* and hold stock/stock options in Takeda. WRL has received consultant fees from Adverum, BioCryst, CSL Behring, Pharming, and Shire*; research grants from BioCryst, CSL Behring, Pharming, and Shire*; and payments for lectures from CSL Behring, Pharming, and Shire*; and is a medical advisory board member of the US Hereditary Angioedema Association.

*A Takeda company.

AUTHOR CONTRIBUTIONS

JH, MAR, PL, and SJ were involved in planning; JH, HJL, and MAR were involved in data collection. All authors were involved in interpretation of results, writing of the manuscript or critically evaluating revisions, and approval of final submission draft.

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321 Post Marketing Safety Determination for Subcutaneous C1-Inhibitor Prophylactic Treatment in Hereditary Angioedema

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RATIONALE: Subcutaneous C1-inhibitor ([C1-INH(SC)] Haegarda®) is newly approved for prophylaxis in hereditary angioedema (HAE). The aim of this quality assessment was to evaluate compliance, tolerability and safety of C1-INH(SC) in our HAE patients.

METHODS: We conducted a telephone safety survey of our patients on C1-INH(SC) prophylaxis to determine their tolerance of therapy. The study met IRB exclusion.

RESULTS: Eleven out of thirteen patients were reached for an interview (median age 39 years; 8 female/3 male). Nine responders (82%) used C1-INH(SC) as directed, at appropriate dose and time interval. Patients tolerated the medication very well, with a mean score of 4.6 (range: 1 to 5). Ease of injection averaged at 4.2 (range: 1 to 5). Even though 73% had local side effects from injections, compliance was not affected. None had any other adverse effects. The average time to inject the medication was 5.9 minutes. All patients had decreased frequency of attacks. Prior to the start of C1-INH(SC), the attack rate averaged at 2.3 attacks per month, while after the start of C1-INH(SC), the attack rate decreased to an average of 0.3 attacks per month. All patients had improved quality of life, and 91% stated they were less anxious.

CONCLUSIONS: Despite C1-INH(SC) being a subcutaneous injectable medication with twice weekly dosing, our quality assessment demonstrated that its use is associated with high compliance, tolerability and safety in our HAE patients as well as improved quality of life.

322 Attack-Free Status of Patients With Hereditary Angioedema (HAE) During Extended Treatment With Lanadelumab in the HELP OLE Study

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RATIONALE: In the HELP study, 44% of patients with HAE were attack-free over 182 days' treatment with 300mg lanadelumab every 2 weeks (Q2W) and 77% during steady state (Days 70-182). We analyzed patient attack-free status during the ongoing HELP open-label extension study (OLE; NCT02741596).

METHODS: Patients ≥12 years old with HAE type I/II who continued from HELP (rollovers) received 300mg lanadelumab on Day 0, then 300mg Q2W after their first attack (treatment period excluded the "dose-and-wait" period). Patients who did not participate in HELP (nonrollovers) but had ≥1 attack/12 weeks at baseline received 300mg Q2W from Day 0 (treatment period started from Day 0). Cumulative results through 31Aug2018 were analyzed.

RESULTS: 212 patients (n=109 rollovers, n=103 nonrollovers) received lanadelumab over a mean (range) of 19.7 (0-26.1) months, including 193 (91.0%) who completed ≥12 months on study. The attack rate during the treatment period was reduced by ≥70% in 99 (93.4%) rollover and 91 (88.3%) nonrollover patients versus baseline. 57.9% of patients (50.9% rollovers, 65.0% nonrollovers) were attack-free for a period of >12 months, and 78.0% (76.4% rollovers, 79.6% nonrollovers) were attack-free for a period of ≥6 months. On average, patients had a mean of 27.3 attack-free days/month, and a mean attack-free duration of 291.3 days.

CONCLUSIONS: Consistent with the HELP Study, nearly 8/10 patients receiving 300mg Q2W were attack-free for a period of ≥6 months, and the majority (nearly 6/10) were attack-free for a period of >1 year, supporting the efficacy of lanadelumab over an extended treatment period.

323 Review of Icatibant Use in the Winnipeg Regional Health Authority

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RATIONALE: Icatibant is indicated to treat Hereditary Angioedema (HAE) types I and II and is used off-label to treat HAE with normal C1-INH (HAE-nC1INH) and ACE-Inhibitor-Induced Angioedema (ACEI-AE). As the Winnipeg Regional Health Authority (WRHA) became the first Canadian jurisdiction to add icatibant to its formulary in 2015, we describe the timeline to icatibant treatment, it's effectiveness and the presence of confounding factors.

METHODS: A retrospective chart review identified 23 icatibant-treated angioedema attacks. Survival analysis was performed on the time (hours) from emergency department (ED) presentation to non-icatibant treatment, allergist consult, icatibant dispensation and administration, onset of symptom relief (TOSR), and discharge or resolution (TR); comparisons were with reference RCT data or between subgroups stratified by various factors. Stratifiers included: etiology (HAE vs ACEI-AE), atopy, smoking, site of angioedema, and initial conventional treatment with antihistamines, epinephrine, glucocorticoids, C1-INH or fresh frozen plasma.

RESULTS: 100% of our HAE subgroup had HAE-nC1INH: the median TOSR and TR were similar to reference HAE type I/II data (1.13 vs 0.8 hours, p = 0.34; 3.50 vs 8.0 hours, p=0.11). Icatibant-treated ACEI-AE had a greater median TOSR than reference HAE type I/II data (4.86 vs 0.8, p=0.01) and had a greater TR compared to our HAE-nC1INH subgroup (19.5 vs 3.5, p=0.02); the median ACEI-AE TR was not different from natural history (19.53 vs 4.0 hours, p=0.18). Conventional trials of non-icatibant treatment significantly delays time to treatment (7.78 vs 2.06, p=0.03)

CONCLUSIONS: Icatibant may be an effective treatment for HAE-nC1INH but not for ACEI-AE. Trialing conventional treatment delays icatibant treatment.

324 Current Medical Management of Hereditary Angioedema (HAE): Follow-up to a Large Survey of US Physicians

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RATIONALE: Clinician surveys on HAE management in 2010 and 2013 revealed important trends in HAE care. The objectives of this follow-up survey were to further evaluate current HAE management and the impact of new treatment options on evolving clinician practice patterns over time.

METHODS: During June and July 2019, 5387 physicians were contacted via postal mail (from HAEA and ACAAI mailing lists) to complete a 47-question survey, of whom 177 responded (3%).

RESULTS: Across the three surveys, use of danazol as the most frequently prescribed long-term prophylactic (LTP) HAE treatment dropped from 56% in 2010 to 20% in 2013 to 6% in 2019 ($P<.001$). Conversely, clinicians reporting C1-INH as the most commonly prescribed LTP increased from 23% to 57% to 60% ($P<.001$), respectively, with the majority now prescribing the subcutaneous (SC) form (41% SC vs 19% intravenous). Regarding the strongest non-efficacy factor influencing treatment choice, cost/insurance coverage surpassed adverse effects for clinicians, increasing to 44% (from 24% in 2010 and 40% in 2013; $P=.001$), while concern over adverse effects dropped to 16% (from 56% in 2010 and 30% in 2013; $P<.001$). The percentage of patients self-treating attacks doubled since 2013 (27% to 54%; $P<.001$), and the home replaced the emergency department (ED) as the most commonly reported setting for attack treatment (54% vs 35%). Clinicians reported patient satisfaction remains high, with only 1.5% of clinicians indicating patients are not satisfied with treatment.

CONCLUSIONS: These findings confirm current HAE treatment options allow for higher rates of home treatment, decreased ED visits, and increased patient satisfaction.

MINIREVIEW

Antibody Structure, Instability, and Formulation

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ABSTRACT: The number of therapeutic monoclonal antibody in development has increased tremendously over the last several years and this trend continues. At present there are more than 23 approved antibodies on the US market and an estimated 200 or more are in development. Although antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior. This article reviews the structure and function of antibodies and the mechanisms of physical and chemical instabilities. Various aspects of formulation development have been examined to identify the critical attributes for the stabilization of antibodies. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:1–26, 2007

Keywords: biotechnology; stabilization; protein formulation; protein aggregation; freeze drying/lyophilization

INTRODUCTION

Protein therapies are entering a new era with the influx of a significant number of antibody pharmaceuticals. Generally, protein drugs are effective at low concentrations with less side effects relative to small molecule drugs, even though, in rare cases, protein-induced antibody formation could be serious.[1] Therefore, this category of therapeutics is gaining tremendous momentum and widespread recognition both in small and large drug firms. Among protein drug therapies, antibodies play a major role in controlling many types of diseases such as cancer, infectious diseases, allergy, autoimmune diseases, and inflammation. Since the approval of the first monoclonal antibody (MAb) product -OKT-3 in 1986, more than 23 MAb drug products have entered the market (Tab. 1). The estimated number of antibodies and antibody derivatives constitute 20% of biopharmaceutical products currently in development (about 200).[2] The global therapeutic antibody market was predicted to reach $16.7 billion in 2008.[3]

There are several reasons for the increasing popularity of antibodies for commercial development. First, their action is specific, generally leading to fewer side effects. Second, antibodies may be conjugated to another therapeutic entity for efficient delivery of this entity to a target site, thus reducing potential side effects. For instance, Mylotarg is an approved chemotherapy agent composed of calicheamicin conjugated to humanized IgG4, which binds specifically to CD33 for the treatment of CD33-positive acute myeloid leukemia. Another example is the conjugation of immunotoxic barnase with the light chain of the anti-human ferritin monoclonal antibody F11 as potential targeting agents for cancer immunotherapy.[4] Third, antibodies may be conjugated to radioisotopes for specific diagnostic purposes. Examples include CEA-Scan for detection of colorectal cancer and ProstaScint for detection of prostate cancer. Lastly, technology advancement has made complete human MAb available, which are less immunogenic.

