STATISTICAL ANALYSIS PLAN

NCT Number: NCT02741596

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

Study Number: DX-2930-04

SAP Version and Date:

Original: 10 December 2019
PK/PD Statistical Analysis Plan: 29 January 2020
PRO Report HELP Study Extension: 24 March 2020

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Protocol Number:	DX-2930-04
Protocol Version/Date:	Amendment 3.0 29 June 2017
Indication:	Prevention of angioedema attacks in subjects with HAE
Study Phase	III
SAP Analysis Type	Final
SAP Version/Date	10 December 2019

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LIST OF IN-TEXT TABLES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
AESI	Adverse event of special interest
aPTT	Activated partial thromboplastin time
BLQ	Below the limit of quantification
BMI	Body mass index
C1-INH	C1 esterase inhibitor
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level Measure
eCRF	Electronic case report form
EDC	Electronic data capture
HAARP	HAE Attack Assessment and Reporting Procedures
HADS	Hospital Anxiety and Depression Scale
HAE	Hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IP	Investigational product
IRB	Institutional review board

Abbreviation	Definition
IV	Intravenous
KM	Kaplan-Meier
LTP	Long-term prophylaxis
MedDRA	Medical Dictionary for Regulatory Activities
PCS & MCS	Physical and Mental Health Composite Scores
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SF-12	12-Item Short Form Survey
SMQ	Standardized MedDRA Queries
SOC	System organ class
VAS	Visual analog scale
WHO-DD	World Health Organization-Drug Dictionary
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is being developed after review of the DX-2930-04 protocol amendment 3.0, but before the final database lock. This SAP contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR) and publication. 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), immunogenicity, 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 the 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 final CSR. Table, figure, and listing specifications are provided in separate documents.

The DX-2930-04 protocol amendment 3.0 was finalized on 29JUN2017. The purpose of this amendment was to add new objectives and related measurements, QoL endpoints, and extend the study from 12 months to 30 months to continue to obtain data important for the assessment of DX-2930 (ie, safety and efficacy data).

2.2 Background

DX-2930-04 is an open-label, long term safety and efficacy extension study of DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in subjects with Type I or Type II hereditary angioedema (HAE). Details of the study design, rationale, and procedures are documented in Protocol DX-2930-04 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 subjects with HAE, a serious and life-threatening disease.

3. STUDY OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

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

3.3 Tertiary Objectives

- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health-related QoL
- To characterize the PK and PD profile of SC administration of DX-2930
- To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930
- To evaluate breakthrough attack characteristics while receiving DX-2930 compared with historical baseline breakthrough attack characteristics
- To evaluate subject experience with self-administration of DX-2930, including ease of SC administration of DX-2930
- To assess the clinical response of rescue medications for the treatment of acute angioedema attacks while on DX-2930 therapy (applicable for subjects ≥18 years of age)
- To assess treatment satisfaction
- To assess global impression of treatment response
- To assess control of angioedema

The following objectives included in Amendment 3.0 will not be evaluated for the final CSR due to data unavailability at the time of the analysis:

- To evaluate subject experience and ease of use of the prefilled syringe, if available

[redacted]

4. STUDY DESIGN

4.1 General Description

DX-2930-04 is an open-label, long-term safety and efficacy extension study of DX-2930-03, to evaluate the IMP, DX-2930, in preventing acute angioedema attacks in subjects with Type I or Type II HAE. Figure 1 in the protocol shows a schematic of DX-2930-04.

Two types of subjects will be enrolled into this study:

- Subjects who roll over from the DX-2930-03 study
- Subjects who are non-rollover (ie, were not participants in DX-2930-03)

Rollover Subjects

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

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

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

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

Non-rollover subjects

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

Screening Period:

Rollover subjects

There is no screening period for rollover subjects.

Non-rollover subjects

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

Treatment Period:

Rollover Subjects

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

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedules (Appendix 2.16) for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-lead electrocardiogram (ECG), QoL, PK, PD, and anti-drug antibody (ADA) sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events (AEs), concomitant therapy, and HAE attack data. See the Study Activities Schedules (Appendix 2.16) to determine which visits must be conducted at the study site.

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

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

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

For the purpose of efficacy and safety analyses defined in this SAP, the treatment period for rollover subjects is further divided into two stages: The Dose-and-wait stage and Regular Dosing stage. The Dose-and-wait stage starts on the day of first study drug administration, or Day 0, and ends right before the date/time of the second dose. The Regular Dosing stage starts on the date/time of second dose and runs through the end of treatment period. For a detailed definition on these two stages, refer to Appendix 2.7.2.1 and Appendix 2.7.2.2.

Non-rollover Subjects

Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1 esterase inhibitor (C1-INH) therapy, attenuated androgens (eg, danzol), or anti-fibrinolytics (eg, tranexamic acid) for HAE can continue their current LTP until as late as Day 21.

For the purpose of safety analyses defined in this SAP, the treatment period for non-rollover subjects are further divided into two stages: The Tapering stage and Non-tapering stage. The Tapering stage starts on the day of first study drug administration, or Day 0, and ends at the last date/time of LTP use. The Non-tapering stage starts right after last date/time of LTP use and runs through the end of the treatment period. For a detailed definition on these two stages, refer to Appendix 2.7.2.3 and Appendix 2.7.2.4.

All Subjects:

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

After the second DX-2930 dose is given, either within the study window (±4 days) or at an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the Study Activities Schedules (Appendix 2.16).

Regardless of when a subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, subjects will continue to receive repeated SC administrations of open-label DX-2930 every 2 weeks for the remaining duration of the treatment period. The treatment period will last approximately 30 months from the date of the first open label dose. The number of doses

administered during this period will vary by subject based on the date of each subject's second dose. The Day 910 study visit is the last visit at which a dose may be administered.

Self-Administration

All subjects (adolescent or adult) who are considered suitable candidates (ie, those with the physical and mental capability of learning and willingness to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and have their understanding of the procedures confirmed by the investigator or designee. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits), the subject's home, or other agreed upon location (when the study permits off-site dosing). See Study Activities Schedules in Appendix 2.16 for details. Adolescent subjects self-administering DX-2930 will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer the investigational product to an adolescent without study site personnel supervision. Site personnel will call subjects after the planned self-administration to ensure the administration occurred, to collect AEs and concomitant medications, and to ensure all attacks have been appropriately documented. No monitoring of vital signs will be performed for subjects who elect to self-administer at home.

Follow-up Period:

After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period.

Modifications to Open-Label Dosing

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

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

4.2 Discussion of Study Design, Including the Choice of Control Group

This study is an open-label, long-term safety and efficacy extension study of DX-2930-03, to evaluate the IMP, DX-2930, in preventing acute angioedema attacks in subjects with Type I or 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 long-term safety of repeated SC administrations of DX-2930. Safety endpoints include AEs, clinical laboratory results, vital signs, and electrocardiography.

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

- **Control group selection:** This is an open-label extension study that does not include any control groups.

- **Study population:** Subjects 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who have a historical baseline HAE attack rate of at least 1 per 12 weeks.

- **Baseline symptom severity:** To be eligible to participate in the study, subjects had to have a historical baseline HAE attack rate of at least 1 per 12 weeks.

- **Stratified randomization:** There is no randomization for this study.

- **Safety monitoring:** AEs, clinical laboratory results, vital signs, and ECG recordings will be monitored throughout the study.

4.3 Sample Size Determination

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

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

- Time from first open-label study dose to the first investigator-confirmed HAE attack for rollover subjects
- Number of investigator-confirmed HAE attacks during the treatment period
- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period
- Number of moderate or severe HAE attacks during the treatment period
- Number of high-morbidity HAE attacks during the treatment period; a high-morbidity HAE attack is defined as any attack that has at least one of the following characteristics: severe in intensity, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires intravenous [IV] hydration, or associated with syncope or near-syncope) or laryngeal angioedema.

5.2 Safety Endpoints

The safety and tolerability of DX-2930 will be evaluated through the assessment of AEs, clinical laboratory testing, vital sign measurements, ECG recordings, and concomitant medications.

5.3 Other Endpoints

Additional endpoints of interest in this study are the plasma concentration of DX-2930, PD biomarker assays, ADAs, and QoL data as collected with the EuroQoL Group 5-Dimension (EQ5D) Questionnaire, the Angioedema Quality of Life (AE-QoL) Questionnaire, 12 Item Short Form v2 Health Survey (SF-12v2)., Hospital Anxiety and Depression Scale (HADS), Work Productivity and Activity Impairment – General Health (WPAI-GH) Questionnaire, Angioedema Control Test (AECT), Treatment Satisfaction Questionnaire for Medication (TSQM-9), Subjects' and Investigators' Global Impression of Treatment Response, the DX-2930 injection report, and the DX-2930 self-administration and SC injection survey.

6. EFFICACY AND SAFETY VARIABLES

6.1 Study Activities Schedule

Please refer to Appendix 2.16 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). Study site personnel will be trained on HAARP prior to screening and enrolling subjects at their site.

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

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

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

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

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

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

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

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, will be recorded on the AE page of the electronic case report form (eCRF). Any AE reported to the site meeting criteria for a serious adverse event (SAE) 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 SAEs that are reported as HAE attacks, the investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate whether it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate whether it represented a confirmed HAE attack. If necessary for the evaluation, the investigator or designee may contact the subject to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis recorded. All subject-reported and investigator/physician designee-confirmed HAE attacks will be recorded in the eCRF.

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

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

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

6.3 Safety Assessments

6.3.1 Adverse Events

AEs will be collected from the signing of the informed consent through the last study visit. For a detailed definition of 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 open-label DX-2930 through the final follow-up visit or, in the event that onset time precedes first DX-2930 administration, the AE increases in severity during the open-label treatment period. If onset date and times are missing, then the AE will be classified as being treatment-emergent unless there are partial dates and times that clearly demonstrate that the AE occurred prior to first DX-2930 administration.

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

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) (See Appendix 2 in the protocol) and the DMID Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (See Appendix 3 in the protocol). 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 DX-2930 and the AE will be assessed using the following categories:

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

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

Related: Factors consistent with an assessment of Related include:

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

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

6.3.1.1 Adverse Events of Special Interest

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. For a detailed description on the tracking of AESI during the study, refer to Protocol section 6.16.1.6.

6.3.2 Vital Signs

Vital signs will be assessed by the investigator or his/her qualified designee according to the Study Activities Schedules (Appendix 2.16) unless the subject has qualified and elected to self-administer away from the investigational site for that visit. Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate, blood pressure, and respiratory rate. Blood pressure should be determined using the same arm and the same equipment for each assessment. For subjects who roll over from DX-2930-03, vital signs taken during the final study visit in DX-2930 will serve as the Day 0 pre-dose vital signs in this study and will not be duplicated.

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 Schedules (Appendix 2.16). The physical examination will be performed in accordance with standards at the site.

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

6.3.4 Electrocardiogram (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedules (Appendix 2.16). The date and time of each ECG and its results will be documented in the source documents and eCRF. ECGs will be sent to a central reading vendor for assessment. For subjects who roll over from DX-2930-03, the ECG taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose ECG in this study and will not be duplicated.

6.3.5 Clinical Laboratories

Laboratory testing will be performed according to the Study Activities Schedules (Appendix 2.16).

Laboratory testing includes general safety parameters (hematology, coagulation, urinalysis, and serum chemistry), pregnancy tests (in females of childbearing potential), C1-INH functional assay, C4 assay, C1q assay, PK sampling, PD sampling, and plasma ADA 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, ADAs, PD. Aliquots from the PK, PD, and ADA samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each rollover subject will be approximately 269.8 mL. The total blood draw for each non-rollover subject will be approximately 283 mL. For rollover subjects, testing performed on samples collected during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose laboratory testing in this study and will not be duplicated.

6.3.5.1 Hematology

The following hematology assessments will be made:

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count with differential
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Absolute platelet count

6.3.5.2 Coagulation

The following coagulation assessments will be made:

- Prothrombin time
- Activated partial thromboplastin time
- International Normalized Ratio

6.3.5.3 Chemistry

The following chemistry assessments will be made:

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

6.3.5.4 Urinalysis

The following urinalysis assessments will be made:

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

6.3.5.5 Pregnancy Test

Pregnancy tests will be either serum or urine based.

6.3.5.6 Assays

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the screening visit unless they were previously drawn in Study DX-2930-02 or Study DX-2930-03. Results of a C4 assay may also be required for eligibility assessment. The C4 sample will be drawn at the same time as the C1-INH sample is drawn during the screening visit unless previously drawn in Study DX-2930-02 or Study DX-2930-03. Results of the C1-INH

and C4 assays from Study DX-2930-02 or Study DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

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

6.3.6 Prior and Concomitant Therapies

The Sponsor representatives and investigator at the site conducting the trial will review and evaluate prior (4 weeks prior to study screening) and concomitant medication usage on an ongoing basis. For subjects not rolling over from DX-2930-03, all prescription and over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from the time of screening through the duration of the study will be regarded as concomitant medications and must be documented on the source document and eCRF following informed consent. For subjects rolling over from DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the duration of the study.

6.4 Other Assessments

6.4.1 Pharmacokinetic Assessment

Blood samples for the measurement of plasma DX-2930 concentration will be obtained as specified in the Study Activities Schedules (Appendix 2.16).

6.4.2 Pharmacodynamic Assessment

To evaluate the PD effects of DX-2930-03 on plasma kallikrein activity, blood samples will be obtained as specified in the Study Activities Schedules (Appendix 2.16).

6.4.3 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained as specified in the Study Activities Schedules (Appendix 2.16).

6.4.4 Quality of Life Assessments

Quality of life assessments will be conducted using the AE-QoL, EQ-5D-5L, WPAI-GH, HADS, AECT, TSQM-9, Subject's and Investigator's Global Impression of Change and SF-12v2. See Study Activities Schedules (Appendix 2.16) for timing of assessments. For subjects who rollover from DX-2930-03, QoL assessments obtained during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose QoL assessments in the current study and will not be duplicated.

6.4.4.1 AE-QoL

The AE-QoL is a self-administered, symptom-specific tool developed and validated to assess QoL impairment in recurrent angioedema subjects (Weller et al. 2012). The AE-QoL consists of

17 questions covering four domains/dimensions (functioning, fatigue/mood, fear/shame, nutrition). Each of the 17 items has a five-point Likert-type response scale ranging from 1 (Never) to 5 (Very Often). The AE-QoL is scored to produce a score for each domain and a total score ranging from 0 to 100, with higher scores indicating stronger impairment. It takes approximately 5 minutes to complete the AE-QoL. Details of how to compute scores for the domains and the total score are included in Appendix 2.13.

6.4.4.2 EQ-5D-5L

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

6.4.4.3 WPAI-GH

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

6.4.4.4 HADS

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

6.4.4.5 SF-12v2

The SF-12v2 Health Survey is a reliable and valid generic measure of functional health and wellbeing. The SF-12v2 consists of 12 questions, all selected from the SF-36 Health Survey (Ware et al. 1996). The SF-12v2 yields eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Physical and Mental Health Composite Scores (PCS & MCS) can be computed using the scores of 12 questions and range from 0 to 100, where a zero score indicates the lowest level of health

measured by the scales and 100 indicates the highest level of health. The standard form of the instrument asks patients to reply to questions according to how they have felt over the last 4 weeks.