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Table 1. Commercial Monoclonal Antibody Products

#	Brand name	Molecule	MAb	Year	Company	Route	Indication	MAb Conc	Buffer	Excipients	Surfactant	pH
1	Avastin	Bevacizumab	Humanized IgG1, 149 kDa	2004	Genetech and BioOncology	IV infusion	Metastatic carcinoma of colon or rectum, binds VEGF	100 mg and 400 mg/vial (25 mg/mL) solution	5.8 mg/mL monobasic NaPhos H_2O; 1.2 mg/mL dibasic NaPhos anhydrous (4 mL, 16 mL fill in vial)	60 mg/mL α-Trehalose dihydrate (4 mL, 16 mL fill in vial)	0.4 mg/mL PS20 (4 mL, 16 mL fill in vial)	6.2
2	Bexxar	Tositumomab and I-131Tositumab	Murine IgG2λ	2003	Corixa and GSK	IV Infusion	CD20 positive follicular nonHodgkins lymphoma	Kit: 14 mg/mL MAb solution in 35 mg and 225 mg vials; 1.1 mg/mL *I131-MAb* solution	10 mM phosphate (MAb vial)	145 mM NaCl, 10 % w/v Maltose; *I131-MAb*: 5–6% Povidone, 1–2, 9–15 mg/mL Maltose, 0.9 mg/mL NaCl, 0.9–1.3 mg/mL Ascorbic acid		7.2
3	Campath	Alemtuzumab	Humanized, IgG1k, 150 kDa	2001	Ilex Oncology; Millenium and Berlex	IV infusion	B-cell chronic lymphocytic leukemia, CD52-antigen	30 mg/3 mL solution	3.5 mg/3 mL dibasic NaPhos, 0.6 mg/3 mL monobasic KPhos	24 mg/3 mL NaCl, 0.6 mg/3 mL KCl, 0.056 mg/3 mL Na2EDTA	0.3 mg/3 mL PS80	6.8–7.4
4	CEA-Scan (lyo)	Acrituomab; Tc-99	Murine Fab, 50 kDa	1996	Immunomedics	IV injection or infusion	Imaging agent for colorectal cancer	1.25 mg/vial Lyophilized MAb. Reconstitute w 1 mL Saline w Tc99m	0.29 mg/vial Stannous chloride, potassium sodium tartrate tetrahydrate, NaAcetate.$3H_2O$, NaCl, glacial acetic acid, HCl	Sucrose		5.7
5	Erbitux	Cetuximab	Chimeric human/ mouse IgG1k, 152 kDa	2004	ImClone and BMS	IV infusion	Treatment of EGFR-expressing colorectal carcinoma	100 mg MAb in 50 mL; 2 mg/ mL solution	1.88 mg/mL DibasicNaPhos · $7H_2O$; 0.42 mg/mL MonobasicNaPhos · H_2O	8.48 mg/mL NaCl		7.0–7.4
6	Herceptin (lyo)	Trastuzumab	Humanized IgG1k	1998	Genetech	IV infusion	Metastatic breast cancer whose tumor overexpress HER2 protein	440 mg /vial, 21 mg/mL after reconstitution	9.9 mg/20 mL L-HistidineHCl, 6.4 mg/20 mL L-Histidine	400 mg/20 mL α-Trehalose Dihydrate	1.8 mg/20 mL PS20	6
7	Humira	Adalimumab	Human IgG1k, 148 kDa	2002	CAT and Abbott	SC	RA patients not responding to DMARDs. Blocks TNF-alpha	40 mg/0.8 mL solution (50 mg/mL)	0.69 mg/0.8 mL Monobasic NaPhos · $2H_2O$; 1.22 mg/0.8 mL DibasicNaPhos · $2H_2O$; 0.24 mg/0.8 mL NaCitrate, 1.04 mg/ 0.8 mL Citric acid · H_2O	4.93 mg/0.8 mL NaCl; 9.6 mg/0.8 mL Mannnitol	0.8 mg/0.8 mL PS80	5.2
8	Lucentis	Ranibizumab	Humanized IgG1k fragment	2006	Genentech	Intravitreal injection	Age-related macular degeneration (wet)	10 mg/mL solution	10 mM HistidineHCl	10% α-Trehalose-Dihydrate	0.01% PS20	5.5

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9	Mylotarg (lyo)	Gemtuzumab ozogamicin	Humanized IgG4k conjugated with calicheamicin	2000	Celltech and Wyeth	IV infusion	Humanized Ab linked to calicheamicin for treatment of CD33 positive acute myeloid leukemia	5 mg protein-equivalent lyophilized powder/20-mL vial	Monobasic and dibasic NaPhosphate	Dextran 40, Sucrose, NaCl		
10	OncoScint	Satumomab pendetide	Murine IgG1k conjugated to GYK-DTPA	1992	Cytogen	IV injection	Imaging agent for colorectal and ovarian cancer	0.5 mg conjugate/mL solution (2 mL per vial)	Phosphate buffer saline			6.0
11	Orthoclone OKT	Muromomab-CD3	Murine, IgG2a, 170 kDa	1986	Ortho Biotech	IV injection	Reversal of acute kidney transplant rejection (anti CD3-antigen)	1 mg/mL solution	2.25 mg/5 mL monobasic NaPhos, 9.0 mg/5 mL dibasic NaPhos	43 mg/5 mL NaCl	1 mg/mL PS80	7 ± 0.5
12	ProstaScint	Indium-111 capromab pendetide	Murine IgG1k-conjugated to GYK-DTPA	1996	Cytogen	IV injection	Imaging agent for prostate cancer	0.5 mg conjugate/mL solution (1 mL per vial)	Phosphate buffer saline			5–7
13	Raptiva (lyo)	Efalizumab	Humanized IgG1k	2003	Xoma and Genentech	SC	Chronic moderate to severe plaque psoriasis, binds to CD11a subunit of LFA-1	150 mg MAb/vial; 125 mg/ 1.25 mL (100 mg/mL) after reconstitution with 1.3 mL SWFI	6.8 mg/vial L-HistidineHCl · H_2O; 4.3 mg/vial L-Histidine	123.2 mg/vial Sucrose	3 mg/vial PS20	6.2
14	Remicade (lyo)	Infliximab	Chimeric human/ murine MAb against TNFalpha (app. 30% murine, 70% corresponds to human IgG1 heavy chain and human kappa light chain constant regions)	1998	Centocor	IV infusion	RA and Crohn's disease (anti TNFalpha)	100 mg / 20-mL Vial, 10 mg/mL on reconstitution	2.2 mg/10 mL MonobasicNaPhos H_2O, 6.1 mg/10 mL DibasicNaPhos · $2H_2O$	500 mg/10 mL Sucrose	0.5 mg/10 mL PS80	7.2
15	ReoPro	Abciximab	Fab. Chimeric human-murine, 48 kDa	1994	Centocor / Lilly	IV injection and infusion	Reduction of acute blood clot related complications	2 mg/mL solution	0.01 M NaPhosphate	0.15 M NaCl	0.001% (0.01 mg/ mL) PS80	7.2
16	Rituxan	Rituximab	Chimeric mouse/ human IgG1k with murine light and heavy chain variable region (Fab domain), 145 kDa	1997	IDEC and Genentech	IV infusion	NonHodgkin's lymphoma. (anti CD20-antigen)	10 mg/mL solution	7.35 mg/mL NaCitrate · $2H_2O$	9 mg/mL NaCl	0.7 mg/mL PS80	6.5

(*Continued*)

Table 1. (*Continued*)

#	Brand name	Molecule	MAb	Year	Company	Route	Indication	MAb Conc	Buffer	Excipients	Surfactant	pH
17	Simulect (lyo)	Basiliximab	Chimaric IgG1k, 144 kDa	1998	Novartis	IV injection and infusion	Prevention of acute kidney transplant rejection, IL-2 receptor antagonist	10 mg and 20 mg/ vial, 4 mg/mL on reconstitution	3.61 mg, 7.21 mg Monobasic KPhos; 0.50 mg, 0.99 mg Na_2HPO_4	0.8 mg, 1.61 mg NaCl; 10 mg, 20 mg Sucrose; 40 mg, 80 mg Mannitol; 20 mg 40 mg Glycine		
18	Synagis (lyo)	Palivizumab	Humanized IgG1k, CDR of murine MAb 1129, 148 kDa	1998	MedImmune	IM injection	Prevent replication of the Respiratory syncytial virus (RSV)	50 mg and 100 mg / vial, 100 mg/mL on reconstitution	47 mM Histidine, 3.0 mM Glycine	5.6 % Mannitol		
19	Tysabri	Natalizumab	Humainzed IgG4k	2004	Biogen IDEC	IV Infusion	MS relapse	300 mg/15 mL solution	17.0 mg MonobasicNa Phos $\cdot H_2O$, 7.24 mg diBasicNaPhos $\cdot 7H_2O$ for 15 mL	123 mg/15 mL NaCl	3.0 mg/15 mL PS80	6.1
20	Verluma	Nofetumomab	Murine Fab	1996	Boehringer Ingelheim and DuPont Merck	IV injection	Imaging agent for lung cancer	10 mg/mL solution	Phosphate buffer saline			?
21	Xolair (lyo)	Omalizumab	Humanized IgG1k, 149 kDa		Genentech w Novartis and Tanox	SC	Asthma, inhibits binding of IgE to IgE receptor FCeRI	202.5 mg/vial, Deliver 150 mg/ 1.2 mL on reconstitution with 1.4 mL SWFI	2.8 mg LHistidineHCl $\cdot H_2O$; 1.8 mg LHistidine	145.5 mg Sucrose	0.5 mg PS20	
22	Zenapax	Daclizumab	Humanized IgG1, 144 kDa	1997	Roche	IV infusion	Prophylaxis of acute organ rejection in patients receiving renal transplants. Inhibits IL-2 binding to the Tac subunit of IL-2 receptor complex	25 mg/5 mL MAb Solution	3.6 mg/mL MonobasicNa Phos $\cdot H_2O$; 11 mg/mL DibasicNaPhos $\cdot 7H_2O$	4.6 mg/mL NaCl	0.2 mg/mL PS80	6.9
23	Zevalin	Ibritumomab-Tiuxetan	Murine IgG1k-thiourea covalent linkage to Tiuxetan		IDEC	IV infusion	CD20 antigen. (Kit with Ytterium-90 induces cellular damage by beta emission)	3.2 mg/2 mL solution		09% NaCl		7.1

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Development of commercially viable antibody pharmaceuticals has, however, not been straightforward. This is because the behavior of antibodies seems to vary, even though they have similar structures. In attempting to address some of the challenges in developing antibody therapeutics, Harris et al.[5] reviewed the commercial-scale formulation and characterization of therapeutic recombinant antibodies. In a different review, antibody production and purification have been discussed.[2] Nevertheless, the overall instability and stabilization of antibody drug candidates have not been carefully examined in the literature. This article, not meant to be exhaustive, intends to review the structure and functions of antibodies, discuss their instabilities, and summarize the methods for stabilizing/formulating antibodies.

ANTIBODY STRUCTURE

Antibodies (immunoglobulins) are roughly Y-shaped molecules or combination of such molecules (Fig. 1). Their structures are divided into two regions—the variable (V) region (top of the Y) defining antigen-binding properties and the constant (C) region (stem of the Y), interacting with effector cells and molecules. Immunoglobulins can be divided into five different classes –IgA, IgD, IgE, IgM, and IgG based on their C regions, respectively designated as α, δ, ε, μ, and γ (five main heavy-chain classes).[6] Most IgGs are monomers, but IgA and IgM are respectively, dimmers and pentamers linked by J chains. IgGs are the most abundant, widely used for therapeutic purposes, and their structures will be discussed as antibody examples in detail.

Primary Structure

The structure of IgGs have been thoroughly reviewed.[6] The features of the primary structure of antibodies include heavy and light chains, glycosylation, disulfide bond, and heterogeneity.