6.4.4.6 Angioedema Control Test (AECT)

The Angioedema Control Test (AECT) is a patient reported outcome measure. The concept of the AECT is comparable to those of the well-established Asthma Control Test (ACT) and Urticaria Control Test (UCT) (Nathan et al. 2004; Weller et al. 2014). The AECT could be used to assess control of angioedema among patients with recurrent angioedema (including hereditary angioedema) and to aid treatment decisions. The AECT consists of up to 10 questions. Each question has 5 answer options (verbal rating scale) that are scored from 0 to 4 points, which ultimately comprise the total AECT score.

6.4.4.7 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a validated 9-item questionnaire developed to measure subjects' satisfaction with their medication and includes three scale scores: effectiveness, convenience, and global satisfaction (Bharmal et al. 2009). Scale scores for each of the 3 scales, as well as a combined score are calculated separately. Scores are transformed to a 0 to 100 scale, where higher scores indicate greater treatment satisfaction. The TSQM-9 has been applied in clinical studies in several chronic conditions.

6.4.4.8 Subject's and Investigator's Global Impression of Change

The subjects' and investigators' global impression of treatment response will be assessed using a one-item question. The item will assess overall perception of treatment response. Assessment will be performed separately by the subject and investigator. The subjects and investigators will be asked to think of "today" while rating the question (or an appropriate translation, as applicable): "Overall, how would you rate your response to the study medication?" There will be five response options; namely, poor; fair; good; very good, excellent.

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

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

After receiving appropriate training, to include retention of all used and unused vials of IMP for drug accountability, subjects are allowed to self-administer DX-2930 after receiving the first 2 doses of DX-2930 at the study site. Subjects who choose to self-administer or have a parent/legal guardian/caregiver administer DX-2930 must complete an assessment of their experience with self-administration and SC injection for each dose received. Study personnel will document the subject's responses in the subject's medical record and eCRF.

7. STATISTICAL ANALYSIS

7.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, North Carolina, USA). Separate analytic plans will be developed to support analysis of PK data and quality of life data.

All data listings will be sorted by rollover status, prior treatment group for roll-over subjects and LTP therapy for non-rollover subjects, 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, 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 for least squares mean treatment differences will be provided. The time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier methods for the 03 study treatment groups, and DX-2930 total groups combined. Kaplan-Meier estimates of the 10^{th}, 20^{th}, 25^{th}, 30^{th}, 40^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals for the median, as well as percentage of censored observations and the number of events, will be presented. The number and percentage of subjects, as estimated using the Kaplan-Meier method, with the first HAE attack by 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, and 8 weeks are presented for each group. Plots of the KM curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

No formal statistical hypothesis testing will be performed. All p-values will be considered descriptive.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as the data collected. 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 Appendix 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 Safety Population

The Safety Population will include all subjects who received any study drug after entering the DX-2930-04 study (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Safety Population will be presented by the subject's study entry type (rollover or non-rollover) and overall.

7.2.2 Rollover Safety Population

The Rollover Safety Population is the subset of subjects who participated in the DX-2930-03 study and received any study drug after entering the DX-2930-04 study (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Rollover Safety Population will be presented by the subject's prior treatment group from the DX-2930-03 study (Placebo, DX-2930 150 mg every 4 weeks, DX-2930 300 mg every 4 weeks, DX-2930 300 mg every 2 weeks).

7.2.3 Non-Rollover Safety Population

The Non-rollover Safety Population is the subset of subjects who entered the DX-2930-04 study directly and received any study drug after entering the DX-2930-04 study (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Non-rollover Safety Population will be presented by subject's prior type of LTP therapy prior to study entry (No LTP Use, C1-INH only, Oral Therapy, and C1-INH and Oral Therapy). The purpose of subdividing the Non-rollover Safety Population based on the subjects' prior type of LTP therapy is to explore the impact of prior LTP on transitioning to the new treatment.

7.3 Subject Disposition

The number of subjects with informed consent, treated with study drug, completed study, completed study or transitioned to commercial product, and discontinued prematurely by reason, including subjects transitioned to commercial product, will be summarized for each analysis population. Within each analysis population, these categories will be presented by prior DX-2930-03 treatment group for rollover subjects, LTP therapy prior to study entry for non-rollover subjects, 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 of institutional review board/ethics committee (IRB/EC), temperature excursion, investigational product (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 safety reporting, IRB/EC reporting, EQ-5D, Angioedema Quality of Life, lab collection, and other (not otherwise defined).

Summary tables of protocol deviations by rollover status and overall will be provided for the Safety 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 for each analysis population.

Demographic variables to be presented include the following:
- age (years),
- age group (<18, 18 to <40, 40 to <65, ≥65 years),
- sex (male, female),
- ethnicity (Hispanic, Non-Hispanic, Not Reported, Unknown),
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, 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 (Underweight: <18.5, Normal: 18.5 to <25, Overweight: 25 to <30, Obese: ≥30 kg/m^2) ,
- BMI percentile group for subjects < 18 years of age (Underweight: < 5^{th} percentile, Healthy or Overweight: 5^{th} – 95^{th} percentile, Obese: ≥ 95^{th} percentile),
- long term prophylactic (LTP) therapy use (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP),
- type of LTP therapy (C1-INH, Oral Therapy, C1-INH and Oral Therapy, not on LTP)

For rollover subjects, the LTP presented is the LTP used prior to randomization into the DX-2930-03 study.

A separate table will be created for HAE history 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, and baseline HAE attack rate (attacks/4 weeks) (refer to Appendix 2.9.1 for a definition of the baseline HAE attack rate). All baseline and demographic data will be presented in subject listings.

In order to explore the demographics of those subjects who self-administer the study drug, an additional table will be included that presents demographics for the subgroup of administration types (subjects with ≥ 80% self-administration, subjects with ≥ 80% administration by study staff in-clinic, and subjects with < 80% self-administration and < 80% administration by study staff in-clinic).

7.6 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 and summarized by system organ class (SOC) and preferred term (PT) for each analysis population. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency of the overall population. Medical History events reported in the DX-2930-03 study are included for rollover subjects. 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 eCRF, including whether the injection was given by study staff in clinic, self-administered in clinic, or self-administered at home; whether a full, partial, or no dose was given; date and time of dose; and location of the injection.

Because of the Dose-and-wait stage of the treatment period for rollover subjects, the number of planned doses is defined as the number of doses a subject is scheduled to receive during the Regular Dosing stage (refer to Appendix 2.7.2.2 for a definition of the regular dosing stage) plus 1 (to include the initial dose of study drug on the DX-2930-04 study). Treatment compliance will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects that received at least 80% of planned doses, summarized for each analysis population.

For each analysis population, exposure to the study treatment will be summarized using total dose (the total number of mg of DX-2930 a subject receives on the DX-2930-04 study), time on study (exposure duration during the treatment period), exposure duration excluding drug interruption (efficacy), exposure duration excluding drug interruption (safety).Duration of participation categorized by <1 month, 1-<3 months, 3-<6 months, 6-<12 months, 12-<18 months, 18 - <24 months, and 24-≤33 months; or ≥ 6 months, ≥9 months, ≥ 12 months, ≥18 months, ≥ 24 months, and ≥ 30 months will be provided for the exposure duration during the treatment period. Summaries will also be provided for each analysis population of the total number of doses received, percentage of injections that were self-administered at home, self-administered in the clinic, and administered by the study staff in-clinic. Listings of study administrations by subject will also be provided.

A listing of subjects with drug interruption will be provided.

7.8 Analysis of Efficacy

All efficacy analyses will be performed separately on the Safety Population, Rollover Safety Population and Non-Rollover Safety Population.

7.8.1 Primary Efficacy Analysis

The primary objective for this study is safety. All efficacy endpoints are secondary.

7.8.2 Secondary Efficacy Analyses

There are 5 secondary efficacy endpoints for this study:

- Time from first open-label study dose to the first investigator-confirmed HAE attack for rollover subjects
- Number of investigator-confirmed HAE attacks during the treatment period
- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period
- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period

Time to first investigator-confirmed HAE attack

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

These data will be used to explore the potential "outer bounds" of dosing frequency against a background of prior exposure to DX-2930 from Study DX-2930-03. A KM plot of time to first investigator-confirmed HAE attack will be produced by the prior treatment group from Study DX-2930-03. Additionally, a similar plot will be presented for only the first 8 weeks in the DX-2930-04 study. Additionally, a KM plot of time to first investigator-confirmed HAE attack will be produced for the DX-2930 total group and placebo group, and another KM plot will present the DX-2930 total group and placebo group for the first 8 weeks. If a subject has not had an attack, the subject will be censored at the earlier of the early discontinuation date, database cut date, or Day 924 visit of the DX-2930-04 study. Subjects who received the second dose of study drug prior to the first attack will be censored at the date of their second dose of study drug. Each subject's censoring status and time to event will be provided in a listing. Details on the calculation of time to first investigator-confirmed HAE attack can be found in Appendix 2.9.3.

In addition, the impact of baseline covariates on the time to the first investigator-confirmed HAE attack will be examined using Cox proportional hazards regression models. A Cox proportional hazards model will be conducted using DX-2930 concentration level at Day 0 of the DX-2930-04 study prior to the first dose of the study drug as the independent variable and time to first HAE attack as the dependent variable. Additional Cox PH models will be run using age group, weight group, BMI group , sex, race group, baseline HAE attack rate group, HAE type, geographic region, and history of laryngeal attacks as independent variables adjusting for DX-2930 concentration level at Day 0 in the DX-2930-04 study with time to first HAE attack as the dependent variable. Additional models may be considered as appropriate. Results of this exploratory analysis will be summarized and will include hazard ratios, corresponding 95% confidence intervals and p-values for each factor.

Number of investigator-confirmed HAE attacks

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through the end of treatment period), expressed as a monthly HAE attack rate, will be summarized for each analysis population. For non-rollover subjects, the monthly attack rate will be reported for the entire treatment period. For rollover subjects, the monthly attack rate will be reported for the Regular Dosing stage of the treatment period (refer to Appendix 2.7.2.2 for a definition of the Regular Dosing stage).

Detailed information on calculating the baseline HAE attack rate and the HAE attack rate during the treatment period can be found in Appendix 2.9.1 and Appendix 2.9.2 respectively.

For the Rollover Safety Population, the following will be summarized: the baseline investigator-confirmed HAE attack rate per month (DX-2930-03 run-in period monthly investigator-confirmed HAE attack rate), DX-2930-03 treatment period investigator-confirmed HAE attack rate per month, the Regular Dosing stage investigator-confirmed HAE attack rate per month, the Regular Dosing stage investigator-confirmed HAE attack rate change from the monthly attack rate in the DX-2930-03 run-in period, the Regular Dosing stage investigator confirmed HAE attack rate change from the monthly attack rate in the DX-2930-03 treatment period, the percent change of the Regular Dosing stage investigator-confirmed HAE attack rate from the run-in period attack rate in the DX-2930-03 treatment period , and the percent change of the Regular Dosing stage investigator-confirmed HAE attack rate from the monthly attack rate in the DX-2930-03 treatment period.

An additional table for the Rollover Safety Population will be added that categorizes rollover subjects by their prior LTP and the following will be summarized: the historical HAE attack rate (HAE attack rate as reported in the last 3 months in the HAE history Appendix 2.9.1), the Regular Dosing stage investigator-confirmed HAE attack rate per month, the Regular Dosing stage investigator-confirmed HAE attack rate change from the historical monthly attack rate, and the percent change of the Regular Dosing stage investigator-confirmed HAE attack rate from the historical attack rate.

For the Non-rollover Safety Population, the baseline HAE attack rate for non-rollover subjects are derived from the number of attacks reported in the last 3 months in the HAE history (Appendix 2.9.1). The following will be summarized for the Non-Rollover Safety population: the baseline investigator-confirmed HAE attack rate per month, the treatment period investigator-confirmed HAE attack rate per month, and the treatment period investigator-confirmed HAE attack rate change from baseline.

Pooled results for the Rollover Safety Population and Non-Rollover Safety Population will be presented for the Safety Population. The summaries will include the total number of investigator-confirmed HAE attacks reported during each period, total subject-time in months that each subject contributed to each period, summary statistics for the baseline investigator-confirmed HAE attack rate per month, the treatment period (Regular Dosing stage for rollover subjects) investigator-confirmed HAE attack rate per month, and the treatment period (Regular Dosing stage) investigator-confirmed HAE attack rate change and percent change from baseline. Figures will be created for each analysis population plotting the on-study investigator-confirmed HAE

attacks reported during the treatment period by prior LTP use for the Non-Rollover Safety Population and the Regular Dosing stage by prior treatment in the DX-2930-03 study for the Rollover Safety Population for each subject (ie, birds on a wire plots). A graph showing results in the Safety Population by pooling results from rollover subjects and non-rollover subjects. All subjects with less than 50% reduction in HAE attacks from the run-in period to the treatment period will be presented in a listing which include the unique subject id, age, sex, race, weight, weight group, timepoints of anti-drug antibody testing, confirmation of anti-drug antibody testing, time point of test for neutralizing antibody, result of test for neutralizing anti-body, baseline attack rate, attack rate during the treatment period (regular dosing stage for rollover subjects), treatment period percent change from baseline, steady state treatment period percent change from baseline.

In addition, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized descriptively by study month (per 28-day interval) for each study population. The summary will include baseline number of attacks, the number, change from baseline, and percentage change from baseline of investigator-confirmed HAE attacks for each study month.

For the Rollover Safety Population, investigator-confirmed HAE attack per month for each study month will be summarized for the Regular Dosing stage. A bar chart representing the number of attacks per month during the Regular Dosing stage and a separate bar chart presenting the percent change from the DX-2930-03 treatment period attack rate for each study month during the Regular Dosing stage will be presented. An additional bar chart presenting the percent change from baseline, the DX-2930-03 run-in period will be presented for each study month during the Regular Dosing stage.

For the Non-rollover Safety Population, the number of investigator-confirmed HAE attacks per month will be grouped into 28-day intervals using the start date of the HAE attack using Table 1 below.

For the Safety Population, investigator-confirmed HAE attack per month for each study month will be presented for the Safety Population, pooling results from Rollover Safety Population and Non-rollover Safety Population. In this summary, for Rollover Safety Population, the DX-2930-03 study baseline HAE attack rate will be used as the baseline.

Table 1 Defining Treatment Months for Non-Rollover Subjects

Visit	Month	Study Day
3	1	0-27
5	2	28-55
7	3	56-83
9	4	84-111
11	5	112-139
13	6	140-167
15	7	168-195
17	8	196-223
19	9	224-251
21	10	252-279

Table 1 Defining Treatment Months for Non-Rollover Subjects

Visit	Month	Study Day
23	11	280-307
25	12	308-335
27	13	336-363
29	14	364-391
31	15	392-419
33	16	420-447
35	17	448-475
37	18	476-503
39	19	504-531
41	20	532-559
43	21	560-587
45	22	588-615
47	23	616-643
49	24	644-671
51	25	672-699
53	26	700-727
55	27	728-755
57	28	756-783
59	29	734-811
61	30	812-839
63	31	840-867
65	32	868-895
67 (End of Treatment Period)	33	896-924
68 (Follow-up 1)	-	925-938
69 (Follow-up 2; End of Study; Early Termination)	-	939-952

For the Safety Population, the baseline investigator-confirmed HAE attack rate, treatment period (Regular Dosing Stage for rollover subjects) investigator-confirmed HAE attack rate, and treatment period (Regular Dosing Stage for rollover subjects) change from baseline on investigator-confirmed HAE attack rate will be summarized by the percentage of self-administration during the study. Subjects will be subgrouped by the percentage of self-administration during the treatment period:

Predominant Self-administration: greater than or equal to 80% self-administration

Predominant HCP-administration: greater than or equal to 80% administration by study staff in-clinic

Mixed administration: less than 80% self-administration and less than 80% administration by study staff in-clinic

All HAE attacks will be presented in a listing. All laryngeal HAE attacks will be presented in a listing.

Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period

This endpoint will be analyzed using the same methods as for the overall number of investigator-confirmed HAE attacks with the exception of the monthly line graphs. The listing of HAE attacks will include the specific acute treatments given during the attack.

Number of moderate or severe investigator-confirmed HAE attack

The severity of the HAE attack will be determined by the investigator. See Appendix 2.8.6 for details. The number of moderate or severe investigator-confirmed HAE attacks will be presented using the methods for the overall number of investigator-confirmed HAE attacks with the exception of the monthly line graphs. The listing of HAE attacks will include severity.

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 edema. This endpoint will be analyzed using the methods for the overall number of investigator-confirmed HAE attacks with the exception of the monthly line graphs. The listing of HAE attacks will include a high morbidity flag.

7.8.3 Exploratory Efficacy Analyses

Number and percentage of subjects that are attack-free during the treatment period

The number and percentage of subjects who are attack-free for 3 months or 6 months or for the entire treatment period (Regular Dosing stage for the Rollover Safety Population) will be summarized for each analysis population.

In addition, the number and percentage of subjects who are attack-free for 6 months during each of the 6 month intervals (0- <6 months, 6- <12 months, 12- <18 months, 18-<24 months, and 24-<30 months) for the treatment period (regular Dosing Stage for the Rollover Safety Population) will be summarized. Also, the number and percentage of subjects who are attack-free for 4 months during each of the 4 month intervals (0-<4 months, 4-<8 months, 8-<12months, 12-<16 months, 16-<20 months, 20-<24 months, 24-<28 months, and 28-<32 months) for the treatment period (regular Dosing Stage for the Rollover Safety Population) will be summarized.

Subjects who have not completed the full interval but are attack-free for the time observed, will be counted as attack-free for the full interval in the analysis.

Percentage of HAE attack-free days

The percentage of HAE attack-free days will be summarized for each analysis population. An attack-free day is defined as a calendar day with no investigator-confirmed HAE attacks.

For the Non-Rollover Safety Population, 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 spends in the treatment period. For the Rollover Safety Population, the percentage of HAE attack-free days will be calculated by counting the number of days in the Regular Dosing stage of the treatment period without an HAE attack and dividing by the number of days the subject spends in the regular dosing stage of the treatment period. For the Safety Population, pooled results in the Non-Rollover Safety Population and the Rollover Safety Population will be presented. Summaries of the percentage of HAE attack-free days will be provided by treatment group in the DX-2930-03 study for the rollover subjects and by prior LTP use for the non-rollover subjects for overall treatment period for non-rollover subjects and the Regular Dosing stage of the treatment period for the rollover subjects.

Summary of attack-free period

For each subject, the mean duration of an attack-free period will be derived by taking the average of the attack-free periods for the subject. Summary of the mean attack-free period will be provided for the Safety Population, Rollover Safety Population, and the Non-Rollover Safety Population. In this analysis, an attack-free day is defined as a calendar day with no investigator-confirmed HAE attack. An attack-free period is defined as a continuous number of days without any investigator-confirmed HAE attacks. For the Rollover Safety Population, the summary of mean attack-free periods will be described during the regular dosing stage of the treatment period.

For each subject, the longest duration of an attack-free period will be derived by taking the longest duration of the attack-free periods for the subject. Summary of the longest attack-free period will be provided for the Safety Population, Rollover Safety Population, and the Non-Rollover Safety Population. For the Rollover Safety Population, the summary of longest attack-free periods will be described during the regular dosing stage of the treatment period.

Additionally, a categorical summary for the longest duration of an attack-free period will be presented. The number and percentage of subjects with the longest duration that are within the categories of 0 to < 3 months, 3 to < 6 months, 6 to < 9 months, 9 to < 12 months, and $\geq$ 12 months will be summarized.

Achievement of a pre-specified reduction from baseline in the investigator-confirmed HAE attack rate (ie, responder analysis)

Achievement of a pre-specified reduction from baseline in the investigator-confirmed HAE attack rate will be analyzed for each analysis population. There will be five classes of responders based on pre-specified percentage reduction in the investigator-confirmed HAE attack rate from the baseline 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 baseline HAE attack rate will be calculated. See Section 10.2.9 for details. The percentage reduction will be calculated as the baseline HAE attack rate minus the treatment period (regular dosing stage for rollover subjects) HAE attack rate divided by the baseline 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.

The Non-rollover Safety Population subjects with 0 baseline attack rate will be excluded from this analysis.

Achievement of <1 investigator-confirmed HAE attacks per month during the treatment period (regular dosing stage for rollover subjects)

The number and percentage of subjects who had less than 1 investigator-confirmed HAE attack per month will be presented for each analysis population.

Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location, trigger, and medication use during the treatment period

For each analysis population, attack characteristics at the subject level and event level, as described below, will be summarized for the treatment period for non-rollover subjects and the Regular Dosing stage for rollover subjects.

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 Appendix 2.8 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 Appendix 2.8.6 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 total number of attacks, 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 laryngeal attacks. 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.

7.8.4 Rescue Medication Use

The number and percentage of subjects with rescue medication use for an HAE attack, as well as the number of rescue medications, 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.

7.8.5 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.

7.8.6 Trigger

The number and percentage of subjects with trigger for an HAE attack, as well as the number of triggers, will be tabulated by type of triggers as reported in the AE CRF.

The subject-level and event-level HAE characteristics analyses will be repeated for the safety population for the primary endpoints in subgroups of subjects with ≤50% reduction in attack-rate from baseline and subjects with > 50% reduction in attack-rate from baseline. Subjects with 0 baseline attack rate will be excluded from this analysis.

Rescue Medication Use

A summary of the number of HAE attacks by type and number of rescue medication uses will be calculated for the Safety Population. The summary will present the overall number of HAE attacks, and number of HAE attacks by number of rescue medication uses (no rescue medication use, 1 rescue medication use, or more than 1 rescue medication use). The attacks that required rescue medication use will be further summarized by type of rescue medication (C1-INH, icatibant, other, or a mixture of rescue medications) and number of rescue medication uses (1 rescue medication or more than 1 rescue medication).

An additional table will be created for an event level summary of duration (hours) of investigator-confirmed HAE attacks by severity, location, and rescue medication use for the Safety Population. Investigator-confirmed HAE attacks will be classified by severity (Mild, Moderate, Severe) and rescue medication use (No rescue medication use, C1-INH, icatibant, other) or by location (Laryngeal, Abdominal, Peripheral) and rescue medication use. Duration of HAE attacks will then be summarized for each subset of the attacks using summary statistics.

7.9 Analysis of Safety

All safety analyses will be performed separately on the Safety Population, Rollover Safety Population, and Non-Rollover Safety Population, unless otherwise specified. No inferential statistics are planned.

7.9.1 Adverse Events

AEs will be coded using the MedDRA coding dictionary version 20.0.

The analyses described in this section will be based on treatment-emergent AEs, referred to simply as AEs in this section for brevity. The definition of treatment-emergent AEs can be found in Appendix 2.10.1.

Related AEs are AEs classified as related to study drug by the investigator. Severe AEs are AEs classified as severe (GRADE 3) or life-threatening (GRADE 4) by the investigator.

For this analysis, AEs will be classified to one of two analysis periods:

Treatment Period AEs will include all AEs starting at or after the first exposure to open-label DX-2930 in the current study to those starting before or at the subject's last visit date during the treatment period in the current study (AEs starting at or after treatment on Day 0 but before or at the end of treatment period).

Follow-up Period AEs will include all AEs starting at or after the subject's last visit date of the treatment period in the current study (AEs starting after the Day 924 visit, the last visit during the treatment period). For AEs with partial onset times, non-missing date parts will be used to determine whether the AE falls within the period. If a determination cannot be made using the non-missing date parts, the AE will be conservatively counted as a treatment-period AE. Follow-up period AEs will be presented in listings.

For each analysis of the Rollover Safety Population, the AEs will be presented for the treatment period, and the Dose-and-wait stage and the Regular Dosing stage of the treatment period (refer to Appendix 2.7.2.1 for a definition of the Dose-and-wait stage and Appendix 2.7.2.2 for a definition of the Regular Dosing stage) unless otherwise specified. For each analysis of the Non-rollover Safety Population, the AEs will be presented for the treatment period and the Tapering stage and Non-tapering stage of the treatment period (refer to Appendix 2.7.2.3 for a definition of the Tapering stage and Appendix 2.7.2.4 for a definition of the Non-tapering stage of the treatment period) unless otherwise specified. For each analysis of the Safety Population, pooled results from the Rollover Safety Population and Non-rollover Population will be presented for the treatment period.

For each study population and each treatment stage, the total subject-time in years, average subject-time (years), total number of doses across all subjects, and average number of doses for each subject will be presented for the summary AE tables, as well as the number and percentage of subjects with any AE, any related AE, any SAE, any related SAE, any severe AE, any related severe AE, and any investigator-reported AESI, as well as the total number of events for each category, will be summarized for the treatment period. The number of deaths due to an AE, hospitalizations due to an AE, and study discontinuations due to an AE will be summarized for the treatment period.

For each analysis population, the number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC and PT for the treatment period. This

tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs for treatment period AEs. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the total column of the Safety Population.

For each analysis population, the number and percentage of subjects with an AE will be summarized by maximum severity, SOC, and PT for the treatment period. Subjects will be counted once per SOC and once per PT at the maximum severity. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the total column of the Safety Population.

For each analysis population, the number of AEs will be summarized by severity, SOC, and PT 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 total column of the Safety Population.

For each analysis population, the number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by PT for treatment period AEs only. This tabulation will be repeated for related AEs and severe AEs for treatment period AEs for each study population.

All AEs will be provided in subject listings. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and AESIs will be produced.

Adverse Events of Special Interest (AESI)

Adverse events of special interest AESIs for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Investigators are required to document any potential AESIs on the CRF page, and notify the sponsor within 24 hours. In addition to investigator-reported AESIs, standardized MedDRA Queries (SMQ) for each AESI category will be performed using the study data.

Summaries of AESIs will be presented for the treatment period for the Safety Population, for the treatment period and regular dosing stage of the treatment period for the Rollover Safety Population, and for the treatment period and Tapering stage of the Non-Rollover Safety Population.

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

Summary of AESI: For each analysis population, the number and percentage of subjects with any AESI, any related AESI, any severe AESI, any related severe AESI, any serious AESI, and any related serious AESI, as well as the total number of events for each category, will be summarized. The number of deaths due to an AESI, hospitalization due to an AESI and study discontinuation due to an AESI will be summarized for each analysis period.

AESIs by SOC and PT: For each analysis population, the number and percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized by SOC and PT for each analysis period. This tabulation will be repeated for related AESIs 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.

Related AESIs by SOC and PT: For each analysis population, 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. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the rollover subjects and then in the non-rollover subjects.

SMQ-defined hypersensitivity AESIs during the treatment period include several different terms describing injection site reactions. The Data Monitoring Committee (DMC) pointed out that including these terms in the tabulation could detract from the focus on systemic AESIs. Therefore, tables on SMQ-defined hypersensitivity AESIs 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. Additionally, HAE preferred terms will be removed from SMQ-defined hypersensitivity summaries.

A listing of investigator-reported AESIs will be provided.

Injection Site Reactions (ISR)

ISR AEs were not predefined in the protocol, but instead are identified using the algorithm detailed in Appendix 2.10.5 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 for each analysis population. 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 for each analysis population.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs, will be summarized for each analysis population by SOC, and PT for the treatment period. The number and percentage of subjects with an ISR AE will be summarized for each analysis population 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 rollover subjects, then non-rollover subjects.

For each analysis population, the number ISR AEs will be summarized by severity, SOC, and PT 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 total column of the Safety Population.

The number of injections, number of injection site reactions, and the percent of injections with ISR AEs will be summarized by the administration type of the injection and location of the injection.

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). Definition of the duration of ISR is provided in Appendix 2.10.5.1.

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

A listing detailing the PT within the SMQ will be provided.

Table 2 provides a summary of the AE tabulations by analysis population and stage as described in this section.

Table 2 Adverse Event Tabulations by Analysis Population and Stage

	Safety Population *	**Rollover Safety Population**			**Non-rollover Safety Population**		
	Treatment Period	Dose-and-Wait Stage	Regular-Dosing Stage	Treatment Period	Tapering Stage	Non-Tapering Stage	Treatment Period
AE summary	x	x	x	x	x	x	x
AE by SOC and PT	x	x	x	x	x	x	x
AE by PT	x	x	x	x	x	x	
Related AE by SOC and PT	x	x	x	x	x	x	x
Related AE by PT	x	x	x	x	x	x	
Severe AE by SOC and PT	x	x	x	x	x	x	x
Related Severe AE by SOC and PT	x	x	x	x	x	x	x
SAE by SOC and PT	x	x	x	x	x	x	x
SAE by PT	x	x	x	x	x	x	
Related SAE by SOC and PT	x	x	x	x	x	x	x
AE by max severity, SOC, and PT (subject level)	x	x	x	x	x	x	x
AE by severity, SOC, and PT (event level)	x	x	x	x	x	x	x
Summary of Investigator-reported AESI	x	x	x	x	x	x	x
Investigator-reported AESI by SOC and PT	x	x	x	x	x	x	x
Related Investigator-reported AESI by SOC and PT	x	x	x	x	x	x	x
SMQ-defined AESI by SOC and PT	x	x	x	x	x	x	x
Related SMQ-defined AESI by SOC and PT	x	x	x	x	x	x	x
Summary of ISR AEs	x	x	x	x	x	x	x
ISR AEs by SOC and PT	x	x	x	x	x	x	x

Table 2 Adverse Event Tabulations by Analysis Population and Stage

	Safety Population *	Rollover Safety Population			Non-rollover Safety Population		
ISR AEs by Max Severity, SOC, and PT (subject level)	x	x	x	x	x	x	x
ISR AEs by Severity, SOC, and PT (event level)	x	x	x	x	x	x	x
Number and duration of ISR AEs	x	x	x	x	x	x	x

AE = adverse event; AESI = AE of special interest; PT = preferred term; SOC = system organ class
*Summary in the Safety Population will be presented for the overall treatment period

In this study, the efficacy endpoints are based on AEs. If DX-2930 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 results. Thus, the collection of tabulations described above and summarized in Table 2 (with the exception of the analyses of AESI and ISR)will be produced for 2 mutually exclusive subgroups of AEs based on whether the AE was identified in EDC as a subject-reported HAE attack, 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.