Heavy and Light Chains

IgGs contain two identical heavy (H, 50 kDa) and two identical light (L, 25 kDa) chains (Fig. 1). Therefore, the total molecular weight is approximately 150 kDa. There are several disulfide bonds linking the two heavy chains, linking the heavy and light chains, and residing inside the chains (also see next section). IgGs are further divided

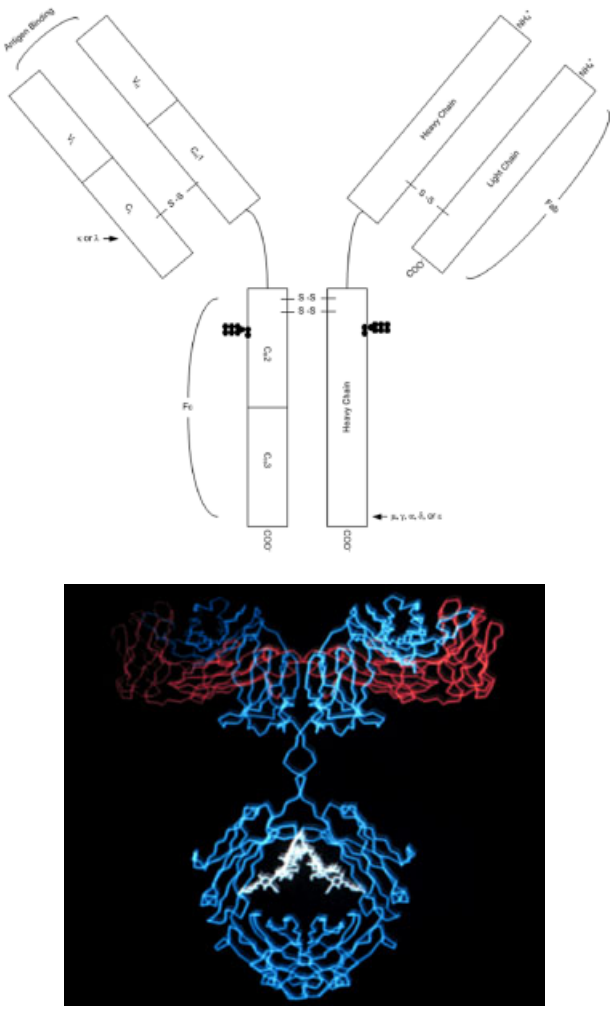


Figure 1. Linear (upper panel) and steric (lower panel) structures of immunoglobulins (IgG).

into several subclasses—IgG1, IgG2, IgG3, and IgG4 (in order of relative abundance in human plasma), with different heavy chains, named γ1, γ2, γ3, and γ4, respectively. The structural differences among these subtypes are the number and location of interchain disulfide bonds and the length of the hinge region. The light chains consist of two types—lambda (λ) and kappa (κ). In mice, the average of κ to λ ratio is 20:1, whereas it is 2:1 in humans.[6] The variable (V) regions of both chains cover approximately the first 110 amino acids, forming the antigen-binding (Fab) regions, whereas the remaining sequences are constant (C) regions, forming Fc (fragment crystallizable) regions for effector recognition and binding.[6] The N-terminal sequences of both the heavy and light chains vary greatly between different antibodies. It was suggested that the conserved sequences in human IgG1 antibodies

are approximately 95% and the remaining 5% is variable and creates their antigen-binding specificity.[5]

The V regions are further divided into three hypervariable sequences (HV1, HV2, and HV3) on both H and L chains. In the light chains, these are roughly from residues 28 to 35, from 49 to 59, and from 92 to 103, respectively.[6] Other regions are the framework regions (FR1, FR2, FR3, and FR4). The HV regions are also called the complementarity determining regions (CDR1, CDR2, and CDR3). While the framework regions form the β-sheets, the HV sequences form three loops at the outer edge of the β barrel (also see Section 2.2).

Disulfide Bonds

Most IgGs have four interchain disulfide bonds—two connecting the two H chains at the hinge region and the other two connecting the two L chains to the H chains.[6] Exceptions do exist. Two disulfide bonds were found in IgG1 and IgG4 linking the two heavy chain in the hinge region but four in IgG2.[7] In IgG1 MAb, HC is linked to the LC between the fifth Cys (C217) of HC and C213 on the LC. In IgG2 and IgG4 MAbs, it is the third Cys of HC (C123) linking to the LC.[7] A disulfide bond between HC C128 and LC C214 was found for mouse catalytic monoclonal antibodies (IgG2a).[8]

IgGs have four intrachain disulfide bonds, residing in each domain of the H and L chains, stabilizing these domains. The intrachain disulfide bonds in V_H and V_L are required in functional antigen binding.[9] Native IgG MAbs should not have any free sulfhydryl groups.[7] However, detailed examination of the free sulfhydryl groups in recombinant MAbs (one IgG1, two IgG2, and one IgG4) suggests presence of a small portion of free sulfhydryl group (approximately 0.02 mol per mole of IgG2 or IgG4 MAb and 0.03 for IgG1.[7] In rare cases, a free cysteine is found. A nondisulfide-bonded Cys at residue 105 was found on the heavy chain of a mouse monoclonal antibody, OKT3 (IgG2a).[10]

Oligosaccharides

There is one oligosaccharide chain in IgGs.[6] This N-linked biantennary sugar chain resides mostly on the conserved Asn 297, which is buried between the C_H2 domains.[5,11] For example, the oligosaccharide resides on Asn-297 of the C_H2 domain of chimeric IgG1 and IgG3 molecules[12] but on Asn 299 in a monoclonal antibody, OKT3 (IgG2a).[10] The oligosaccharide, often microheterogeneous, is typically fucosylated in antibodies produced in CHO or myeloma cell lines[5] and may differ in other cell lines.[2,11] There are many factors that dictate the nature of the glycan microheterogenity on IgGs. These include cell line, the bioreactor conditions and the nature of the downstream processing. An additional oligosaccharide can be found in rare cases. A human IgG produced by a human-human-mouse heterohybridoma contains an additional oligosaccharide on Asn 75 in the variable region of its heavy chain.[13] In addition, O-linked carbohydrates could also exist in this antibody.

Proper glycosylation is critical for correct functioning of antibodies.[11] It was demonstrated that removal of the oligosaccharide in IgGs (IgG1 and IgG3) made them ineffective in binding to C1q, in binding to the human FcγRI and activating C; and generally more sensitive to most proteases than their corresponding wild-type IgGs (one exception).[12] This is because the binding site on IgG for C1q, the first component of the complement cascade, is localized in the C_H2 domains.[11] Furthermore, the glycosylation can affect the antibody conformation.[12]

Oligosaccharides in other regions can also play a critical role. Removal of an oligosaccharide in a Fv region of the CBGA1 antibody resulted in a decreased antigen-binding activity in several ELISA systems.[13] In addition, this oligosaccharide might play critical role in reducing the antigenicity of the protein.[14]

The sugar composition of the oligosaccharide is also critical in antibody functions. It has been shown that a low fucose (Fuc) content in the complex-type oligosaccharide in a humanized chimeric IgG1 is responsible for a 50-fold higher antibody-dependent cellular cytotoxicity (ADCC) compared with a high Fuc counterpart.[15]

Heterogeneity

Purified antibodies are heterogeneous in structure. This is true for all monoclonal antibodies (MAbs) due to differences in glycosylation patterns, instability during production, and terminal processing.[5] For example, five charged isoforms were found in recombinant humanized monoclonal antibody HER2 as found by capillary isoelectric focusing (cIEF) and sodium dodecyl sulfate–capillary gel electrophoresis (SDS–CGE).[16] Six separate bands were focused under

IEF for two mouse monoclonal antibodies IgG2a (κ) and IgG1 (κ).[17] A mature monoclonal antibody, OKT3 (IgG2a), contain cyclized N-terminus (pyroglutamic acid, −17 D) in both H and L chains, processed C-terminus (no Lys, −128 D) of the H chains, and a small amount of deamidated form.[10] Similar observation was also reported for a humanized IgG1 (κ).[18] In rare cases, gene cross-over may lead to formation of abnormal heavy chains. For example, a purified monoclonal anti-IgE antibody contains a small amount of a variant H chain, which had 16 fewer amino acid residues than the normal H chain (position is between Arg108 of the L chain and Ala124 of the H chain).[19]

Secondary and Higher-Order Structure

The basic secondary and higher-order structural features of IgGs have been reviewed.[6] Only a small portion of the three-dimensional structures of IgGs has been solved.[20] The antibody's secondary structure is formed as the polypeptide chains form anti-parallel β-sheets. The major type of secondary structure in IgGs is these β-sheets and its content is roughly 70% as measured by FTIR.[21] The light chain consists of two and the heavy chain contains four domains, each about 110 amino acid long.[6,20] All these domains have similar folded structures—β barrel, also called immunoglobulin fold, which is stabilized by a disulfide bond and hydrophobic interaction (primary). These individual domains (∼12 kDa in size) interact with one another (V_H and V_L; C_H1 and C_L; and between two C_H3 domains except the carbohydrate-containing C_H2 domain) and fold into three equal-sized spherical shape linked by a flexible hinge region. These three spheres form a Y shape (mostly) and/or a T shape.[22]

The less globular shape of IgGs is maintained both by disulfide bonds and by strong noncovalent interactions between the two heavy chains and between each of the heavy-chain/light-chain pairs.[23] Through noncovalent interactions, a less stable domain becomes more stable, and thus, the whole molecule can be stabilized.[24] A detailed study indicates that the interaction between two CH3 domains are dominated by six contact residues, five of these residues (T366, L368, F405, Y407, and K409) forming a patch at the center of the interface.[25] These noncovalent interactions are spatially oriented such that variable domain exchange (switching V_H and V_L; inside-out IgG; ioIgG) induces noncovalent multimerization.[26]

The six hypervariable regions in CDR (L1, L2, L3, H1, H2, and H3) form loops of a few predictable main-chain conformations (or canonical forms), except H3 loop, which has too many variations in conformation to be predicted accurately.[27,28] There is a slight difference in the loop composition and shape between the two types of light chains.[20] However, no functional difference was found in antibodies having λ or κ chain.[6]

Basic Functions of Antibodies

The basic functions of antibodies have been reviewed.[6] There are two functional areas in IgGs—the V and C regions. The V regions of the two heavy and light chains offer two identical antigen-binding sites. The binding of the two sites (bivalent) can be independent of each other and does not seem to depend on the C region.[29] The exact antigen-binding sites are the CDR regions with participation of the frame work regions.[30] Binding of antigens seems through the induced-fit mechanism.[31,32] The induced-fit mechanism allows multispecificity and polyreactivity. It has been suggested that about 5–10 residues usually contribute significantly to the binding energy.[32]

The C regions of antibodies have three main effector functions (1) being recognized by receptors on immune effector cells, initiating antibody-dependent cell cytotoxicities (ADCC), (2) binding to complement, helping to recruit activated phagocytes, and (3) being transported to a variety of places, such as tears and milk.[6] In addition, C domains also modulate *in vivo* stability.[23,29,33] The function of Fc is affected by the structure of Fab. Variable domain exchange (switching V_H and V_L; inside-out IgG; ioIgG) affected Fc-associated functions such as serum half-life and binding to protein G and FcγRI.[26]

The hinge region provides flexibility in bivalent antigen binding and activation of Fc effector functions.[26] Two chimeric IgG3 antibodies lacking a genetic hinge but with Cys residues in CH2 regions was found to be deficient in their intermolecular assembly, and both IgG3 ΔH + Cys and IgG3 ΔH + 2Cys lost greatly their ability to bind FcγRI and failed to bind C1q and activate the complement cascade.[34]

Alternative Forms of Antibodies

In addition to species-specific antibodies, other antibody forms are generated to meet various needs. In the early development of antibody therapies, antibodies were made from murine

sources. However, these antibodies easily elicit formation of human anti-mouse antibody (HAMA). Therefore, humanized chimeric antibodies were generated. Chimeric monoclonal antibodies (60–70% human) are made of mouse variable regions and human constant regions.[2] Such antibodies can still induce formation of human anti-chimeric antibody (HACA). Highly humanized antibodies, CDR-grafted antibodies, are made by replacing only the human CDR with mouse CDR regions (90–95% human).[2] These antibodies are almost the same in immunogenicity potential as completely human antibodies, which may illicit formation of human anti-human antibody (HAHA).

Other alternative forms of antibodies have also been generated and these different forms have been reviewed.[35] Treatment with papain would cleave the N-terminal side of the disulfide bonds and generate two identical Fab fragments and one Fc fragment. Fab's are 50 kDa ($V_H + C_H1$)/($V_L + C_L$) heterodimers linked by a single disulfide bond. Treatment with pepsin cleaves the C-terminal side of the disulfide bonds and produces a F(ab)'$_2$ fragment. The remaining H chains were cut into several small fragments.[6] Cleavage by papain occurs at the C-terminal side of His-H228[36] or His-H227.[37] Reduction of F(ab')$_2$ will produce two Fab'.[23]

Fv fragments are noncovalent heterodimers of V_H and V_L. Stabilization of the fragment by a hydrophilic flexible peptide linker generates single-chain Fv (scFvs).[2] Fragments without constant domains can also be made into domain antibodies (dAbs). These scFvs are 25–30 kDa variable domain ($V_H + V_L$) dimers joined by polypeptide linkers of at least 12 residues. Shorter linkers (5–10 residues) do not allow pairing of the variable domains but allow association with another scFv form a bivalent dimer (diabody) (about 60 kDa, or trimer: triabody about 90 kDa).[38] Two diabodies can be further linked together to generate bispecific tandem diabody (tandab).[39] Disulfide-free scFv molecules are relatively stable and useful for intracellular applications of antibodies—"intrabodies."[38] The smallest of the antibody fragments is the minimal recognition unit (MRU) that can be derived from the peptide sequences of a single CDR.[2]

ANTIBODY INSTABILITY

Antibodies, like other proteins, are prone to a variety of physical and chemical degradation pathways, although antibodies, on the average, seem to be more stable than other proteins. Antibody instabilities can be observed in liquid, frozen, and lyophilized states. The glycosylation state of an antibody can significantly affect its degradation rate.[40] In many cases, multiple degradation pathways can occur at the same time and the degradation mechanism may change depending on the stress conditions.[41] These degradation pathways are divided into two major categories—physical and chemical instabilities. This section will explore the possible degradation pathways of antibodies and their influencing factors.

Physical Instability

Antibodies can show physical instability via two major pathways—denaturation and aggregation.

Denaturation

Antibodies can denature under a variety of conditions. These conditions include temperature change, shear, and various processing steps. Compared with other proteins, antibodies seem to be more resistant to thermal stress. They may not melt completely until temperature is raised above 70°C,[21,42,43] while most other mesophilic proteins seem to melt below 70°C.[44] Shear may cause antibody denaturation. For example, the antigen-binding activity of a recombinant scFv antibody fragment was reduced with a first-order rate constant of 0.83/h in a buffer solution at a shear of approximately 20,000/s.[45]

Lyophilization can denature a protein to various extents. An anti-idiotypic antibody (MMA 383) in a formulation containing mannitol, saccharose, NaCl, and phosphate was found to loose its *in vivo* immunogenic properties (only 10–20% of normal response rate) upon lyophilization.[46] Since the protein showed no evidence of degradation after lyophilization, no change in secondary structure by CD (29% β-sheet, 14% α-helix, and 57% "other"), the loss of activity was attributed to the conformational change. Indeed, tryptophan fluorescence properties were different between the lyophilized and unlyophilized antibodies.[46]

Aggregation

Antibody aggregation is a more common manifestation of physical instability. The concentration-dependent antibody aggregation was considered the greatest challenge to developing protein formulations at higher concentrations.[47] This is

because protein aggregates generally have reduced activity and more importantly, greater immunogenicity potential because of the multiplicity of epitopes and/or conformational changes.[14,48] Immunoglobulin aggregates have been shown to cause serious renal failure[49] and anaphylactoid reactions such as headache, fever, and chills.[50] Therefore, the aggregate level in commercial intravenous immunoglobulin products is limited to less than 5% based on the WHO standards.

Aggregates can form easily both in liquid and solid states under a variety of conditions (Tab. 2). Since protein aggregation is often the consequence of protein–protein interactions, a process influenced by diffusion rate and geometric constraints of the interaction sites, such factors would influence significantly the aggregation rate, including protein concentration change, viscosity, ionic strength, pH, and temperature.[51] Other conditions may also affect protein aggregation, including shaking, long-term storage, freeze-thaw process, lyophilization process, etc.

Increasing the concentration of antibodies often increases the aggregation tendency of the protein. It was demonstrated that increasing the IgG1 concentration (in 10 mM citric acid, 100 mM NaCl pH 5.5) from 2.7 mg/mL to 50 mg/mL almost linearly increased the Nephelometric Unit (NU) from 2 to 40.[52] Since EP defines a clear solution as having equal or less than three NU, most antibody solutions in the study are opalescent except those at 5 mg/mL or less. However, as the weight average molecular weight was found to be 0.9–1.3 times that expected of a monomer (about 149 kDa), minimal protein–protein association (and readily reversible) is suggested.[52] Shaking can accelerate antibody precipitation and the shape of the precipitates may depend on the sample volume in a container.[53] It appears that protein solutions exhibiting lower surface tension are more susceptible to protein denaturation and precipitation.[53]

Low-temperature treatment may induce aggregation of antibodies. The reversible low-temperature-induced aggregation (below 37°C) of serum cryoglobulins is well known.[54] Human IgM cryoglobulin preparations easily precipitate or gel at temperatures below 10–12°C and the process is reversible at a higher temperature.[20] In a recent study, aggregation of IgG1 at low temperature at above 18 mg/mL was reversible as measured by light scattering.[52] The low-temperature-induced aggregation of cryoglobulins is poorly understood and was thought to involve sites within both Fab and Fc.[20] The authors of this article believe that low temperature reduces the hydrophobic interaction, which is the major force in protein folding. Without enough hydrophobic interaction at low temperature, hydrophobic regions of antibodies become more exposed to solvent and lead to increased intermolecular hydrophobic interaction, leading to aggregation.

In close relation to the low-temperature effect, freeze-thaw process often induces protein aggregation. However, freeze-thaw-induced antibody aggregation does not seem to be a major issue, partly due to the reversibility of antibody aggregates. Freeze-thawing of a chimeric (L6) antibody solution at pH 7.2 for as many as 35 times led to formation of dimers (not larger aggregates).[41] Maximum amount of dimers (about 20%) was observed at pH 6.5 and minimum was below 5.5 or above 8.5 (less than 2%). The freeze-thaw-induced aggregation is apparently reversible after treatment at 37°C for a few hours.[41] Freeze-thawing of rhuMAb anti-CD20 three times (freezing to either −20 or −70°C, thawing to 5°C) did not lead to significant change in aggregation, no significant loss of monomer by RP-HPLC or SEC-HPLC.[55] On the other hand, isolated Fabs seems to be more prone to freeze-thaw-induced aggregation relative to full-length antibodies. For example, Lee[56] found that freeze-thawing of a scF_v (MW 27,000 d) at 1.45 mg/mL in sodium phosphate buffered saline (PBS) at pH 7.3 dropped the %monomer content (due to aggregation) from 95% to 84%, 59%, 44%, and 37%, respectively after 1–4 cycles.

Lyophilization may induce antibody aggregation to a variable degree. It was demonstrated that lyophilization of a recombinant humanized monoclonal antibody (rhuMAb HER2), in the absence of sugars, led to a slight increase in aggregate (less than 1.2%).[57] Lyophilization caused detectable aggregation of a human monoclonal antibody in PBS or physiological saline as measured by OD600,[58] and aggregation of a mouse monoclonal antibody (MN12) [IgG2a (κ)] in the absence or presence of 5% sucrose, dextran, or hydroxypropyl-beta-cyclodextrin (HP-β-CD), as measured by visual examination.[59] In a different study, lyophilization of a monoclonal antibody-vinca conjugate in PBS at pH 7.4 caused 6.2% aggregation.[60] The lyophilization-induced aggregates could be non-covalent-linked monomers and/or even disulfide-linked.[61,62]

Antibody aggregation can easily occur during storage in a liquid state. Storing of a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2)

Table 2. Instabilities of Antibodies

Instability	Antibody	Formulation	Condition	Effect	References
Denaturation	scFv	3 μg/mL in 10 mM phosphate-buffered saline containing 0.02% sodium azide	Shaking at a mean velocity gradient approximately 20,000/s	Loss of activity at a first-order rate of 0.83/h	45
Aggregation	Chimeric mouse/human IgG1	2 mg/mL in PBS at pH 7.2	Stirring for 48 h with Teflon bar at 600 RPM	Increased turbidity Formation of >15 k particles (>10 μ)	91
	Human Anti-IL-8 (IgG2)	55 mg/mL, 5 mM His, pH 6	Freeze/thaw three times (room/−70°C)	About 0.6% aggregates (by SEC-HPLC)	21
	Anti-IL-8 (IgG2)	100 mg/mL, 200 mM Sucrose, 15 mM Arg, 15 mM His, pH 6	Incubation at 40°C for 6 months	About 11% aggregates (by SEC-HPLC)	21
	rhuMAbE25	10 mg/mL in excipient-free solution	Spray drying Tin = 105°C, Tout = 50–55°C	5–6% aggregate (by SEC-HPLC)	65
	MAb (type not specified)	MAb at 40 mg/mL, 85 mM sucrose, 5 mM His at pH 6, 0.01% Tween 20	Lyophilization	Cloudy (OD350 > 0.2)	1
	Human Anti-IL-8 (IgG2)	50 mg/mL, 20 mM Gly, 4 mM His, 0.2% mannitol, 16 mM Glu, 0.03% Tween 20 pH 5.7	Incubation of lyophilized form at 37°C for 1 month	4.8% aggregates (by SEC-HPLC)	21
	RhuMAb HER2	50 mg/mL in 100 mM trehalose, 5 mM His at pH 6.0	Incubation of lyophilized form at 40°C for 23 months	9.7% aggregates (by SEC-HPLC)	57
Deamidation	OKT3 (IgG2a)	1 mg/mL, PBS at pH 7.0 + Tween80	Incubation at 37°C for 2 months	90% deamidation of Asn386	10
	LA298 (IgG1)	0.5 mg/mL in 10 mM citrate at pH 7	Incubation at 25°C for 6 weeks	~12% increase in deamidation at Asn55	78
Isomerization	MAb	Lyophilized at 40 mg/mL, 85 mM sucrose, 5 mM His, 0.01% Tween 20, pH 6.0, containing 8.4% moisture	Incubation at 5°C	First-order rate constant $\sim 0.33 \times 10^{-4}$/day	1
Oxidation	rhuMAb HER2	5 mg/mL, 147 mM NaCl, 0.01% polysorbate 20, 5 mM sodium acetate at pH 5.0	5, 30, and 40°C for 2 weeks	10, 17, and 52% (total peak area)	81