7.9.2 Clinical Laboratory Evaluation

Laboratory test results will be summarized by panel type (hematology, coagulation, chemistry, urinalysis) using the Safety Population. Laboratory test results will be presented in conventional units.

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

Actual values and change from baseline clinical laboratory tests will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. See Appendix 2.12 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 below the lower limit of normal, clinically non-significant result below the lower limit of normal, within the normal range, clinically non-significant result above the upper limit of normal, and clinically significant result above the upper limit of normal will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe

classification will be selected for analysis. In the event of a tie, the earlier measurement will be used.

Categorical laboratory test results (urinalysis excluding pH) will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Subjects with clinically significant abnormal laboratory test results will be listed by panel type. 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 visits to identify any trends. Subjects whose lab profile that may need further examination will be identified by the study physician. A line plot or related analysis will be generated.

Additional Lab Analyses

For the Safety Population, additional analyses will be conducted on liver function tests using the highest pre-treatment and highest treatment period measurements. The number and percentage of subjects with highest results falling into the categories of normal, 1-<3 x the upper limit of normal, 3-5 x the upper limit of normal, and greater than 5 x the upper limit of normal on the liver function tests for ALT and AST will be summarized for all pre-treatment measurements and treatment period measurements. Total bilirubin will be summarized by the number and percentage of subjects with highest results fall into the categories of $\leq$ 2x the upper limit of normal (ULN) and > 2 x the upper limit of normal for all pre-treatment measurements and treatment period measurements. .

Hepatic profiles that plot the individual levels of ALT, AST, and total bilirubin will be further created for subjects identified by the study physician. A line plot or related analysis will be generated. As of last subject last visit date, or 31OCT2019, subjects identified as having elevated LFT results are:

03 study:

[redacted] Discontinued – no further update

[redacted] Ongoing

[redacted] Ongoing

[redacted] Ongoing

04 study

[redacted] Discontinued

[redacted] Discontinued

[redacted] Ongoing

[redacted] Ongoing

[redacted] Ongoing

[redacted] Discontinued

[redacted] Ongoing

[redacted] Discontinued

[redacted] Ongoing

[redacted] Ongoing

Additionally, for the Safety Population, a shift table summarizing the shift in categories from highest pre-treatment measurements to the highest treatment period measurements will be created for the liver function tests including ALT, AST, and total bilirubin. For ALT and AST, the categories were normal, 1-<3 x the upper limit of normal, 3-5 x the upper limit of normal, and greater than 5 x the upper limit of normal; for total bilirubin the categories were normal, ≤ 2.0 x the upper limit of normal and > 2.0 x the upper limit of normal. Also, for the Safety Population, shift tables will be presented for hematology, chemistry, and coagulation using the categories defined in Table 3.

An eDISH graph (Paul B. Watkins, 2011) plotting the highest total bilirubin vs. highest ALT in multiples of ULN during the treatment period will be produced. Subject IDs for the subjects not in the area of ≤3 x ULN for ALT and ≤2 x ULN for total bilirubin will be shown in the graph.

Additional lab parameters may be evaluated as identified by the study physician. All laboratory data will be provided in subject listings by panel type.

Table 3 Lab Parameter Criteria Categories

Parameter	Criteria Categories			
Liver Function Tests				
ALT (U/L)	Normal	1-3 x ULN	3-5 x ULN	> 5 x ULN
AST (U/L)	Normal	1-3 x ULN	3-5 x ULN	> 5 x ULN
Total Bilirubin (mg/dL)	Normal	≤2.0 x ULN	> 2.0 x ULN	-
Chemistry				
Albumin (g/dL)	Low (< 0.6 x LLN)	Normal (≥ 0.6 x LLN)	-	-
Creatinine (mg/dL)	Normal (≤ 1.5 x ULN)	High (>1.5 x ULN)	-	-
Glucose (mg/dL)	Low (< 0.6 x LLN)	Normal (0.6 x LLN - 3.5 x ULN)	High (>3.5 x ULN)	-
Potassium (mEq/L)	Low (< 0.85 x LLN)	Normal (0.85 x LLN - 1.2 x ULN)	High (>1.2 x ULN)	-
Urea Nitrogen (mg/dL)	Normal (≤ 3.0 x ULN)	High (> 3.0 x ULN)	-	-
Hematology				
Eosinophils/Leukocytes	Normal (≤4.0 x ULN)	> 4.0 x ULN	-	-
Hematocrit	Low (<0.6 x LLN)	Normal (0.6 x LLN - 1.3 x ULN)	High (>1.3 x ULN)	-
Hemoglobin (g/dL)	Low (<0.6 x LLN)	Normal (0.6 x LLN - 1.3 x ULN)	High (>1.3 x ULN)	-
Leukocytes (10^3/uL)	Low (<0.5 x LLN)	Normal (0.5 x LLN - 2.0 x ULN)	High (>1.3 x ULN)	-
Neutrophils (10^3/uL)	Low (<0.5 x LLN)	Normal (≥0.5 x LLN)	-	-
Platelets (10^3/uL)	Low (<0.4 x LLN)	Normal (0.4 x LLN - 2.0 x ULN)	High (>2.0 x ULN)	-
Coagulation				
Activated Partial Thromboplastin Time (sec)	≤ 1.5 x ULN	> 1.5 X ULN	-	-
Prothrombin Intl. Normalized Ratio	≤ 2 x ULN	> 2 x ULN	-	-
Prothrombin Time (sec)	≤ 1.5 x ULN	> 1.5 x ULN	-	-

7.9.3 Vital Signs

Vital signs will be summarized using the Safety Population. Note that vital signs will not be monitored for subjects who self-administer study drug at optional off-site visits.

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

Actual values and changes from baseline in vital signs will be summarized by study visit and study time point (pre-dose and 1 hour post-dose at dosing visits). In addition the change from pre-dose value (1 hour post-dose value minus pre-dose value) will be summarized for each study visit. 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 clinically non-significant result and clinically significant result will be summarized by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the result yielding the most severe classification will be selected for analysis.

Subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameter that was determined by the investigator to be clinically significant for a subject across study visits and time points to identify any trends.

All vital sign data will be provided in subject listings.

7.9.4 Electrocardiography

ECG results will be summarized using the Safety Population.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG not performed, will be summarized by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study visits to identify any trends.

All ECG data will be provided in subject listings.

7.9.5 Physical Examinations

Physical examinations will be summarized using the Safety Population.

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 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 visits to identify any trends.

All physical examination findings will be provided in subject listings.

7.9.6 Prior and Concomitant Medications

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 for non-rollover subjects. There will be no prior medications for rollover subjects.

Concomitant medications are defined as medications with a start time after the time of study drug administration or medications with a start time prior to study drug administration but continuing after treatment.

For medications with partial onset times, non-missing date parts will be used to determine whether 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.

The number and percentage of subjects with prior or concomitant medications will be summarized by therapeutic class and preferred term for each analysis population. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications. All medications will be presented in subject listings.

7.10 Other Analyses

Additional analyses of PK and PD data will be described in a separate PK/PD report.

Additional analysis of 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 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 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 ADA-positive results will be summarized by study visit and overall and listed by subject using the Safety Population.

7.10.4 Analysis of Quality of Life Data

Quality of life assessments will be summarized using the Safety Population. The number and percentage of subjects at each level of the EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be presented by study visit. In addition, the VAS score for the subject's self-rated health will be summarized by study visit.

The responses to the SF-12 for each item will be tabulated by study visit. In addition, PCS & MCS will be computed using the scores of 12 questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health.

Responses to the HADS for each item will be tabulated by study visit. In addition, continuous and categorical (0-7, normal; 8-10, mild; 11-14, moderate; 15-21, severe) total scores based on the items related to depression and anxiety will be summarized by study visit. Each item in the questionnaire is scored from 0 to 3, with total scores between 0 and 21 for either depression or anxiety. Scores for the entire scale (emotional distress) will also be presented. The total score for the entire scale ranges from 0 to 42, with higher scores indicating more distress.

Responses to the WPAI-GH for each item will be summarized by study visit. In addition, four main scores in relation to general health will be summarized by study visit. Scores will be calculated as absenteeism (percentage of work time missed due to health), presenteeism (percentage impairment while working due to health), work productivity loss (percentage overall work impairment due to health), and activity impairment (percentage activity impairment due to health). The scores are percentages with higher values indicating greater percentage impairment. Only respondents who report being full-time or part-time employed provide data for absenteeism, presenteeism, and overall work productivity loss. All respondents provide data for activity impairment.

The responses to the AE-QoL for each item will be tabulated by study visit. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized by study visit. Each item in the questionnaire is scored from 0 to 4, with domain and total scores calculated using a linear transformation to a 0 to 100 scale. See details in Appendix 2.13.

All QoL data will be provided in subject listings and a separate analysis plan will be developed for QoL data.

7.10.5 Analysis of Study Drug Self-Administration

For each analysis population, the responses to the self-administration and subcutaneous injection survey for each item will be tabulated by study visit.

The number and percentage of subjects who performed study drug administration as well as the total number of injections that were administered via study staff administration in-clinic, self-administration in-clinic, and self-administration at home will be tabulated for the safety population, rollover safety population, and non-rollover safety population overall and by study visit.

For each analysis population, summary statistics for the total number of doses received, percentage of doses self-administered at home, percentage of doses self-administered in clinic, and percentage of doses administered by study staff in clinic will be presented.

The number and percentage of subjects who had ever performed study drug administration as well as the total number of injections administered via study staff administration in-clinic, self-administration in-clinic, or self-administration at home, as well as the total number of injections in each category, will be tabulated for the safety population, rollover safety population, and non-rollover safety population. Additionally, the number and percentage of subjects who received 0, 1 to 5, 6 to 10, 11 to 20, or >20 self-administration in-clinic, or self-administration at home will be summarized for each analysis population. The number and percentage of subjects who received greater than or equal to 50%, greater than or equal to 60%, greater than or equal to 70%, greater than or equal to 80%, greater than or equal to 90% of their doses by the study staff in-clinic will be summarized for the Safety Population.

The number and percentage of study drug administrations whose duration was 0 to 10 seconds, 11 to 20 seconds, 21 to 30 seconds, 31 to 60 seconds, greater than 1 minute to less than or equal to 2 minutes, greater than 1 minute to less than or equal to 3 minutes, greater than 3 minutes to less than or equal to 4 minutes, greater than 4 minutes to less than or equal to five minutes, and greater than 5 minutes will be summarized for each dose that was self-administered at home, self-administered in-clinic, administered by the study staff in-clinic, and overall.

7.10.6 Summary of Angioedema Control Test (AECT) by Study Visit

AECT results will be summarized for the safety population. Number and percentage of subjects in each respond category will be summarized by study visit.

All AECT data will be provided in subject listings.

7.10.7 Summary of Treatment Satisfaction Questionnaire for Medication (TSQM-9) by Study Visit

A summary of TSQM-9 results will be provided for the safety population. Number and percentage of subjects in each respond category will be summarized by study visit.

All TSQM-9 data will be provided in subject listings.

7.10.8 Summary of Subject's Global Impression of Change

A summary of subject's global impression of changed will be provided for the safety population. Number and percentage of subjects in each respond category will be summarized by study visit.

All subjects' global impression of change data will be provided in subject listings.

7.10.9 Summary of Investigator's Global Impression of Change

A summary of investigator's global impression of changed will be provided for the safety population. Number and percentage of subjects in each respond category will be summarized by study visit.

All investigators' global impression of change 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 Cox Proportional Hazard Model

Instead of a multivariate analysis, univariate cox-proportional hazard models will be conducted controlling for DX-2930 concentration at Day 0 of the DX-2930-04 study in order to explore the factors which impact the time to first HAE attack for the Rollover Safety Population.

8.2.2 Drug Interruption

A subset of subjects missed consecutive doses due to safety concerns. In order to handle the safety and efficacy data in these subjects appropriately, the definition of drug interruption, and data handling approach for drug interruptions were added in the section Appendix 2.7.3.

8.2.3 Self-Administration Subgroup

Instead of presenting the self-administration subgroup as ever self-administered vs. never self-administered, the subgroup is now defined as subjects with ≥80% self-Administration, ≥ 80% administration by study staff in-clinic, and mixed administration (< 80% Self-Administration and < 80% Administration by Study Staff in-clinic).

9. STATISTICAL/ANALYTIC ISSUES

9.1 Adjustment for covariates

Univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack controlling for DX-2930 concentration at Day 0 in the DX-2930-04 study. Results of this exploratory analysis will be summarized and will include hazard ratios and the corresponding 95% confidence intervals.

9.2 Handling of Dropouts or Missing Data

All available data for investigator-confirmed HAE attacks will be included in the analysis. The HAE attack rate will be normalized to 28 days using all available data.

9.3 Interim Analysis and Data Monitoring

Two formal interim analyses were conducted after database lock of the DX-2930-03 study. The interim analyses were defined within the statistical analysis plans for the respective interim analyses.

An independent DMC has been established to provide ongoing, independent review and assessment of the safety data for the DX-2930-03 study. An independent DMC has looked at data from DX-2930-04 3 times and additional reviews may be scheduled by the DMC established for the DX-2930-03 study as part of the collection of safety information available on DX-2930.

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

All p-values will be considered descriptive. No adjustments for multiple comparisons will be made.

9.6 Examination of Subgroups

Subgroup analyses are planned for the time to first HAE attack in Rollover Safety Population, number of investigator-confirmed HAE attacks during the treatment period and adverse events (non-HAE attack treatment period AEs, related AEs, and severe AEs) using the Safety Population. 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/m^2)
- Baseline HAE Attack Rate Group (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- DX-2930 Administration Type (≥80% Self-Administration, ≥ 80% Administration by Study Staff in-clinic, Mixed Administration (< 80% Self-Administration and < 80% Administration by Study Staff in-clinic)
- History of Laryngeal Attack (history of laryngeal attack, no history of laryngeal attack)
- Type of Long-term Prophylactic Therapy Prior to Study Enrollment (C1-INH, Oral Therapy, C1-INH and Oral Therapy, Not on LTP) (for the Safety Population and Rollover Safety Population ONLY)

For the time to event subgroup analysis, the DX-2930 administration type will not be included because subjects only receive one dose. Data analyses and summaries will parallel those described for the primary analysis of the efficacy endpoints and the primary analysis of the adverse events.

9.7 Sensitivity Analyses

9.7.1 Steady State Analyses

The following sensitivity analyses will be performed to evaluate the robustness of the results. Data summaries will parallel those described for the number of investigator-confirmed HAE attacks during the treatment period.