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in aqueous solutions at 2–8°C or 25°C led to formation of high-molecular-weight (HMW) species.[21] Incubation of two mouse monoclonal antibodies IgG2a (κ) and IgG1 (κ) at 37°C for 32 days caused precipitation in pH 3 and 4 solutions for both antibodies.[17] Aggregation can also occur to an antibody conjugate. Storing a monoclonal antibody-vinca alkaloid conjugate (murine IgG2a) in phosphate-buffered saline solutions at 5°C between pH 4.5 and 7.4 for 1.5 months caused precipitation regardless of solution pH and aggregation was accelerated at 30°C throughout the pH range.[63]

Antibody aggregation is a common phenomenon during storage in a lyophilized state. Aggregation (OD350 > 0.2) was observed of a high concentration, lyophilized, monoclonal antibody (type not specified) by SEC under accelerated conditions.[1] So did a lyophilized chimeric monoclonal antibody during storage at 5°C (0.4% after 2 months).[64] In the absence of sugars, the extent of rhuMAb HER2 aggregation increased from about 1% to >10% after 3 months at 40°C and the rate of aggregation for these formulations was about 0.2% per month at 40°C.[57]

Antibody aggregation can readily occur in other solid forms during storage.[5] It was found that the primary degradation upon storage of a spray-dried anti-IgE (protein:mannitol = 80:20) is aggregation, and the amount of aggregates increased with increasing temperature and relative humidity (Maa et al., 1998a).[65] As much as 52% aggregate was observed by SEC-HPLC of a spray-dried anti-IgE (protein:mannitol = 80:20) after 1 year at 40°C and 38% RH (Maa et al., 1998b).[66]

Antibody aggregation is usually accelerated upon thermal treatment. In the study of chimeric (human/mouse) monoclonal antibody (BR96), Alexander and Hughes demonstrated that thermal treatment at 60°C for 166 h generated noncovalently linked aggregates.[67] In the evaluation of the relative stability of murine IgG2a (κ), chimeric IgG1(κ), trioma IgG1 (λ), and murine IgG1 (κ), Hartmann et al. demonstrated that IgG2a (κ) aggregated and precipitated after heating at 55°C for 8 h and the half-life for the loss of monomer for those four IgGs is 1, 18.1, 3.4, and 8.2 h with different aggregate species (dimer, trimer...) by SEC-HPLC.[68]

Surface Adsorption

Antibodies, like other proteins, can easily adsorb to a variety of surfaces. Surface adsorption can significantly reduce the antibody concentration in a solution. For example, a mouse monoclonal IgG1 has been shown to be adsorbed on the surface of glass shake flasks, causing a loss of protein in plant culture media.[69] Such a loss was minimized by coating the glass vessels or by addition of Pluronic F127.

Chemical Instability

A variety of chemical degradation pathways have been observed. These chemical degradants may or may not loose protein activity depending on the site of changes. For examples, deamidation of a monoclonal antibody, OKT3 (IgG2a) as measured by change in IEF pattern does not correlate with loss of antigen binding potency (90% deamidation of Asn386 vs. 80% activity in the potency assay).[10] In comparison, the activity of light chain deamidated recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb) at Asn30 (to aspartate) is only 70% of the main species and that of the isomerized (heavy chain) asp102 species is only 9–21% of major species.[37] The major chemical degradation pathways in an antibody include cross-linking, deamidation, isomerization, oxidation, and fragmentation.

Disulfide Formation/Exchange

Disulfide bond formation/exchange is probably the most common cross-linking pathway, leading to chemical aggregation. This degradation pathway can occur readily in various processing steps. For example, lyophilization of a murine monoclonal antibody (IgG2a) without additives reduced the average number of −SH groups per molecule from 6.65 to 6.28, suggesting disulfide formation.[70] Since the thiolate ions are often the initiating species for this chemical degradation, increasing formulation pH usually leads to increased formation of disulfide formation. This is the case for an antifebrin T2G1s Fab′ (IgG1 (κ)), containing free −SH groups, where the percentage of dimers increased with increasing the pH from 5.8 to 9.5.[61]

Storage often leads to disulfide-based aggregation. Storage of a lyophilized excipient-free antibody (IgG1, containing 12 intra and 4 interchain disulfides) formulation for 1 year at 30°C resulted in formation of reducible dimer and trimers.[62] Similarly, reducible aggregates of a monoclonal antibody (type not specified) were detectable

by SDS–PAGE after storage of the lyophilized formulation at 50°C for 6 months.[1] Such disulfide-linked covalent dimers and trimers were also observed during storage of spray-dried anti-IgE humanized monoclonal antibody.[71]

Nonreducible Cross-Linking

Nonreducible cross-linking was observed in several studies. Incubation of a human monoclonal antibody (C23) in solution at a basic pH at 37°C for 14 days resulted in formation of nonreducible bands above the light chains at pH 4 and 10.[72] Incubation of two mouse monoclonal antibodies—IgG2a (κ) and IgG1 (κ), between pH 3.0 and 10 at 37°C for 32 days led to formation of a nonreducible 88 kDa species by SDS–PAGE.[17] A species with the same molecular weight was observed after incubation of another monoclonal antibody, OKT3 (IgG2a), at 37°C for 2 months.[10,73] Further examination suggests that this species is a cross-linked product of H and L chains between the L46-52 and H99-121 regions. Although the exact chemical nature was not determined, an oxidative step is apparently involved as inhibition of oxidation delayed the formation of this species.[10,73]

A recent study shows that a nonreducible thioether bond can be formed between C223 of the heavy chain and the C-terminal Cys residue of the light chain in humanized IgG1 antibodies. This cross-linked product has a molecular weight of 75 kDa by MS but shows an apparent molecular weight of 92 kDa by SDS–PAGE.[74]

Nonreducible cross-linked products were also observed in solid dosage forms. Incubation of a lyophilized mouse monoclonal antibody [IgG2a (κ)] without lyoprotectant or in the presence of 5% sucrose, dextran, or hydroxypropyl-beta-cyclodextrin (HP-β-CD) at 56°C for 18 days led to formation of 100-kDa band under reduced conditions by SDS–PAGE.[59]

Deamidation

Antibody deamidation has been extensively reported in the literature. This common protein degradation pathway is so prevalent that purified antibody preparations may contain many deamidated forms. For example, several deamidated forms of recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb) were found by cation-exchange chromatography, including (1) deamidated Asn30 (to aspartate) on one light chain, (2) deamidated Asn30 (to aspartate) on two light chains, and (3) deamidated Asn55 on the heavy chain (to iso-aspartate).[37] The sole conversion of Asn30 to aspartate (not isoaspartate) suggests that the deamidation mechanism in cell culture may be different from that during storage.

Storage can easily generate large amounts of deamidated products. Incubation of a monoclonal antibody, OKT3 (IgG2a) in a PBS solution at pH 7 containing Tween 80 at 37°C for 2 months led to more than 90% deamidation at Asn H386.[10] By monitoring the ammonia generation, Poborji et al.[41] estimated that 4% of the total number of Asn and Gln residues in a chimeric antibody (L6) was deamidated after storing the solution at pH 7.2 at 50°C for 3 weeks.

Deamidation also occurs in solid state. In the evaluation of storage stability of a model recombinant humanized monoclonal antibody (rhuMAb HER2), Cleland et al. reported that incubation of a high-moisture formulation (8.4% moisture) for 12 months at 40°C resulted in a 19% drop in the main peak by IEX due to deamidation.[57]

Deamidation in proteins goes mostly through the intermediate of succinimide at Asn (more readily) and Gln (see reviews[75,76]).This seems to be the case for antibodies, even though alternative mechanisms were reported, such as deamidation of Asn30 on the light chain of recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb).[37] A method has been developed to detect the formation of succinimide.[77]

The rate of deamidation via succinimidation in proteins can be affected by a variety of factors, such as pH, sequence, and steric effect (see review[44]). A recent report demonstrated a strong pH-dependency of deamidation at Asn55 (pH 7 > pH 6 > pH 5 > pH 4) in a fully human IgG1 in the pH range of 4–7 during storage at 25°C.[78] Using small peptide as a model, Tyler-Cross and Schirch[79] found that deamidation of Asn residues depends on the amino acid residue on the carboxyl side of Asn in neutral and alkaline solutions. Increasing the size and branching of these amino acids decreased the rate of deamidation by as much as 70-fold compared with the N–G sequence (greatest rate of deamidation) but under acidic conditions, these amino acids lost their protective effect.

Isomerization

The most common isomerization in antibodies is iso-aspartic acid formation, which results not only

from direct isomerization of Asp but also, mostly, from hydrolysis of succinimide intermediate. The pH-dependent formation of succinimide intermediate can occur either from Asn deamidation or Asp dehydration.[36] In neutral and alkaline condition, the isoAsp and Asp products formed in a peptide were at a ratio of about 3:1.[79]

Isomerization is also prevalent and difficult to control. Again, many purified proteins contain significant amount of isomerized products, either from deamidation or direct isomerization. A typical example is recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb).[37] In addition, since isomerization occurred at Asp H102 in CDR regions, the activity of the isomerized species is only 9–21% of the major species.[37] Similarly, isomerization of Asp L32 on one light chain in a recombinant monoclonal anti-IgE antibody (E25) reduced the relative binding activity of $F(ab)'_2$ to 42% and the activity of isomerized form on both chains (iso-Asp-iso-Asp) to 15%.[36]

Since formation of the succinimide intermediate does not need participation of water, it can readily occur in solid state. Asp isomerization is one of the major degradation pathways for a lyophilized, monoclonal antibody (type not specified), and increases with increasing storage temperatures both above and below their Tg values.[1]

Like deamidation, the relative rate of isomerization can be influenced strongly by steric effect. For example, a recombinant monoclonal anti-IgE antibody (E25) contains two Asp-Gly sequences within its CDRs, but only one site was found to be labile to isomerization (Asp L32). The unreactivity of one Asp residue is suggested to be due to hydrogen bonding.[36]

Oxidation

The oxidizable residues in proteins include Met, Tyr, Trp, His, and Cys. Although oxidation is not as prevalent as deamidation and isomerization in antibodies, it can easily occur during storage of antibodies. For example, the major route of degradation of a monoclonal antibody, OKT3 (IgG2a), in solution during storage at 5°C is oxidation of a nondisulfide Cys and several Met residues.[10] Oxidation was also observed in rhuMAb anti-CD20 in solution during storage at 40°C for 2 months.[55]

Oxidation of CDP870, a pegylated one-half antibody (one light and one heavy chain) at a Met residue (M3) was also observed after incubation of the protein at 25°C or 40°C for 12 weeks (14% at pH 4.1 and 4.2% at pH 5.5).[80] Light exposure can accelerate baseline oxidation. For example, light exposure (20,000 lux for 2 weeks at 27°C) of recombinant humanized monoclonal antibody HER2, rhuMAb HER2 caused 5–10% increase in oxidation in various liquid formulations at Met H255 (primary site) and Met H431 at temperatures 30 and 40°C.[81]