The analyses in Table 4 will be repeated for events occurring during the Steady State Period on Day 70 after administration of study drug through the end of Treatment Period, instead of Day 0 to the end of Treatment Period for non-rollover subjects and the Regular Dosing Stage for rollover subjects. For these analyses, the analysis period would be a subset of the treatment period (Regular Dosing Stage for non-rollover subjects), defined as Day 70 to the end of treatment period.

Table 4 List of Analyses during the Treatment Period and Steady State Period

	Treatment Period (Regular Dosing Stage for Rollover Subjects)	Steady State Period (Day 70 through the end of treatment period)
Number of Investigator-confirmed (IC) HAE attacks	x	x
Number of IC HAE attacks requiring acute treatment	x	x
Number of moderate or severe investigator-confirmed HAE attacks	x	x
Number of high-morbidity investigator confirmed attacks	x	x
Number and percentage of subjects that are attack-free	x	x
Percentage of attack-free days	x	x
Summary of attack-free period	x	x
Achievement of a pre-specified reduction from baseline in the investigator confirmed HAE attack rate	x	x
Achievement of <1 IC HAE attack per month	x	x
Subject level attack characteristics	x	x
Event level attack characteristics	x	x

9.7.2 Analyses on Number of All HAE Attacks

The efficacy endpoint analysis on the number of investigator-confirmed HAE attacks during the treatment period will be repeated using all subject-reported HAE attacks instead of the analysis to only those attacks that were investigator-confirmed.

9.7.3 Analyses Excluding Subjects Without Confirmed Type I or Type II HAE

Subjects [redacted] and [redacted] were listed as having a major protocol deviation because they did not have Type I or Type II HAE confirmed by C1 INH and C4 measurements. Sensitivity analyses will be performed on the following tables in Table 5 excluding subjects [redacted] and [redacted] in order to evaluate the robustness of the efficacy results.

Table 5 List of Analyses Excluding Subjects without Confirmed Type I or Type II HAE

	Safety Population	Safety Population Excluding subjects without confirmed Type I or Type II HAE
Number of Investigator-confirmed (IC) HAE attacks during the Treatment Period	x	x
Number of IC HAE attacks during Day 70 to the End of Treatment Period	x	x
Subject Level Characteristics of IC HAE attacks during the Treatment Period	x	x
Subject Level Characteristics of IC HAE attacks during Day 70 to the End of the Treatment Period	x	x
Event Level Characteristics of IC HAE attacks during the Treatment Period	x	x
Event Level Characteristics of IC HAE attacks during Day 70 to the End of the Treatment Period	x	x
Number and Percentage of Subjects that are Attack-free during the Treatment Period	x	x
Number and Percentage of Subjects that are Attack-free during Day 70 to the End of the Treatment Period	x	x
Responder Analysis using IC HAE attacks during the Treatment Period vs. baseline by responder threshold during the Treatment Period	x	x
Responder Analysis using IC HAE attacks during Day 70 to the End of the Treatment Period vs. baseline by responder threshold during the Treatment Period	x	x

10. APPENDICIES

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14.2.13.4	Responder Analysis using Investigator-confirmed HAE Attacks during the Treatment Period vs. Baseline by Responder Threshold during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population
14.2.13.5	Responder Analysis using Investigator-confirmed HAE Attacks during the Treatment Period vs. Baseline by Responder Threshold during Day 70 of the Regular Dosing Stage through the End of Treatment Period – Rollover Safety Population
14.2.13.6	Responder Analysis using Investigator-confirmed HAE Attacks during the Treatment Period vs. Baseline by Responder Threshold during Day 70 to the End the Treatment Period – Non-Rollover Safety Population

Table No.	Title
14.2.14.1	Achievement of Investigator-Confirmed HAE Attack-Free Interval of 1 Month, 3 Months, 6 Months, 9 Months, or until the End of Treatment Period during the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population
14.2.14.2	Achievement of Investigator-Confirmed HAE Attack-Free Interval of 1 Month, 3 Months, 6 Months, 9 Months or until the End of Treatment Period during the Regular Dosing Stage of the Treatment Period – Rollover Safety Population
14.2.14.3	Achievement of Investigator-Confirmed HAE Attack-Free Interval of 1 Month, 3 Months, 6 Months, or until the End of Treatment Period during the Treatment Period – Non-Rollover Safety Population
14.2.14.4	Achievement of Investigator-Confirmed HAE Attack-Free Interval of 1 Month, 3 Months, 6 Months, 9 Months or until the End of Treatment Period during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population
14.2.14.5	Achievement of Investigator-Confirmed HAE Attack-Free Interval of 1 Month, 3 Months, 6 Months, 9 Months, or until the End of Treatment Period during Day 70 of the Regular Dosing Stage through the End of Treatment Period – Rollover Safety Population
14.2.14.6	Achievement of Investigator-Confirmed HAE Attack-Free Interval of 1 Month, 3 Months, 6 Months, 9 Months, or until the End of Treatment Period during Day 70 to the End the Treatment Period – Non-Rollover Safety Population
14.2.15.1	Achievement of <1 Investigator-Confirmed HAE Attack per Month during the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population
14.2.15.2	Achievement of <1 Investigator-Confirmed HAE Attack per Month during the Regular Dosing Stage of the Treatment Period – Rollover Safety Population
14.2.15.3	Achievement of <1 Investigator-Confirmed HAE Attack per Month during the Treatment Period – Non-Rollover Safety Population
14.2.15.4	Achievement of <1 Investigator-Confirmed HAE Attack per Month during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population
14.2.15.5	Achievement of <1 Investigator-Confirmed HAE Attack per Month during Day 70 of the Regular Dosing Stage through the End of Treatment Period – Rollover Safety Population
14.2.15.6	Achievement of <1 Investigator-Confirmed HAE Attack per Month during Day 70 to the End the Treatment Period – Non-Rollover Safety Population
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142.16.2	Subject Level Summary of Mean Duration (hours) of HAE Attacks by Rescue Medication Use, Severity, and Location – Safety Population
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Table No.	Title
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14.2.19.6	Summary of Angioedema Control Test (AECT) by Study Visit – Safety Population
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14.2.20.5	Summary of Self-Administration and Subcutaneous Injection Survey – Rollover Safety Population
14.2.20.6	Summary of Self-Administration and Subcutaneous Injection Survey – Non-Rollover Safety Population
14. 2.20.7	Summary of Study Drug Administration by Visit -Safety Population
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14. 2.20.11	Study Drug Self-Administration Categories -Rollover Safety Population
14.2.20.12	Study Drug Self-Administration Categories -Non-Rollover Safety Population
14.2.21.1	Number of Investigator-Confirmed HAE Attacks During the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.2	Number of Investigator-Confirmed HAE Attacks During Day 70 to the End of the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.3	Subject Level Characteristics of Investigator-confirmed HAE attacks during the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.4	Event Level Characteristics of Investigator-confirmed HAE attacks during the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.5	Subject Level Characteristics of Investigator-confirmed HAE Attacks during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.6	Event Level Characteristics of Investigator-confirmed HAE Attacks during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.7	Number and Percentage of Subjects that are Attack-Free during the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]

Table No.	Title
14.2.21.8	Number and Percentage of Subjects that are Attack-Free during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.9	Responder Analysis using Investigator-confirmed HAE Attacks during the Treatment Period vs. Baseline by Responder Threshold during the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.2.21.10	Responder Analysis using Investigator-confirmed HAE Attacks during the Treatment Period vs. Baseline by Responder Threshold during Day 70 to the End the Treatment Period (Regular Dosing Stage for Rollover Subjects) – Safety Population excluding subjects [redacted] and [redacted]
14.3.1.1.1	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period – Safety Population
14.3.1.1.2	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Age Group – Safety Population
14.3.1.1.3	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Sex – Safety Population
14.3.1.1.4	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Race Group – Safety Population
14.3.1.1.5	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Weight Group – Safety Population
14.3.1.1.6	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by BMI Group – Safety Population
14.3.1.1.7	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Baseline HAE Attack Rate Group – Safety Population
14.3.1.1.8	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by HAE Type – Safety Population
14.3.1.1.9	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Geographic Region – Safety Population
14.3.1.1.10	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by DX2930 Administration Type – Safety Population
14.3.1.1.11	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by History of Laryngeal Attack – Safety Population
14.3.1.1.12	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Prior Long-Term Prophylaxis – Safety Population
14.1.1.13	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period – Rollover Safety Population
14.3.1.1.14	Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period – Non-Rollover Safety Population
14.3.1.2.1.1	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.2.1.2	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.2.1.3	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population

Table No.	Title
14.3.1.2.2.1	Treatment-Emergent Adverse Events during the Treatment Period by Preferred Term – Safety Population
14.3.1.2.2.2	Treatment-Emergent Adverse Events during the Treatment Period by Preferred Term – Rollover Safety Population
14.3.1.2.2.3	Treatment-Emergent Adverse Events during the Treatment Period by Preferred Term – Non-Rollover Safety Population
14.3.1.2.3	Treatment-Emergent Adverse Events during the Treatment Period by Age Group, System Organ Class and Preferred Term – Safety Population
14.3.1.2.4	Treatment-Emergent Adverse Events during the Treatment Period by Sex, System Organ Class and Preferred Term – Safety Population
14.3.1.2.5	Treatment-Emergent Adverse Events during the Treatment Period by Race Group, System Organ Class and Preferred Term – Safety Population
14.3.1.2.6	Treatment-Emergent Adverse Events during the Treatment Period by Weight Group, System Organ Class and Preferred Term – Safety Population
14.3.1.2.7	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by BMI Group, System Organ Class and Preferred Term – Safety Population
14.3.1.2.8	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Baseline HAE Attack Rate Group, System Organ Class and Preferred Term – Safety Population
14.3.1.2.9	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by HAE Type, System Organ Class and Preferred Term – Safety Population
14.3.1.2.10	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Geographic Region, System Organ Class and Preferred Term – Safety Population
14.3.1.2.11	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by DX-2930 Administration Type, System Organ Class and Preferred Term – Safety Population
14.3.1.2.12	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by History of Laryngeal Attack, System Organ Class and Preferred Term – Safety Population
14.3.1.2.13	Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Prior Long-Term Prophylaxis, System Organ Class, and Preferred Term – Safety Population
14.3.1.3.1	Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Treatment Group, System Organ Class, Preferred Term, and Maximum Severity – Safety Population
14.3.1.3.2	Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Treatment Group, System Organ Class, Preferred Term, and Maximum Severity – Rollover Safety Population
14.3.1. 3.3	Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Treatment Group, System Organ Class, Preferred Term, and Maximum Severity – Non-Rollover Safety Population
14.3.1.3.4	Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Treatment Group, System Organ Class, Preferred Term, and Severity – Safety Population

Table No.	Title
14.3.1.3.5	Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Treatment Group, System Organ Class, Preferred Term, and Severity – Rollover Safety Population
14.3.1.3.6	Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Treatment Group, System Organ Class, Preferred Term, and Severity – Non-Rollover Safety Population
14.3.1.4.1.1	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.4.1.2	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.4.1.3	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.4.2.1	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Preferred Term – Safety Population
14.3.1.4.2.2	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Preferred Term – Rollover Safety Population
14.3.1.4.2.3	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Preferred Term – Non-Rollover Safety Population
14.3.1.4.3	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Age Group, System Organ Class and Preferred Term – Safety Population
14.3.1.4.4	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Sex, System Organ Class and Preferred Term – Safety Population
14.3.1.4.5	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Race Group, System Organ Class and Preferred Term – Safety Population
14.3.1.4.6	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Weight Group, System Organ Class and Preferred Term – Safety Population
14.3.1.4.7	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by BMI Group, System Organ Class and Preferred Term – Safety Population
14.3.1.4.8	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Baseline HAE Attack Rate Group, System Organ Class and Preferred Term – Safety Population
14.3.1.4.9	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by HAE Type, System Organ Class and Preferred Term – Safety Population
14.3.1.4.10	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Geographic Region, System Organ Class and Preferred Term – Safety Population
14.3.1.4.11	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by History of Laryngeal Attacks, System Organ Class and Preferred Term –Safety Population

Table No.	Title
14.3.1.4.12	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by DX-2930 Administration Type, System Organ Class and Preferred Term –Safety Population
14.3.1.4.13	Related Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Prior Long-Term Prophylaxis, System Organ Class and Preferred Term –Safety Population
14.3.1.5.1.1	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.5.1.2	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.5.1.3	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.5.2.1	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Preferred Term – Safety Population
14.3.1.5.2.2	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Preferred Term – Rollover Safety Population
14.3.1.5.2.3	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Preferred Term – Non-Rollover Safety Population
14.3.1.5.3	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Age Group, System Organ Class and Preferred Term – Safety Population
14.3.1.5.4	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Sex, System Organ Class and Preferred Term – Safety Population
14.3.1.5.5	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Race Group, System Organ Class and Preferred Term – Safety Population
14.3.1.5.6	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Weight Group, System Organ Class and Preferred Term – Safety Population
14.3.1.5.7	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by BMI Group, System Organ Class and Preferred Term – Safety Population
14.3.1.5.8	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Baseline HAE Attack Rate Group, System Organ Class and Preferred Term – Safety Population
14.3.1.5.9	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by HAE Type, System Organ Class and Preferred Term – Safety Population
14.3.1.5.10	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Geographic Region, System Organ Class and Preferred Term – Safety Population
14.3.1.5.11	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by History of Laryngeal Attacks, System Organ Class and Preferred Term – Safety Population

Table No.	Title
14.3.1.5.12	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by DX-2930 Administration Type, System Organ Class and Preferred Term – Safety Population
14.3.1.5.13	Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Prior Long-Term Prophylaxis, System Organ Class and Preferred Term – Safety Population
14.3.1.6.1.1	Related Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.6.1.2	Related Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.6.1.3	Related Severe Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.7.1.1	Serious Treatment-Emergent Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.7.1.2	Serious Treatment-Emergent Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.7.1.3	Serious Treatment-Emergent Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.8.1.1	Related Serious Treatment-Emergent Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.8.1.2	Related Serious Treatment-Emergent Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.8.1.3	Related Serious Treatment-Emergent Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.9.1.1	Summary of Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period – Safety Population
14.3.1.9.1.2	Summary of Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period – Rollover Safety Population
14.3.1.9.1.3	Summary of Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period – Non-Rollover Safety Population
14.3.1.9.2.1	Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.9.2.2	Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.9.2.3	Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.9.3.1	Related Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Safety Population
14.3.1.9.3.2	Related Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.9.3.3	Related Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period by System Organ Class, and Preferred Term – Non-Rollover Safety Population