Formation of Acidic or Basic Species

Antibodies can form acidic or basic species, which are often monitored by IEF or ion exchange chromatography. Among all the possibilities, deamidation is the most likely degradation pathway, leading to formation of acidic species. Therefore, formation of such species is used loosely as an indication of deamidation in the absence of other confirmatory studies. Strictly speaking, formation of such species can only be considered as an indication of chemical instability (see below). A pH-dependency is almost certain for this kind of degradation. In the stabilization of CDP870, a one-half antibody (one light and one heavy chain), which is linked through Cys to a branched (20 kDa each) PEG, Johnson et al.[80] found that the protein generated more acidic species (up to 17% at pH 4.1 and 41% at pH 5.5) by IEF as the solution pH was increased from 4.1, 4.5, 5.0, to 5.5 during storage at 25°C for 12 weeks.[80]

Another possible mechanism for generating acidic species in antibodies is the Maillard reaction, where reducing sugars can react with lysine residues. Such a reation will result in loss of positive charges and formation of apparently more acidic species. This is the case for an spray-dried anti-IgE humanized monoclonal antibody with lactose during storage.[71]

Formation of basic species was also observed in antibodies. Its formation can result from several possibilities, most likely as a result of succinimide formation, removal of sialic acids, or pyroGlu formation. Such a basic species was observed after incubation of a human monoclonal antibody (C23) at 37°C for 14 days in a solution at an acidic pH by IEF.[72]

C-Terminal Clipping

Terminal cleavages can easily occur during normal production of antibodies. For example, the majority of a purified chimeric protein rCD4-IgG lacks the heavy chain C-terminal Lys.[82]

This is also the case for recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb)[37] and a recombinant monoclonal anti-IgE antibody (E25).[36] It was suggested that the cleavage was due to the action of basic carboxypeptidases during production.[37]

Fragmentation

The most likely sequences leading to fragmentation in proteins are Asp-Gly and Asp-Pro,[83] although other sequences can also experience cleavages, such as Asn-Ser.[79] Fragmentation can easily occur in antibodies even during production processes. A small amount of fragment (MW < LC) was detectable under reduced condition in a purified recombinant MAb IgG4 produced in Chinese hamster ovary (CHO) cells.[7] Half molecules should be monitored routinely for IgG4s.[84]

A variety of processing conditions may accelerate fragmentation of antibodies, such as acidic or basic treatment,[72] thermal treatment,[41,67] freeze-thaw,[41] and storage.[17,73,78] Fragments can simply include masses with a loss of a light chain (M-LC), a loss of a Fab arm (M-Fab), and separated heavy-chain (HC) and light-chain (LC), as well as species less than common antibody subunits, resulting from both peptide and/or disulfide bond cleavage.[67] Antibodies are also subject to radiation-induced cleavages.[85]

Maillard Reaction

Proteins may form adducts with sugars. In an investigative study, mouse MAbs were found to form glucose adducts after incubation with 0.5 M glucose at pH 7.4 for 14–21 days at 37°C and the glycated antibodies significantly increased the dissociation of the antibody-antigen binding complex.[86]

ANTIBODY FORMULATION

As mentioned above, antibodies, like other proteins, may generate a variety of degradants during production, processing, and storage both in liquid and solid states. Their tendency to generate such degradants depends very much on their individual sequence, pI, hydrophobicity, and carbohydrate content.[23] The antibody degradation products may have reduced activity and more importantly, increased immunogenicity.[14,87] A strong immune response (antibody formation) may lead to severe neutralization of the protein drug product and even endogenous proteins.

The major purpose of formulating antibodies as therapeutic agents is to control the rate of antibody degradation to provide an acceptable shelf life for worldwide shipping and storage. This can be done by choosing proper formulation excipients and other formulation conditions. It should be stressed that one formulation excipient stabilizing a specific antibody may not be suitable for another because of the differences in their sequence. A proper formulation composition should not only maximally preserve the activity of the antibody but also minimize the potential immune response, as excipients could alter the immune response by changing the presentation of the protein (such as the spacing of epitopes).[14] The following section will discuss critical factors in formulating both liquid and lyophilized antibody products. Advanced formulations will also be briefly described.

Liquid Formulation

Liquid dosage form is usually preferable to lyophilized products as it is easier to administer and less expensive to manufacture. Among all the commercial antibody products, about half are stable enough to be formulated in a liquid form (Tab. 1). Formulating a successful liquid product needs consideration of at least the following aspects.

Protein Concentration

Since the EC50 values of antibodies are often 10–1,000 times higher than for other proteins such as hormones and cytokines,[35] a relatively large amount of antibodies needs to be dosed to achieve any therapeutic effect. A large dose requires that an antibody product needs to be formulated/reconstituted at a high concentration to reduce dose volume, especially for subcutaneous injections; otherwise, a large volume of antibody preparation has to be infused. Since the aggregation process is usually concentration-dependent, antibodies at high concentrations have at least two potential issues: high tendency to aggregate during storage and likely high viscosity, leading to more difficulty during injection (injection time correlated with viscosity).[47] It has been suggested that the concentration-dependent protein aggregation is the greatest challenge to developing high-concentration

protein formulations.[47] On the other hand, moderate increase in protein concentration may not have a significant effect. In fact, increasing the concentration of antifebrin T2G1s Fab′ (IgG1 (κ)), from 0.05 to 5.0 mg/mL in solution resulted in a decrease in dimer formation during storage (73.2% to 22.9% after 13 weeks at 22°C).[61]

An effective way to reduce the viscosity of an antibody solution is to add sufficient amount of NaCl.[5,88] Adjustment of formulation pH could potentially reduce the viscosity of an antibody solution.[88] Although not very effective, histidine has been shown to reduce the solution viscosity of a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2) from 20 to about 9 centistokes when its concentration was increased from 0 to 60 mM.[21] However, use of such excipients in reducing viscosity can be limited, as the excipient can adversely affect the stability of the antibody, such as MAb anti-CD20.[55]

Another potential issue in formulating high-concentration antibody products is their solubility limits, as presence of undissolved proteins are generally not acceptable for intravenous injection. Fortunately, the solubility of antibodies seems to be relatively high and solubility-limited formulation difficulty has rarely been reported to our knowledge. To increase the solubility of antibodies, excipients such as surfactants may be used. In a recent report, Golovanov[89] found that a combination of L-Arg and L-Glu at an equimolar concentration (50 mM) significantly increased the solubility of several proteins (either alone does not have a significant effect). In addition, the room-temperature storage stability (fragmentation) of proteins was significantly improved as monitored by SDS–PAGE.

One potential advantage of formulating a protein product at higher concentrations is the greater freeze-thaw stability. Often, proteins at high concentrations are more resistant to freeze-thaw-induced aggregation, as the interface-induced protein denaturation can easily reach a saturation point. However, it does not seem to be the case for antibodies. Increasing the concentration of a chimeric antibody (L6) did not inhibit freeze-thaw-induced aggregation.[41] In addition, surfactants such as Pluronic F68 and Tween 80 did not appreciably prevent antibody aggregation. In a different study, Tween 80 alone (or Pluoronic F68) at 0.1% failed to offer any protection against freeze-thaw-induced aggregation of a single-chain antigen-binding protein CC49/218 sF_v (MW 27,000 d) at 1.45 mg/rnL in sodium PBS at pH 7.3.[56] These results suggest that freeze-thaw-induced antibody aggregation may not be a surface phenomenon.

Effect of Formulation pH

Formulation development often starts with determination of a stable formulation pH. Like other proteins, the pH effect on the stability of antibodies depends on the formulation composition,[55] stress conditions,[41] and even antibody concentration.[84] Formulation pH may affect the physical stability of antibodies as it alters the number and distribution of charges on the protein surface. For example, low pH (below 3) caused a loss of tertiary structure in rhuMAb anti-CD20.[55] Low pH (pH 3 and 4) is also responsible for the precipitation of two mouse monoclonal antibodies IgG2a (κ) and IgG1 (κ) during incubation at 37°C for 32 days.[17] Susceptibility to pH stress varies among different IgG molecules.[68]

Regarding chemical stability, formulation pH may play a critical role in controlling many degradation pathways, such as disulfide bond formation/exchange, deamidation, fragmentation, isomerization, etc. Due to variable effects on different degradation pathways, the optimum pH value varies depending on both the sequence of an antibody and the analytical methods used in monitoring the stability. By IEF, Lam et al. found that rhuMAb anti-CD20 is most stable at pH 5 within the pH range of 3–6 irrespective of protein concentration in formulations containing 10 mM citrate, 8% trehalose, and 0.05% Tween 20.[55] By SEC-HPLC, Usami et al. found that pH 6 was the most stable condition during incubation of a human monoclonal antibody (C23) at 37°C for 14 days in a solution containing isotonic sodium chloride between pH 4 and 10.[72] Sometimes, the optimum pH values reside outside a certain range. In the study of the stability of a chimeric antibody (L6), minimum amount of dimmer formation was observed at pH below 5.5 or above 8.5 (less than 2%) during freeze-thaw.[41]

It needs to be mentioned that oxidation could be inhibited by adjusting formulation pH. In a formulation containing 40 mg/mL MAb anti-CD20, 150 mM trehalose, 0.9% benzyl alcohol, 0.02% Tween 20, and 50 mM histidine, reducing the pH from 7.5 to 5 virtually eliminated the oxidation during storage at 40°C for 2 months.[55] In a different study, oxidation (M3) of PEG-CDP870, a one-half antibody, in a formulation containing 160 mg/mL CDP870, 10 mM sodium acetate, and

125 mM NaCl was slower at pH 5.5 than at pH 4.1 (4.2% vs. 14% after 12 weeks at 40°C).[80]

Due to the simultaneous presence of multiple antibody degradation pathways, the formulation pH has to be adjusted to balance all the potential degradations. Generally, a weakly acidic condition seems to be the optimum for most antibodies (see Tab. 1).

Effect of Buffering Agents

It has been long recognized that both the type and concentration of a buffering agent may affect the stability of proteins (see review[44]). For example, phosphate buffer accelerated deamidation of an IgG1 relative to citrate buffer at both pH 6.5 and 7.0 during storage at 25°C.[78] Therefore, proper choice of a buffering agent can potentially achieve both pH control and stabilization of antibodies. In rare cases, a buffering agent good for one antibody may be harmful to another. One of these agents is histidine, which has a pKa of pH 6 and potentially good in controlling a weakly acidic condition. It has been shown to provide better protection against precipitation for a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2) upon thermal incubation both at 50 and 40°C than citrate at pH 6.[21] Addition of a small amount of histidine (0.4 mM) also increased the freeze-thaw (4×) recovery of a single-chain antigen-binding protein CC49/218 sF_v (MW 27,000 d) at 1.45 mg/rnL in PBS solution at pH 7.3 from 37% to 90%.[56] On the contrary, histidine was found not only to increase the rate of aggregation of rhuMAb anti-CD20 during storage but also to induce coloration of the solution compared to a acetate-buffered antibody solution at pH 5.[55] In addition, oxidation of Fc was also faster in histidine solution.

The concentration effect of a buffering agent was demonstrated in a study where freeze-thaw-induced aggregation of a chimeric antibody (L6) was higher with increasing phosphate buffer concentration (0.01 vs. 0.05).[41] Therefore, both the type and concentration of buffering agents need to be examined.

Effect of Formulation Excipients

Use of formulation excipients remains a major and convenient approach in stabilizing antibodies in solutions. It is so at least in reducing antibody aggregation.[47] A variety of formulation excipients have been shown to stabilize antibodies under different processing conditions and during storage, including sugars,[41] polyols,[41] amino acids,[41,84] surfactants,[84] and polymers.[45,84]

Formulation excipients are effective generally in protecting the physical stability of an antibody. Among these excipients, sugars are the most commonly used. A variety of sugars, such as sucrose, trehalose, glucose, have been shown to reduce the freeze/thaw-induced aggregation of rhuMAb anti-CD20,[55] a chimeric antibody (L6),[41] a human anti-IL8 monoclonal antibody (ABX-IL8; IgG2),[21] and a single-chain antigen-binding protein CC49/218 sF_v (27 kDa).[56] Other excipients can be equally or even more effective in protecting antibodies. Histidine was shown to be equally effective as sucrose in reducing freeze-thaw induced aggregation of a human anti-IL8 monoclonal antibody (ABX-IL8; IgG2) and combination with Arg resulted in a better protection than sucrose in solution stability at different incubation temperatures.[21] Sugars are not always effective. In the evaluation of freeze-thaw stability of a single-chain antigen-binding protein CC49/218 sF_v (MW 27 kDa) at 1.45 mg/mL in sodium phosphate buffered saline (PBS) at pH 7.3, addition of 10 mM trehalose, lactose, glucose, or mannitol did not offer any protection.[56] In a rare case, sucrose has been shown to promote agitation-induced aggregation of an IgG1 antibody.[90]

Formulation excipients may inhibit chemical degradation of antibodies. Replacing 0.14 M NaCl with 8% trehalose or 4% mannitol in a rhuMAb anti-CD20 increased the chemical stability as measured by IEX during storage at 40°C.[55] Such an effect is likely a result of stabilization of antibody conformation. Some excipients may protect antibodies against oxidation. Replacing NaCl with 4% mannitol and 1% benzyl alcohol protected recombinant humanized monoclonal antibody HER2, rhuMAb HER2, against oxidation (primarily Met-255) at 30 or 40°C.[81] This effect is likely due to a function of mannitol as a free radical scavenger. Some commonly used antioxidants, such as thiosulfate and methionine, are effective in inhibiting antibody oxidation. The minimum effective levels (molar ratios of antibody to antioxidant) required to inhibit temperature-induced oxidation of rhuMAb HER2 were 1:5 and 1:25 for methionine and thiosulfate, respectively.[81] However, use of thiosulfate has led to formation of a thiosulfate adduct of rhuMAb HER2.[81] The safety of such a thio-containing adduct has not been reported.

One of the main excipients often used in antibody formulation is surfactants. They are usually

effective in reducing shaking/stirring-induced aggregation[91] but may have negative effect during long-term storage.[92] One obvious concern is that such compounds may contain a residual level of peroxides, which have been shown to cause protein oxidation.[93] Therefore, use of surfactants should be kept to a minimum in an antibody formulation if possible. For example, removing Tween 20 in a recombinant humanized monoclonal antibody HER2, rhuMAb HER2 solution reduced the oxidized antibody from 52% to <10% at 40°C.[81]

Effect of Shaking/Shearing

Both shaking and shearing can denature antibodies. It was found that shaking murine antibody-based products caused antibody precipitation and the shape of the precipitates are different depending on the fill volume.[53] In the evaluation of shear effect on the antigen-binding activity of a recombinant scFv antibody fragment in a buffer solution, Harrison et al.[45] found that the binding activity decayed at a mean rate constant of 0.83/h at a shear of approximately 20,000/s.

Effect of Preservatives

A limited number of studies have been conducted on the compatibility of preservatives with antibodies. Compatibility depends both on the antibody and the preservative. In the evaluation of the effect of several preservatives, including benzyl alcohol, chlorobutanol, methylparaben, propylparaben, phenol, and m-cresol, on the stability of a humanized monoclonal antibody, Gupta and Kaisheva[94] found that the antibody was most stable in the presence of methylparaben and propylparaben, compatible with benzyl alcohol and chlorobutanol at low concentrations, and not compatible with phenol and m-cresol, as measured by a variety of assays, including SEC-HPLC, DSC, light scattering, UV, and potency assay.

Effect of Processing Equipment

Another important issue in antibody formulation is the choice of proper processing equipment/containers. A few studies have shown that antibody stability can be significantly affected if an inappropriate choice is made. In the study of the stability of recombinant humanized monoclonal antibody HER2, rhuMAb HER2, in liquid formulations, Lam et al.[81] found that replacing the stainless steel filler with a nonstainless steel filler reduced the oxidized antibody (primarily Met-255) from 52% to 18% after storage for 2 weeks at 40°C. It was suggested that Fe ions, released from erosion of stainless steel by chloride ion at low pH, catalyzed the oxidation. In a similar case, Chen et al.[21] demonstrated that a fully human anti-IL8 monoclonal antibody (ABX-IL8) in aqueous formulations containing 60 mM His had a higher level of aggregates after freeze-thaw in a stainless steel vessel and subsequent storage at 40°C, possibly due to the effect of Fe ions generated from a similar mechanism. In addition, proteins have been shown to facilitate metal corrosion.[95]

Effect of Product Containers

The effect of product containers was clearly demonstrated in a recent study. McCormick et al.[96] reported that Tween 80, intended to replace human albumin in the original formulation, interacted with uncoated rubber stoppers in single-use Eprex syringes. The stoppers leached a small amount of plasticizers in the drug solution, which acted as an adjuvant, and caused a strong IgG response to the recombinant human erythropoietin. The immune response was significantly minimized later by switching to PTFE-coated rubber stoppers. In addition, headspace oxygen can accelerate oxidation of antibodies and replacement with an inert gas could minimize such a reaction.[73]

Accelerated Stability Studies

To accelerate formulation development process, accelerated stability studies are usually conducted. However, estimation of room temperature or 5°C stability based on accelerated stability studies for antibodies, like other proteins, may or may not be possible or accurate. The unpredictability is due to the presence of complex and multiple degradation pathways, which may have different degree of temperature dependencies.[10] Kroon et al.[10] found that relative to other degradation pathways of a monoclonal antibody, OKT3 (IgG2a), Asn deamidation was preferentially accelerated with increasing temperature. Therefore, caution needs to be applied in interpreting such high-temperature-induced deamidation. On the other hand, Poborji et al.[41] found that loss of monomeric chimeric antibody (L6) at pH 7.2 followed Arrhenius behavior in the temperature range of 30–50°C and extrapolation of the high temperature SEC data to 2–8°C at pH 7 and

5.5 resulted in comparable stability estimates with the available real-time data.

Lyophilized Formulation

Preparation of lyophilized protein formulations has been extensively reviewed.[97–101] Like most proteins, some antibodies are not stable enough in a liquid form and lyophilized dosage forms will have to be considered. Lyophilization was suggested to be one of the two approaches in solving antibody aggregation.[47] This section will discuss some critical issues in formulating a lyophilized antibody product.

Amorphous Versus Crystalline State

It has been commonly believed that proteins are more stable in an amorphous state.[103] This is mainly because proteins need another excipient(s) to replace water molecules to from the required H-bonds as water molecules are removed during drying and a crystalline matrix does not provide intimate H-bonding between the excipient and the protein.[104,105] It appears that if the protein itself can be crystallized during the lyophilization process (may be difficult practically), the protein could be more stable and might not need as much stabilizing agent as in the amorphous state. In a recent report, Shenoy et al.[106] compared the stability of two model proteins, glucose oxidase (GO) and lipase, and demonstrated that dry crystalline formulations are significantly more stable than their amorphous counterparts as monitored by size-exclusion chromatography. It remains to be seen whether this can be applicable to antibodies.

Effect of Formulation Excipients

To make a lyophilized antibody product, at least one formulation excipient, a bulking agent, is needed to confer an acceptable cake. If the antibody is not stable enough in the presence of a bulking agent during lyophilization or storage, a stabilizer(s) is included. The relative amount of formulation excipients (bulking and stabilizing agents) should be carefully chosen as these agents may affect each other's behavior, the tonicity, and stability of the lyophilized products.

Commonly used bulking agents include mannitol and glycine. Crystallization of these agents during lyophilization makes them wonderful bulking agents but poor stabilizing agents.[57] Although mannitol could stabilize an antibody as in the case for a monoclonal antibody-vinca conjugate in a PBS solution at pH 7.4 upon lyophilization,[60] many studies showed that mannitol could not stabilize effectively or even destabilizes antibodies. Such examples include the aggregation of a lyophilized model recombinant humanized monoclonal antibody (rhuMAb HER2) in the presence of mannitol during storage.[3,57] In the lyophilization of a human monoclonal antibody at 1 mg/mL, it was demonstrated that addition of 5% mannitol has no effect on the lyophilization-induced aggregation in PBS or physiological saline as measured by OD600 and addition of 10% mannitol actually accelerated aggregation during the lyophilization process.[58] On the other hand, when used in combination with sucrose or trehalose, similar degree of stabilization to that for sugar alone may be achieved such as the case for model recombinant humanized monoclonal antibody (rhuMAb HER2).[57] The disaccharide/mannitol formulations also inhibited deamidation of this antibody during storage to a greater extent than the lyoprotectant formulations alone.[57]

Sugars are the most common stabilizing agents used in lyophilized formulations. Among these, two nonreducing sugars, sucrose and trehalose, are usually the first choice. Both sugars protected the stability of a few lyophilized antibodies equally well. These antibodies include lyophilized recombinant humanized monoclonal antibody, rhuMAb HER2,[57] IgG1 (containing 12 intra and 4 interchain disulfides),[62] anti-IgG,[107] and chimeric monoclonal antibody.[64] However, sucrose seemed to be more effective in protecting a lyophilized IgG1 against aggregation during storage at 40°C at a sugar:protein weight ratio of 1:1 (Chang et al. 2005b).[102] In another study, sucrose at 5% failed to offer any protection to a lyophilized mouse monoclonal antibody (MN12) (IgG2a (κ)) during storage at 56°C for 18 days.[59] Again, as mentioned in the liquid formulation section, even the most commonly used stabilizers may not stabilize all antibodies in the solid state and antibodies need to be treated as individually different molecules.