Table No.	Title
14.3.1.9.4.1	Severe Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period (Day 0 to Day 364) by, System Organ Class, and Preferred Term – Safety Population
14.3.1.9.4.2	Severe Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period (Day 0 to Day 364) by, System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.9.4.3	Severe Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period (Day 0 to Day 364) by, System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.9.5.1	Related Severe Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period System Organ Class, and Preferred Term – Safety Population
14.3.1.9.5.2	Related Severe Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.9.5.3	Related Severe Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.9.6.1	Serious Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period System Organ Class, and Preferred Term – Safety Population
14.3.1.9.6.2	Serious Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.9.6.3	Serious Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.9.7.1	Related Serious Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period, System Organ Class, and Preferred Term – Safety Population
14.3.1.9.7.2	Related Serious Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period, System Organ Class, and Preferred Term – Rollover Safety Population
14.3.1.9.7.3	Related Serious Treatment-Emergent HAE Attack Reported Adverse Events during the Treatment Period, System Organ Class, and Preferred Term – Non-Rollover Safety Population
14.3.1.10.1.1	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period – Safety Population
14.3.1.10.1.2	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period – Rollover Safety Population
14.3.1.10.1.3	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period – Non-Rollover Safety Population
14.3.1.10.2.1	Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period by System Organ Class and Preferred Term – Safety Population
14.3.1.10.2.2	Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period by System Organ Class and Preferred Term – Rollover Safety Population
14.3.1.10.2.3	Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period by System Organ Class and Preferred Term – Non-Rollover Safety Population
14.3.1.10.3.1	Related Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period by System Organ Class and Preferred Term – Safety Population

Table No.	Title
14.3.1.10.3.2	Related Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period by System Organ Class and Preferred Term – Rollover Safety Population
14.3.1.10.3.3	Related Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity (Excluding HAE Attacks) during the Treatment Period by System Organ Class and Preferred Term – Non-Rollover Safety Population
14.4.1.10.4.1	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period (Excluding HAE Attacks and ISR)– Safety Population
14.4.1.10.4.2	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period (Excluding HAE Attacks and ISR)– Rollover Safety Population
14.4.1.10.4.3	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period (Excluding HAE Attacks and ISR)– Non-Rollover Safety Population
14.3.1.10.5.1	Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period by System Organ Class and Preferred Term (Excluding HAE Attacks and ISR)– Safety Population
14.3.1.10.5.2	Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period by System Organ Class and Preferred Term (Excluding HAE Attacks and ISR) – Rollover Safety Population
14.3.1.10.5.3	Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period by System Organ Class and Preferred Term (Excluding HAE Attacks and ISR) – Non-Rollover Safety Population
14.3.1.10.6.1	Related Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period by System Organ Class and Preferred Term (Excluding HAE Attacks and ISR)– Safety Population
14.3.1.10.6.2	Related Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period by System Organ Class and Preferred Term (Excluding HAE Attacks and ISR) – Rollover Safety Population
14.3.1.10.6.3	Related Treatment-Emergent Adverse Events of SMQ-Defined Hypersensitivity during the Treatment Period by System Organ Class and Preferred Term (Excluding HAE Attacks and ISR) – Non-Rollover Safety Population
14.3.1.11.1.1	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Bleeding during the Treatment Period – Safety Population
14.3.1.11.1.2	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Bleeding during the Treatment Period – Rollover Safety Population
14.3.1.11.1.3	Summary of Treatment-Emergent Adverse Events of SMQ-Defined Bleeding during the Treatment Period – Non-Rollover Safety Population
14.3.1.11.2.1	Treatment-Emergent Adverse Events of SMQ-Defined Bleeding during the Treatment Period by System Organ Class and Preferred Term – Safety Population
14.3.1.11.2.2	Treatment-Emergent Adverse Events of SMQ-Defined Bleeding during the Treatment Period by System Organ Class and Preferred Term – Rollover Safety Population
14.3.1.11.2.3	Treatment-Emergent Adverse Events of SMQ-Defined Bleeding during the Treatment Period by System Organ Class and Preferred Term – Non-Rollover Safety Population
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Appendix 2. Definitions and Programming Conventions

Appendix 2.1 Age

Age will be calculated as the date of birth minus the date of informed consent of the DX-2930-04 study, truncated to years.

Appendix 2.2 BMI

BMI will be calculated as:

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

Appendix 2.3 Study Day

The study day is calculated as start or stop date – date of first dose + 1 for dates on or after first dose, or start or stop date – date of first dose for dates prior to first dose.

Appendix 2.4 Duration 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.

Appendix 2.5 Algorithm to Identify LTP Use at Baseline

The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to study enrollment will be determined by applying the algorithm presented in Table 6 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 6 LTP Prior to Study Enrollment

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 subgroups, based on the LTP use prior to study enrollment. Table 7 provides the algorithm to classify subjects by type of LTP use prior to study enrollment.

Table 7 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

Appendix 2.6 Definition of Unique Subject ID

The unique subject id consists of the study number of the first DX-2930 study in which a subject participated and is followed by the subject id from the first DX-2930 in which a subject participated.

Appendix 2.7 Analysis Periods

Appendix 2.7.1 Pretreatment Period

The pretreatment period is defined for non-rollover subjects 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*)

The Pretreatment Period is not defined for rollover subjects.

Appendix 2.7.2 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 earliest of the 2 following dates (1) date of study discontinuation or (2) Day 924 visit date. There are two types of subjects in this study, the rollover subjects and the non-rollover subjects. The treatment period is split into two different stages for the rollover subjects- the dose-and-wait stage and the regular dosing stage. For the non-rollover subjects, the treatment period is split into two different stages, the tapering stage and the non-tapering stage.

The treatment period is defined as:

[*date/time of first exposure to study drug*, *date of Day 924 visit or treatment discontinuation*]

Appendix 2.7.2.1 Dose-and-Wait Stage for Rollover Subjects

The dose-and-wait stage of the treatment period for the rollover subjects is defined as the interval of time that starts on the date/time of first study exposure to study drug (Day 0 visit) and ends on the date/time the subject receives the second dose of study drug after the first HAE attack (or the date of treatment discontinuation, if earlier).

[*date/time of first exposure to study drug*, *date/time of the second dose*)

Appendix 2.7.2.2 Regular Dosing Stage for Rollover Subjects

The regular dosing stage for rollover subjects is defined as the interval of time that starts on the date/time of the second dose of the study drug and ends on the earliest of the date of study discontinuation or Day 924 visit date.

[*date/time of the second dose, date of Day 924 visit or treatment discontinuation*]

For rollover subjects, the Day 70 analyses will be performed for the time period start on the Day 70 of the regular dosing stage and ends on the end of regular dosing stage.

For re-enrolled rollover subjects, their regular dosing stage is defined as the interval of time that starts on the date/time of the second dose of the study drug and ends on the earliest of the date of study discontinuation or Day 924 visit date, excluding the time period between Day 364 visit (under protocol amendment 2.0) and the visit they re-enroll into the study.

For re-enrolled rollover subjects, the Day 70 analyses will be performed for the time period of regular dosing stage, excluding the first 69 days from both the first and second enrollments.

Appendix 2.7.2.3 Tapering Stage for Non-rollover Subjects

The tapering stage for the non-rollover subjects is defined as the interval of time that starts on the date/time of the first exposure to study drug (Day 0 visit) and ends on the date/time of the last dose of long-term prophylactic therapy on the DX-2930-04 study.

[*date/time of first exposure to study drug*, *date/time of last LTP use]*

Appendix 2.7.2.4 Non-Tapering Stage for Non-rollover Subjects

The non-tapering stage for non-rollover subjects is defined as the interval of time that starts on the date/time of the last dose of long-term prophylactic therapy to the earliest of the date of the early study discontinuation date or Day 924 visit.

(*date/time of last LTP use, date of Day 924 visit or treatment discontinuation]*

Appendix 2.7.3 Handling of Subjects with Extended Drug Interruption(s)

During this long term safety study, a subset of subjects had drug interruption(s) due to safety concerns such as pregnancy or elevated liver enzymes. For subjects with an extended drug interruption, which is defined as missing ≥3 consecutive study medication doses prior to the earlier of Day 924 visit date or early study discontinuation date, the time period and the

corresponding efficacy and safety events during the presumed low drug exposure drug interruption period will be excluded from safety and efficacy analyses.

Drug Interruption Period Considerations

- Drug interruption period for efficacy analyses impact on efficacy endpoints of HAE attacks.
- Drug interruption period for safety analyses impact on safety endpoints of AEs (including HAE AEs), laboratory measurements, vital signs, ECG, and immunogenicity.
- For efficacy analyses, the time period of 28 days after the last study medication dose prior to drug interruption will not be included in the efficacy drug interruption period. This is because the dosing frequency for the lanadelumab treatment can be once every 4 weeks.
- For safety analyses on HAE attacks, time period of 70 days after the last study medication dose prior to drug interruption will not be included in the safety drug interruption period. This is because the half-life of lanadelumab is around 14 days, and 70 days would be 5 half-lives after the last dose prior to drug interruption.
- For the final CSR, all of the drug interruptions were approved by the Sponsor and the investigator. Therefore, these subjects are considered as compliant during the drug interruption. The expected number of doses for these subjects will be calculated as the total number of expected doses during the treatment period minus doses missed during the drug interruption.
- The gap in study medication use for the subjects who completed the Protocol Amendment 2.0 and later re-enrolled in the Protocol Amendment 3.0 is not considered as a drug interruption.

Existence of Drug Interruption Period

- For efficacy analyses, the existence of drug interruption period is determined by comparing the dates of 1) Date of last study medication prior to drug interruption + 29 days, 2) day 924 visit date, and 3) early study discontinuation date. If date 1) is on or after the earlier of date 2) and 3), then there will be no drug interruption period defined for efficacy analyses.
- For safety analyses, the existence of drug interruption period is determined by comparing the dates of 1) Date of last study medication prior to drug interruption + 71 days, 2) day 924 visit date, and 3) early study discontinuation date. If date 1) is on or after the earlier of date 2) and 3), then there will be NO drug interruption period defined for safety analyses.

Start Date of Drug Interruption Period

When a drug interruption period exists, derive the start date of drug interruption as:

- For efficacy Analyses, the start date of the drug interruption is defined as date last study medication prior to drug interruption + 29 days.

- For safety Analyses, the start date of the drug interruption is defined as date last study medication prior to drug interruption + 71 days.

End Date of Drug Interruption Period

For both efficacy and safety analyses, the end date of drug interruption period is defined as the earlier of the first dose after drug interruption -1, Day 924 visit date, or early study drug discontinuation date. If a subject didn't receive additional study drug after the drug interruption, then the end date of drug interruption period is defined as the earlier of Day 924 visit date or early study drug discontinuation date.

Duration of Drug Interruption

- For efficacy analyses, the duration of drug interruption will be derived as:

  End date of drug interruption period – Start date of drug interruption period (efficacy) + 1

- For efficacy analyses, the duration of drug interruption will be derived as:

  End date of drug interruption period – Start date of drug interruption period (safety) + 1

Duration of Exposure Excluding Drug Interruption Period

- For efficacy analyses, the duration of exposure excluding drug interruption period will be derived as:

  Treatment Period duration – Drug interruption period duration for efficacy

- For safety analyses, the duration of exposure excluding drug interruption period will be derived as:

  Treatment Period duration – Drug interruption period duration for safety

Appendix 2.7.4 Follow-up Period

There were subjects who completed the study under protocol amendment 2.0, and re-enrolled into the study after the approval of Amendment 3.0. Therefore, for these subjects, there are two follow-up periods.

- The follow up period 1 is defined as the interval of time that starts on the date of the Day 364 visit (per protocol amendment 2.0) + 1 and ends on the date of re-enrollment.

  [*date of Day 364 visit + 1*, *date of re-enrollment -1*]

- The follow-up period 2 is defined as the interval of time that starts on the date of the Day 924 visit (or treatment discontinuation) + 1 and ends on the date of the subject's last date of contact for the study.

- [*date of Day 924 visit or treatment discontinuation + 1*, *date of last study contact*]

For all other subjects, the follow-up period is defined as the interval of time that starts on the date of the Day 924 visit (or treatment discontinuation) + 1 and ends on the date of the subject's last date of contact for the study.

[*date of Day 924 visit or treatment discontinuation + 1*, *date of last study contact*]

Appendix 2.8 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.

Appendix 2.8.1 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 Appendix 2.8.2 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 Appendix 2.8.2 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.

Appendix 2.8.2 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.

Appendix 2.8.3 HAE Attack Duration

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

Appendix 2.8.4 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.

Appendix 2.8.5 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 HAARP defined severity and reported as such on the CRF.

Appendix 2.8.6 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 HAARP:

- 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.

Appendix 2.9 HAE Attack Rate

Appendix 2.9.1 Baseline HAE Attack Rate

The baseline investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the run-in period of DX2930-03 for rollover subjects or historical reporting period 3 month prior to the study enrollment for non-rollover subjects divided by the number of days in 3 month (90 days) and multiplied by 28 days.

Appendix 2.9.2 Treatment Period HAE Attack Rate

The treatment period investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the treatment period divided by the number of days the subject contributed to the treatment period multiplied by 28 days. For rollover subjects, the HAE attack rate for the regular dosing stage of the treatment period is calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the regular dosing stage of the treatment period divided by the number of days the subject contributed to the regular dosing stage of the treatment period multiplied by 28 days.

Appendix 2.9.3 Time to First HAE Attack

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date and time of study discontinuation. Subjects who do not experience an HAE attack will be censored at the earlier of the database cut date around 31AUG18 or the date of the Day 924 visit.

Appendix 2.10 Adverse Events

Appendix 2.10.1 Treatment-emergent Adverse Events

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine whether the AE is treatment-emergent. 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.

Appendix 2.10.2 Related Adverse Events

Related AEs are AEs classified as related to study drug by the investigator. If the assessment by the investigator is missing, then the AE will be classified as related.

Appendix 2.10.3 Severe Adverse Events

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator using DMID criteria. If severity is missing, then the AE will be classified as severe.

Appendix 2.10.4 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.

Appendix 2.10.4.1 SMQ-Defined AESI

The broad terms from MedDRA 20.0 SMQ will be used to identify an SMQ-defined AESI. Table 8 shows the SMQ's used to identify AESI of hypersensitivity, hypercoagulable, and bleeding.

Table 8 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)

Appendix 2.10.5 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'.

Appendix 2.10.5.1 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.

Appendix 2.11 Non-standard Laboratory Results

The non-standard laboratory results will be converted to numeric values using the rules shown in Table 9.

Table 9 Convention for Converting Non-Standard Laboratory Results

Non-Standard Lab Values	Standardized Numeric Values
<0.2	Deduct 0.01 from the reference value. i.e., 0.19
<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

Appendix 2.12 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.

For specified analyses, the highest pre-treatment lab value and the highest lab value during the treatment period will be used as well as the criteria presented in Table 3.

Appendix 2.13 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), missing items have little or no influence on the calculated scores.

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 lowest and highest possible domain and total scores are 0 and 100, respectively.

Appendix 2.14 WAPI-GH

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

1 = currently employed

2 = hours missed due to health problems

3 = hours missed other reasons

4 = hours actually worked

5 = degree health affected productivity while working

6 = degree health affected regular activities

Scores:

Multiply scores by 100 to express in percentages.

Percent work time missed due to health: Q2/(Q2+Q4)

Percent impairment while working due to health: Q5/10

Percent overall work impairment due to health:

Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]

Percent activity impairment due to health: Q6/10

Appendix 2.15 HADS

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix 2.16 Study Activity Schedules

Appendix 2.16.1 Study Activity Schedule – Day -28 through Day 365 from Amendment 3.0

Activities Occurring at		**Treatment Period ± 4 days for each visit** ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																												
Non Rollover Visit	Scr[a]	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Rollover Visit	-	Chk[b]		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Dose	-	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Day (± 4 days)	**-28**	**0**		**14**	**28**[c]	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**
Informed Consent[d]	•	•																												
Eligibility Review[e]	•	•																												
Long-term prophylactic therapy cont'd[e]	•	•		•																										
DX-2390-04 Administration[f,g]																														
(rollover subjects)[h]		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
(nonrollover subjects)[e]		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Demographic and Medical History	•																													
Pregnancy Test[i] (females)		•[i]		•	•		•			•		•		•		•			•			•			•				•
Vital Signs[j]	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical Exam[k]	•	•		•	•		•			•				•		•						•								•
Clinical Laboratory Testing[l]	•	•		•	•		•			•				•		•			•			•			•					•

Activities Occurring at		**Treatment Period ± 4 days for each visit** ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																												
Non Rollover Visit	Scr[a]	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Rollover Visit	-	Chk[b]																											
Dose	-	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Day (± 4 days)	-28	0		14	28[c]	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364
12-Lead ECG[m]	•	•								•						•						•							•
Prior (4 wks) & Concomitant Therapy	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
HAE Attack Data[n]	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Quality of Life AE-QoL, EQ-5D-5L, WPAI-GH, HADS, SF-12		•			•		•			•		•		•		•			•			•			•				•
AECT, TSQM v.II, Global Treatment Response																														•
DX-2930 Injection Report	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
DX-2930 Self-administration & SC Injection Survey		•								•						•						•						•	•	•
PK, PD, ADA,[o] & Biomarker[p] Sample collection		•								•						•						•								•

Abbreviations: ADA = anti-drug antibody; AECT = Angioedema Control Test; AE-QOL = Angioedema Quality of Life; Chk = check-in; Cont'd = continued; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimensional 5-Level; HADS = Hospital Anxiety and Depression Scale; PK = Pharmacokinetic; PD = Pharmacodynamic; Scr=screening visit; Scr=screening; SF-12 = Short Form-12; TSQM-vII; WPAI-GH = Work Productivity and Activity Impairment – General Health

Activities Occurring at		**Treatment Period ± 4 days for each visit** ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																												
Non Rollover Visit	Scr[a]	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Rollover Visit	-	Chk[b]		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Dose	-	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Day (± 4 days)	-28	**0**		14	28[c]	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364

[a] Screening visit is for nonrollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.

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

[c] Day 28 is a site check-in call for all rollover and nonrollover subjects.

[d] All subjects must sign informed consent before undergoing study procedures. Nonrollover subjects have up to 28 days to sign informed consent. Rollover subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03. Day 182 of Study DX-2930-03 is also Day 0 of Study DX-2930-04, and informed consent may be completed on this visit, if not already provided.

[e] Screened nonrollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE or AAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930. Since C1-INH therapy may alter the lab results of C1-INH assessments, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility.

[f] Doses are administered every 14 ± 4 days. All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer DX-2930 after (1) completing appropriate training by the investigator or designee, (2) confirming their understanding, and (3) receiving the first 2 doses of DX-2930 at the study site. Subjects are then allowed to initiate home self-administration and may elect to self-administer subsequent doses of DX-2930 at the investigational site. If the subject switches to the PFS, the subject should receive a refresher training focused on the PFS

[g] Site personnel will call subjects within approximately 3 days of the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

[h] Rollover subjects will not receive Dose 2 until they have experienced the first reported, investigator-confirmed attack. In addition, a minimum of 10 days is required between Dose 1 and Dose 2. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit (ie, an unscheduled visit). Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination (performed in accordance with standards at the site), clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data. Following Dose 2, subjects will begin regular administrations every 2 weeks

[i] The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first

Activities Occurring at		**Treatment Period ± 4 days for each visit** ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																												
Non Rollover Visit	Scr[a]	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Rollover Visit	-	Chk[b]																											
Dose	-	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Day (± 4 days)	**-28**	**0**		**14**	**28**[c]	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**

dose. Tests performed at screening and on indicated visits can be serum or urine-based.

[j] There is a recommended ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns).

[k] Physical examinations, including weight, will be conducted for all rollover and nonrollover subjects according to the study activities schedule and in accordance with standards at the site. In addition to the physical examinations specified in the study activities schedule, an additional physical examination (performed in accordance with standards at the site) will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs. Height will be collected at the Screening visit only.

[l] Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis does not need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23). Clinical laboratory testing will be conducted for all rollover and nonrollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[m] In addition to the timepoints shown, ECG is to be performed when clinically indicated.

[n] Historical HAE attack information will be collected at screening. During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site

[o] PK, PD, and anti-drug antibody samples will be drawn for all rollover and nonrollover subjects at the visits shown. An additional sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever

[p] Samples for C1-INH, C4, and C1q assays will be collected at screening, Visit 14, and Visit 26, as applicable. Samples need not be obtained at screening for eligibility assessment if they were already collected as part of Study DX-2930 02 or Study DX-2930-03study visit that occurs.

Appendix 2.16.2 Study Activities Schedule for Day 366 through Day 952

Activities Occurring at	Treatment Period ± 4 days for each visit ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																						Follow Up Period	
Visit	28	29	30	31 32 33	34	35 36 37	38	39 40 41	42	43 44 45	46	47 48 49	50	51 52 53	54	55 56 57	58	59 60 61	62	63 64 65	66	67	68	69 EOS ET[a]
Day (± 4 days)	378	392	406	420 434 448	462	476 490 504	518	532 546 560	574	588 602 616	630	644 658 672	686	700 714 728	742	756 770 784	798	812 826 840	854	868 882 896	910	924	938	952
DX-2930 Administration[b,c]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•			
Physical Exam[d]			•		•		•		•		•		•		•		•		•		•	•		•
Pregnancy Test[e] (females)			•		•		•		•		•		•		•		•		•		•	•		•
Vital Signs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant Therapy	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
HAE Attack Data[g]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Clinical Laboratory Testing[h]			•		•		•		•		•		•		•		•		•		•	•		•
PK, PD Collection, ADA Testing & Biomarkers[i]					•				•				•				•				•	•		•

Activities Occurring at	Treatment Period ± 4 days for each visit ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																						Follow Up Period
Visit	28	29	30	31 32 33	34	35 36 37	38	39 40 41	42	43 44 45	46	47 48 49	50	51 52 53	54	55 56 57	58	59 60 61	62	63 64 65	66	67	68	69 EOS ET[a]
Day (± 4 days)	378	392	406	420 434 448	462	476 490 504	518	532 546 560	574	588 602 616	630	644 658 672	686	700 714 728	742	756 770 784	798	812 826 840	854	868 882 896	910	924	938	952
12-Lead ECG																								•
Quality of Life AE-QoL, EQ-5D-5L, WPAI-GH, HADS, SF-12			•		•		•		•		•		•		•		•		•		•			•
AECT[j]			•		•		•		•		•		•		•		•		•		•			•
TSQM vII									•															•
Global Treatment Response																								•
Exit Interview																								•
Site Check In Call[k]	•	•		•		•		•		•		•		•		•		•		•			•	
DX-2930 Injection Report[l]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•			
DX-2930 Self-administration & SC Injection Survey[l] & Pre-filled			•		•		•		•		•		•		•		•		•		•			

Activities Occurring at	Treatment Period ± 4 days for each visit ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																					Follow Up Period	
Visit	28	29	30	31 32 33	34	35 36 37	38	39 40 41	42	43 44 45	46	47 48 49	50	51 52 53	54	55 56 57	58	59 60 61	62	63 64 65	66	67	68	69 EOS ET[a]
Day (± 4 days)	378	392	406	420 434 448	462	476 490 504	518	532 546 560	574	588 602 616	630	644 658 672	686	700 714 728	742	756 770 784	798	812 826 840	854	868 882 896	910	924	938	952
Syringe Survey																								
Discharge from Study																								•

Abbreviations: AECT=Angioedema Control Test; EOS = End of Study; ET = Early Termination; Treatment Satisfaction Questionnaire for Medication version II = TSQM vII

NOTE: Although the first visit shown on this Schedule is at Day 378, this schedule covers the entire period following the end of the previous schedule. Certain assessments should be collected continuously throughout the study (for example, AEs) are collected continuously throughout the study

[a] Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures at Visit 69, the final study visit.

[b] Doses are administered every 14 ± 4 days

[c] All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may self-administer DX-2930 at all visits. (If the subject switches to the PFS, the subject should receive a refresher training focused on the PFS.) Subjects may administer at home or other agreed upon location (during off-site self-administration visits; non-shaded columns). Subjects can opt to be seen in clinic for this visit

[d] Physical examinations, including weight, will be conducted for all rollover and nonrollover subjects according to the study activities schedule and in accordance with standards at the site

[e] The pregnancy test will only be conducted in females of childbearing potential. Tests performed at screening and indicated visits can be serum or urine-based

[f] There is a recommended ± 15-minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns).

[g] During the study, subjects (or caregivers) are instructed to document attack details on their HAE Attack Log. Subjects will review Attack Log and details of the attacks at the study site during their in-clinic assessments. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site. Study site personnel will utilize the HAARP guidelines in order to confirm the HAE attack within 7 days.

Activities Occurring at	Treatment Period ± 4 days for each visit ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																					Follow Up Period	
Visit	28	29	30	31 32 33	34	35 36 37	38	39 40 41	42	43 44 45	46	47 48 49	50	51 52 53	54	55 56 57	58	59 60 61	62	63 64 65	66	67	68	69 EOS ET[a]
Day (± 4 days)	378	392	406	420 434 448	462	476 490 504	518	532 546 560	574	588 602 616	630	644 658 672	686	700 714 728	742	756 770 784	798	812 826 840	854	868 882 896	910	924	938	952

[h] Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis is performed as part of the clinical laboratory testing at Days 574, 742, 910, and 938/Visits 42, 54, 66, 68

[i] Biomarker samples for C1-INH, C4, and C1q assays will be collected at Visits 34, 42, 50, 58, 67, and 69.

[j] The AECT will be performed once its validated version is available

[k] Site personnel will call subjects within approximately 3 days of the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

[l] Collect subject's injection reports of their experience with DX-2930 self-administration, subcutaneous administration, and prefilled syringe (if relevant) for all doses.

11. REFERENCES

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PRO Report: DX-2930-04

HELP STUDY EXTENSION™

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE): Final PRO Analysis	
Investigational Product Name:	Lanadelumab (DX 2930 ; SHP643)	
Sponsor:	Dyax Corp. (an indirect wholly owned subsidiary of Shire plc.) 300 Shire Way, Lexington, MA 02421 USA	
Date of the Report:	14 Nov 2017	Interim 1
	15 Oct 2018	Interim 2
	24 Mar 2020	Final

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
ACT	Asthma Control Test
C1-INH	C1 Inhibitor
CDF	Cumulative distribution function
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level Measure
HAE	Hereditary angioedema
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-Related Quality of Life
MCID	Minimal clinically important difference
PRO	Patient-reported outcome
q2wks	Every two weeks
q4wks	Every four weeks
SAP	Statistical analysis plan
SC	Subcutaneous
SEM	Standard error of the mean
SF-12v2	12 Item Short Form v2 Health Survey
TSQM	Treatment Satisfaction Questionnaire for Medication
UCT	Urticaria Control Test

4. EXECUTIVE SUMMARY

These analyses of the patient-reported outcome (PRO) data collected in Study DX-2930-04 generated data supporting the benefit of lanadelumab (DX-2930) in terms of patient-centered outcomes. Subjects previously treated with lanadelumab in Study DX-2930-03 maintained or further improved patient-centered outcomes. Subjects not treated with lanadelumab before Study DX-2930-04 experienced clear improvement in outcomes, such as health-related quality of life, functioning or work life.

This report describes the results of the AE-QoL scores and other PROs (EQ-5D-5L, WPAI-GH, HADS, SF-12v2 and TSQM-9) until the end of Study DX-2930-04, an open-label, long-term safety and efficacy extension of Study DX-2930-03. These analyses also investigated change in PRO scores between baseline and end of study according to previous exposure to lanadelumab in Study DX-2930-03. The analyses were conducted using all the planned visits of the study until the end of the study. They were run in the Safety population that included 212 subjects, 109 in the Rollover Safety population (i.e. subjects who completed the double-blind treatment period at Day 182 of Study DX-2930-03) and 103 in the Non-Rollover Safety population (i.e. subjects who did not participate in Study DX-2930-03 and entered directly in Study DX-2930-04).

Overall, improvements in all AE-QoL scores were observed between Day 0 and end of study visit of DX-2930-04 in both subjects who participated in Study DX-2930-03 (Rollover) and subjects who did not (Non-Rollover). Subjects not previously treated with lanadelumab (either Non-Rollover subjects, or Rollover subjects treated with placebo in Study DX-2930-03) showed a greater improvement in all AE-QoL domains in DX-2930-04 study than subjects who had been treated with lanadelumab in Study DX-2930-03, supporting the benefit of lanadelumab treatment.

HADS Anxiety and Depression scores remained stable over the course of the study, with mean scores lower than 6, indicating normal levels of anxiety and depression in both Rollover and Non-rollover subjects. In the Rollover Safety population no changes in the EQ-5D-5L, WPAI-GH and SF-12v2 scores were observed. Subjects who had not been previously treated with lanadelumab (either Non-Rollover patients, or Rollover subjects from the placebo group in DX-2930-03) reported improvement in all PROs when initiating treatment with lanadelumab across the wide range of PRO analyses from Study DX-2930-04.

In both the Rollover and Non-Rollover Safety populations, the TSQM-9 scores showed that the subjects were very satisfied with their treatment effectiveness, found their treatment convenient and were very satisfied with their medication.

A few limitations were observed with the analyses of PRO data from Study DX-2930-04. Especially, the generic instruments showed little to no impairment at baseline making it difficult to show improvements during follow-up. In addition some PRO scores showed floor effects which may have impacted the ability to demonstrate improvement.

5. BACKGROUND

Hereditary Angioedema (HAE) is a rare, long-term and potentially life-threatening genetic disease, characterized by the occurrence of transitory and recurrent subcutaneous and/or submucosal edemas resulting in swelling. It can affect the face, arms, legs, airway and gastrointestinal tract.(Zuraw 2008) Attacks, without treatment, typically occur every couple of weeks and last for a few days.(N.I.H. 2020) Consequences of attacks may be fatal, by asphyxiation, when swelling occurs in the larynx. Prevalence of HAE has been estimated between 10,000 to 1 and 150,000 persons, depending on authors.(Göring, Bork et al. 1998, Bygum 2009, Nordenfelt, Dawson et al. 2014) Disease is caused by a genetic deficiency (HAE type I) or dysfunction (type II) of the C1 inhibitor (C1-INH) protein.(Donaldson and Evans 1963) This results in increased amounts of bradykinin which promotes swelling.(Nussberger, Cugno et al. 1998)

Lanadelumab (DX-2930 or SHP643) is a fully human G subclass 1 (IgG1) recombinant monoclonal antibody that binds specifically to active plasma kallikrein and inhibits its proteolytic activity. Lanadelumab is being developed for routine prophylaxis to prevent angioedema attacks in patients with HAE. Plasma plays a critical role in the pathogenesis of HAE attacks (Davis 2006, Kaplan and Joseph 2010), being a regulator of the release of bradykinin, and being itself regulated by C1-INH proteins. Kallikrein is already the target of a previously FDA approved drug for the prevention of acute HAE attacks. (Thompson 2010, Kalbitor® 2015)

Study DX-2930-04 was an open-label, long-term safety and efficacy extension of Study DX-2930-03. Study DX-2930-04 was conducted in subjects with Type I or Type II HAE to evaluate the long-term safety and efficacy of the investigational product, lanadelumab, in preventing acute angioedema attacks. The primary objective of Study DX-2930-04 was to evaluate the long-term safety of repeated subcutaneous (SC) administrations of lanadelumab; the secondary objectives of the study were to evaluate the long-term efficacy of lanadelumab in preventing acute HAE attacks and to characterize the outer bounds of dosing frequency for lanadelumab. Two types of subjects were enrolled into this study:

- Subjects who rolled over from Study DX-2930-03
- Subjects who were non-rollovers (i.e., were not participants in Study DX-2930-03).