When sugars are used as stabilizing agents (lyoprotectants), a sufficient quantity needs to be used to achieve a significant effect depending on the protein concentration. It has been suggested that a molar lyoprotectant:protein ratio of 300:1 or greater should be used.[47] Indeed, the available literature data indicate a ratio higher than 300 is needed for better stabilization. It was shown that sugars protect the stability (aggregation and Asp isomerization) of a lyophilized, monoclonal

antibody (type not specified) to a significant level when the sugar to protein molar ratio was increased to 500:1, which happens to the theoretical number of water binding sites in the molecule.[1] Similarly, Andya et al.[62] demonstrated that use of sucrose or trehalose inhibited the aggregation of a lyophilized antibody (IgG1—containing 12 intra and 4 interchain disulfides) during storage at 30°C to a maximum degree when the sucrose/trehalose:protein ratio was 500 or higher, which is roughly equivalent to the number of water-binding sites on the surface of the protein (550 estimated). Increasing the trehalose/anti-HER2 ratio from 60 mM (360 molar ratio) to 200 mM (1,200 molar ratio) significantly increased the stability (monomer by SEC-HPLC) of lyophilized formulation at 25 mg/mL at 40°C.[107] In a recent report, it was found that at least a weight ratio of 2:1 (molar ratio of about 800) was needed to achieve a maximum protection of a lyophilized sucrose:IgG1 formulation against both aggregation and chemical degradation during storage at 40°C (Chang et al. 2005a).[101]

Other formulation excipients were also used and some of these are effective in stabilizing certain antibodies. A recent study demonstrated that addition of sorbitol to a sucrose or trehalose formulation resulted in further enhancement of storage stability of a lyophilized IgG1 antibody (Chang et al. 2005b).[102] Either dextran or HB-β-CD (better) protected the activity of a lyophilized mouse monoclonal antibody (MN12) (IgG2a (κ)) during storage.[59] Glucose was shown to inhibit gamma irradiation-induced fragmentation of humanized monoclonal antibodies (hr3).[85]

Effect of Formulation "pH" and Buffering Agents

The pH of the liquid formulation can have a potential effect on the stability of the lyophilized formulation, even though the solid-state "pH" could not be well defined. In the evaluation of the stability of a lyophilized monoclonal antibody-vinca conjugate, aggregation seems to be lower at a neutral pH 7.1 than at either pH 8.5 or 6.1 when the lyophilized formulation was stored at 25°C.[60] In adjusting the formulation pH, use of a buffering agent may have effect on the antibody stability both during lyophilization and storage of the lyophilized products. For example, in the stability study of a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2), Chen et al.[21] demonstrated that addition of histidine inhibited the formation of HMW species upon lyophilization and during storage at 37°C in a concentration-dependent manner. Among several excipients including His, Gly, mannitol, Glu, and polysorbate 20, His is the most critical in protecting solid-state stability of the antibody (minimizing aggregation). In a different study, the aggregation rate of a lyophilized anti-IgE at 5°C at 5 mg/mL in 10 mM buffer is affected both by pH and buffers in the following order: Na Phosphate, pH $7 >$ K Phosphate, pH $7 >$ Na Succinate, pH 6 or $5 >$ Histidine, pH 7.[107] It should be noted that some buffering agents may induce significant pH change due to selective crystallization during lyophilization, such as sodium phosphate. Such buffering agents should be avoided in preparing pH-sensitive antibody formulations.

Effect of Protein Concentration

In many cases, increasing the protein concentration increases the stability of the protein during lyophilization (see review).[98] However, antibodies do not seem to follow this trend and many antibodies have been shown to be less stable both during lyophilization and storage at high concentrations. For example, lyophilization of a human monoclonal antibody caused significant aggregation of MAb formulated in PBS or physiological saline as measured by OD600 and increasing the protein concentration from 1 to 2.5 or 5 mg/mL increased the OD600 from 0.194 to 0.311 or 0.427, respectively.[58] Similar trend was also observed during storage of lyophilized formulation. Increasing the concentration of a chimeric monoclonal antibody from 2.5 mg/mL to 25 mg/mL in a lyophilized formulation, containing 31 mg/mL sucrose, 15 mM NaCl, 0.02% Tween 80, 10 mM citrate, increased the aggregate level from 0.4% to 0.6% after 2 months at 5°C.[64] In the evaluation of the stability of a model recombinant humanized monoclonal antibody (rhuMAb HER2), Cleland et al.[57] demonstrated that increasing the protein concentration from 25 mg/mL to 50 mg/mL in a lyophilized formulation (containing 60 mM trehalose, 5 mM His at pH 6) increased the aggregate level from 8.5% to over 30% by SEC-after storage at 40°C for 44 months. Such behavior was also observed of anti-HER2 from 5 to 21 mg/mL containing 250 mannitol.[107]

Effect of Moisture Content

The effect of moisture on the stability of lyophilized antibodies has not been consistent and seem

to depend on the antibody and the degradation pathways being monitored.[57] Generally, increasing moisture content of a lyophilized antibody will gradually increase the rate of degradation during storage. Such negative effect of moisture was clearly demonstrated in a variety of degradation pathways, including dimerization of T2G1s Fab′ (IgG1 (κ)) in a moisture content range of 1.5–12.3%,[61] aggregation of TNF-MAb between 0.68% and 8%,[108] formation of acidic/basic species of rhuMAb HER2 between 1% and 8.4%[57] and fragmentation of a mouse monoclonal antibody (MN12) with and without secondary drying.[59]

In other cases, the effect of moisture is either complex or not significant. For example, Breen et al.[1] found that high-moisture formulations (8%) of a lyophilized monoclonal antibody (type not specified) showed a higher rate of aggregation, fragmentation, and Asp isomerization during storage than those containing 2% or 5% moisture but formulations containing intermediate moisture levels (2–3%) were less prone to aggregation than those containing a lower moisture levels (1%) as measured by SEC under accelerated storage conditions. Similarly, the aggregation of a lyophilized IgG1 was found to be minimal at an intermediate moisture level around 3% at different storage temperatures. (Chang et al. 2005b).[102] In a different study, Cleland et al.[57] found that using a model recombinant humanized monoclonal antibody (rhuMAb HER2), a residual moisture between 1 and 8.4% had no impact on the rate of aggregation during storage at 2–8 or 40°C for 12 months.

Accelerated Stability Studies

Like antibodies in a liquid state, those in a solid state may or may not undergo degradation that is characteristic of Arrhenius behavior. It is generally believed that stability studies should be conducted at least below the glass transition temperature of the formulation. Duddu et al.[64] found that accelerated stability data generated in the glassy state (40°C) seems to be a better predictor of the relative stability of formulations than the data generated at a higher temperature (60°C). In the study of the stability of a high-concentration, lyophilized, monoclonal antibody (type not specified), Breen et al.[1] demonstrated that chemical and physical degradation pathways followed Arrhenius kinetics during storage in the glassy state. Only Asp isomerization followed the Arrhenius model above the Tg value.

Advanced Formulations

In addition to the liquid and lyophilized dosage forms on the market, other dosage forms have been tried and limited success has been reported.

Spray-Dried Formulations

Spray drying is an efficient way of preparing solid dosage forms because of the rapid removal of a solvent(s) from a drug solution. It is a very attractive alternative to lyophilization in preparing solid protein formulations. So far, a number of studies have been conducted for proteins and partly because of the high-temperature exposure in the process, albeit very short, limited success has been achieved. Protein aggregation during spray drying seems to be the major challenge.[65,66,109,110]

Spray drying of antibodies has also been tried. As for other proteins, process-induced protein aggregation seems to be the major issue.[71,110] Careful selection of proper excipients could minimize this problem. In the evaluation of a spray-dried formulation for a rhuMAbE25, it was demonstrated that trehalose or lactose minimized the aggregation during spray drying (aggregate dropped from 5–6% to ≤1%). For trehalose, the molar ratio for significant inhibition of aggregation is at or above 300:1 to 500:1 (excipient: protein).[71] Such a ratio seems to be comparable with that used in the lyophilized formation. The addition of mannitol also reduced aggregation, but only up to a molar ratio of 200:1 and further increase in mannitol content resulted in crystallization, which had a detrimental effect on protein stability and aerosol performance.[71] In a different study, either trehalose or sorbitol could inhibit IgG aggregation during spray drying.[110]

Stabilized Antibodies via Mutagenesis

Antibody fragments, such as scFv, are alternative antibody therapeutics. However, since their stability is not as good as full-length antibodies, mutagenesis, or chemical modifications have been tried to improve its stability. For example, R71A mutagenesis in the heavy chain of an unstable scFv dramatically increased its stability when incubated in human serum while having only a minor effect on the binding affinity of the molecule.[111] A more stable heavy chain, made through mutation, can increase the stability of

the light chain, and thereby confer more stability to the whole scFv.[24]

Stabilized Antibodies via Chemical Modifications

The clinical performance of an antibody can be desirably changed by conjugation of the antibody to another entity. For example, McIntosh et al.[112] demonstrated that conjugation of carboxymethyl dextran to a tumor-antigen-specific monoclonal antibody (A5B7) increased the clearance of the antibody in mice but conjugation of cisplatin (*cis*-dichlorodiammine platinum II) with the antibody complex restricted its tissue distribution and reduced its systemic clearance.

PEGylated Antibodies

A common method of increasing plasma half-life of proteins is to increase the size of the protein by attaching a PEG moiety. Currently, there are at least four PEGylated commercial protein products on the market. However, the long plasma half-lives (as high as 7–23 days) of antibodies made much less appealing the development of such an antibody product. Since the long half-life was due to the binding of Fc to the Fc-receptor (neonatal Fc receptor, FcRn) in various tissues,[33,35] antibody fragments, such as Fab′ lacking the Fc portion have a much shorter half-life and could be good candidates for PEGylation. Such a modification was made on a humanized IgG Fab′ fragment via site-specific attachment to an additionally engineered Cys residue, as modification via the lysine residues led to substantial losses in binding activity.[29]

Controlled Release Systems

Controlled release systems have been extensively investigated for proteins in the past two decades.[113,114] However, limited work has been conducted in this area for antibodies, partly due to their relatively long plasma half-lives compared with other proteins. To achieve long-term effect, a controlled released system consisting of biodegradable poly (lactic-glycolic) acid (PLGA) was prepared for an anti-cocaine catalytic monoclonal antibody and an *in vivo* release of the antibody for up to 10 days was demonstrated in mice following subcutaneous injection.[115] It is anticipated that such systems could be useful if a minimum of 1-week duration of release is achieved.

SUMMARY

Antibodies have similar tertiary structures. The presence of a significant number of disulfide bonds and intimate domain–domain interactions in antibodies make them relatively stable and more resistant to moderate thermal stress compared to other proteins. Nevertheless, antibodies do experience a variety of instabilities similar to most proteins. These physical and chemical instabilities include denaturation, aggregation, surface adsorption, deamidation, oxidation, isomerization, fragmentation, etc. Due to the significant difference in the primary sequence among different antibodies, the relative severity of these degradation pathways can be significantly different. On the average, aggregation, deamidation, and isomerization seem to be more prevalent in antibodies.

Partly due to the stability difference, some antibody products are made into a liquid form while others are lyophilized (Tab. 1). The solution pH of these commercial products is either neutral or weakly acidic, suggesting that such a pH range is probably optimal for most antibodies. Surfactants have been used in most of these antibody products, presumably to inhibit antibody aggregation, and will likely be used in other antibody drug candidates. Two most commonly used formulation excipients in these antibody formulations are sucrose and NaCl. For liquid formulations, either one can be used if they offer the same level of stability protection. For lyophilized formulations, sucrose is preferable as NaCl does not form intimate H-bonds with the antibody and also reduce the glass transition temperature of formulation, making lyophilization less efficient. All the formulation excipients and buffering agents used in commercial antibody products or discussed in the article should be evaluated individually for each antibody drug candidate through stability studies before they are chosen as part of the product, as antibodies are structurally different.

The available stability data in the literature and the information on the commercial antibody products suggest that antibody formulation seems challenging but relatively manageable, compared to other protein drugs. Three major issues in antibody formulation are apparently challenging and need significant attention in the coming years: (1) development of stable high-concentration formulations, (2) management of the high-concentration-associated viscosity of these formulations,

and (3) minimization of antibody-formulation-induced immune response.

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Patente PCT
INHIBIDORES DE CALICREÍNA PLASMÁTICA Y USOS DE LOS MISMOS PARA TRATAR ATAQUE DE ANGIOEDEMA HEREDITARIO

Detalle del pago

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