Two interim analyses of the patient-reported outcomes (PROs) collected in Study DX-2930-04 have been conducted. They described the PRO data collected during the first months of the study, providing early results on the benefit of lanadelumab on health-related quality of life (HRQoL) in subjects with Type I or Type II HAE.

This final PRO report to Study DX-2930-04 provides an update to the observations made from the second interim analyses issued on 26 Feb 2019. This report provides long-term evidence of the impact of lanadelumab on HRQoL and other PROs including measures of health status, anxiety and depression, and work productivity/activity impairment due to health disability.

6. OBJECTIVES

The objectives of the PRO analyses performed using the PRO data collected in Study DX-2930-04 were:

- To describe PRO scores over the course of the DX-2930-04 study separately for patients who participated in the DX-2930-03 study ('Rollover patients') and patients who did not participate in the DX-2930-03 study ('Non-Rollover patients'):
    - Functioning, Fatigue/Mood, Fear/Shame, Nutrition as assessed by the AE-QoL
    - Work productivity and activity impairment, as assessed by the WPAI-GH
    - Anxiety and depression, as assessed by the HADS
    - Generic health-related quality of life, as assessed by the SF-12v2
    - Treatment satisfaction, as assessed by the TSQM-9
    - Health status, as assessed by EQ-5D-5L
- To investigate change in PRO scores between baseline and end of study according to previous exposure to lanadelumab in Study DX-2930-03.

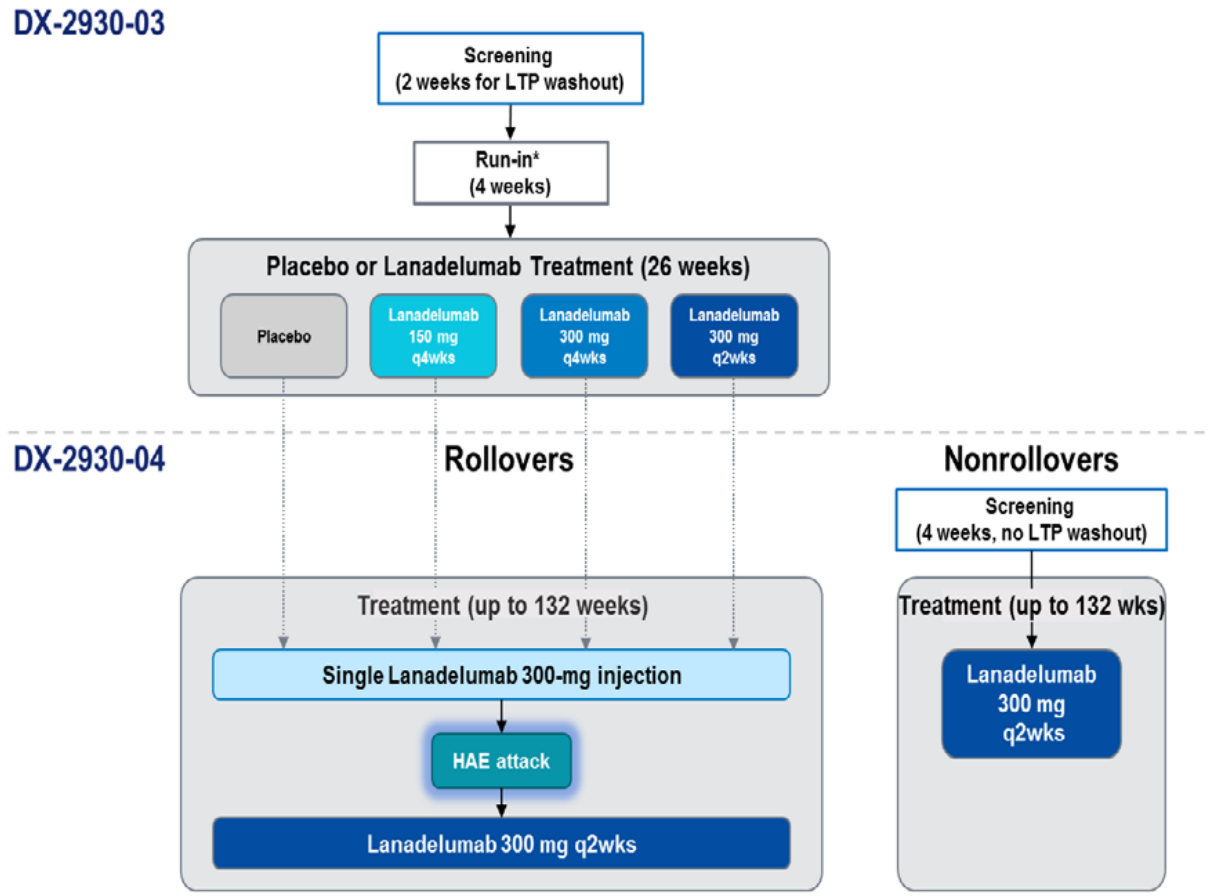
7. METHODS

7.1 DX-2930-04 study

7.1.1 Study design

Study DX-2930-04 was an open-label, long term safety and efficacy extension of Study DX-2930-03, to evaluate lanadelumab for prevention of acute angioedema attacks in subjects with Type I or Type II HAE. A schematic study design of Study DX-2930-04 is provided in Figure 1.

Figure 1 Schematic DX-2930-04 Study Design



Two types of subjects were enrolled into this study: rollover and non-rollover subjects. Rollover subjects were subjects who completed the double-blind treatment period at Day 182 of Study DX-2930-03 and consented to enter Study DX-2930-04. They received a single open-label dose of lanadelumab administered SC on Day 0. Rollover subjects did not receive any additional lanadelumab doses until their first reported and investigator-confirmed HAE attack. They then continued to receive repeated SC administrations of open-label 300mg lanadelumab every 2 weeks for the remaining duration of the treatment period.

Non-rollover subject did not participate to DX-2930-03 and are thus "naïve" of lanadelumab use. They received an open-label dose of 300 mg lanadelumab administered SC on Day 0, then continued to receive SC dose every 2 weeks throughout the duration of the treatment period.

The study duration was planned to be 34 months (952 days), including a 1-month follow up period, after the treatment period. The study was expected to enroll at least 100 rollover subjects, and at least 50 (to approximately 100) non-rollovers, to achieve a total enrollment of at least 150 (maximum of 250).

Additional information on Study DX-2930-04 investigational plan is provided in the final CSR 26 March 2020 in Section 9.

7.1.2 PRO data

Subjects in Study DX-2930-04 were asked to complete the following PRO instruments at various timepoints:

- Angioedema Quality of Life Questionnaire (AE-QoL)
- EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L)
- Work Productivity and Activity Impairment – General Health (WPAI-GH) Questionnaire
- Hospital Anxiety and Depression Scale (HADS)
- Short Form v2 Health Survey 12 Item version 2 (SF-12v2)
- Angioedema Control Test (AECT)
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Global Impression of Treatment Response

The PRO assessment schedule is presented in Table 1. Of those PRO instruments, only the AE-QoL and EQ-5D-5L were administered in Study DX-2930-03.

All PRO instruments are described below.

Table 1 PROs recording schedule in Study DX-2930-04

Day	0	28	56	98	126	154	182	224	266	308	364	406	462	518	574	630	686	742	798	854	910	952[1]
AE-QoL[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WPAI-GH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HADS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SF-12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AECT[3]											✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TSQM[3]											✓				✓							✓
Global Impression of Treatment Response[3]											✓											✓

[1] Records at day 952 corresponds to the end of the study and of the 4-week follow-up period (Day 924 to 952)

[2] AE-QoL=Angioedema Quality of Life

[3] These patient reported outcomes (PRO) questionnaires were added in Protocol Amendment 3

7.2 PRO instruments

HRQoL, health status, anxiety and depression, and work productivity/activity impairment due to health disability were assessed using the Angioedema Quality of Life (AE-QoL) questionnaire, EuroQoL 5-Dimensional 5-Level (EQ-5D-5L) descriptive system and visual analogue scale (VAS), 12-Item Short Form Survey (SF-12v2), Hospital Anxiety and Depression Scale (HADS), and Work Productivity and Activity Impairment: General Health (WPAI-GH) questionnaire (only the AE-QoL and EQ-5D-5L were administered in Study DX-2930-03).

The following patient reported outcome (PRO) questionnaires were added in Protocol Amendment 3: Treatment Satisfaction Questionnaire for Medication (TSQM-9), Global Impression of Treatment Response, and Angioedema Control Test (AECT).

7.2.1 Angioedema Quality of Life (AE-QoL) Questionnaire

The AE-QoL is a self-administered instrument developed and validated to assess health-related quality of life (HRQoL) impairment in subjects with recurrent angioedema.(Weller, Groffik et al. 2012) It consists of 17 items divided in 4 domains/dimensions: functioning, fatigue/mood, fear/shame, nutrition. Items are 5-point Likert-type response scales ranging from “Never” to “Very Often”, asking for patient ratings over the last four weeks. Scores for each domain and a total score can be obtained by taking the mean of the item scores within the scale (or mean item scores of all items, for the total score) and transforming it linearly on a 0-100 scale. The AE-QoL scores range between 0 to 100, with lower scores indicating lower impairment and higher scores indicating greater QoL impairment.

A 6-point difference has been reported to be the minimal clinically important difference (MCID) for the AE-QoL total score. (Weller, Magerl et al. 2016) This value was used as threshold for PRO response in the PRO responder analyses, for all AE-QoL scores (in the absence of specific value for the domain scores).

7.2.2 EuroQol 5-Dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L is a self-administered standardized measure of health status comprised of a descriptive system and a Visual Analogue Scale (VAS).(Herdman, Gudex et al. 2011) The descriptive systems assess five dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression(Herdman, Gudex et al. 2011). Each dimension is rated on a 5-point scale to describe subject health for the current day, with 1 being “no problems” and 5 “extreme problems”. An index score can be derived from the five items to calculate utilities. The index score ranges between 0 and 1, with 1 corresponding to a perfect health. The UK crosswalk value set was used to calculate the EQ-5D-5L index scores.

Separately from the descriptive part, the VAS is a measure of overall self-rated health status. The subject assesses his or her health using a 20-cm vertical VAS, between “the best health you can imagine” and “the worst health you can imagine”. Scores ranges from 0 to 100, with a higher score indicating better health.

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

The WPAI-GH is a 6-item self-assessment of the effect of health problems on the subject's ability to work and perform regular activities, during the past 7 days.(Reilly, Zbrozek et al. 1993) WPAI-GH scoring guidelines lead to the creation of the following scores: percent work time missed due to health, percent impairment while working due to health, percent overall work impairment due to health, and percent activity impairment due to health. Adolescent subjects were asked to complete the WPAI-GH and use the term "school" instead of "work" when completing the questionnaire. The scores are percentages with higher values indicating greater impairment and less work productivity.

The MCID for the WPAI-GH has been suggested in other conditions to be 7.2 for absenteeism, 11.1 for presenteeism, 9.8 for overall work productivity, and 14.3 for activity impairment.(Bolge, Doan et al. 2009) Based on these values, the following values were used as thresholds for PRO response in the PRO responder analyses: 7 for absenteeism, 11 for presenteeism, 10 for overall work productivity, and 14 for activity impairment.

7.2.4 Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-assessed scale developed to detect subjects states of depression, anxiety, and emotional distress.(Zigmond and Snaith 1983) From its 14 items, 7 relate to anxiety and 7 to depression during the past week. Responses are scored on a scale ranging from 0 to 3, with 3 indicating the highest symptom frequency. For each domain, scores range from 0 to 21, and can be categorized as normal (0 to 7), mild (8 to 10), moderate (11 to 14), and severe (15 to 21). Additionally, a total score can be calculated from the full set of items, ranging from 0 to 42, with a higher score indicating more distress.

The MCID has been estimated in other conditions to be in the range 1.5-2.5.(Puhan, Frey et al. 2008, Chan, Friedman et al. 2016) Based on these values, a 2-point value was used as threshold for PRO response in the PRO responder analyses for the HADS scores.

7.2.5 12 Item Short Form v2 Health Survey (SF-12v2)

The SF-12v2 is a validated instrument designed to measure functional health and well-being. It consists of 12 questions, divided into 8 health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.(Ware Jr, Kosinski et al. 1996) Questions asked subjects about their health for the last 4 weeks. Physical and Mental Health Composite, as well as domain scores can be calculated. They range from 0 to 100, with 0 indicating the lowest health level as measured by the scales and 100 the highest. Norm-based scores are obtained using t-scores based on a general US population mean of 50.0, with a standard deviation of 10.0, allowing direct comparisons to the US general population.

The MCID has been estimated in other conditions to be in the range 4.9-5.2. (Schwab, Lafage et al. 2008, Skolasky, Maggard et al. 2015) Based on these values, a 5-point value was defined to be used as threshold for PRO response in the PRO responder analyses for the SF-12v2 scores.

7.2.6 Angioedema Control Test (AECT)

The AECT is a 4-question instrument designed to assess the control of angioedema among subjects with recurrent angioedema (including HAE). It asks the frequency of symptoms, impact on HRQoL, impact of unpredictability, and perceived disease control. This is a useful measure specially to drive treatment decisions. Its concept is similar to the previously developed and established Asthma Control Test (ACT) and Urticaria Control Test (UCT).(Nathan, Sorkness et al. 2004, Weller, Groffik et al. 2014) Questions have 5 answer options (verbal rating scale), scored from 0 to 4 points.

7.2.7 Treatment Satisfaction Questionnaire for Medication version 9 (TSQM-9)

The TSQM-9 is a generic 9-item measure of treatment satisfaction that allows for comparison across medication types and subjects conditions.(Bharmal, Payne et al. 2009) It assesses the subject's perception of treatment effectiveness, convenience, and global satisfaction during the last two to three weeks or when the treatment was last used. Scores for each of the 3 domains, as well as a combined score are calculated separately. Scores are transformed to a 0 to 100 scale, with a higher score indicating higher satisfaction with treatment.

7.2.8 Global Impression of Treatment Response

The subjects' and investigators' global impression of treatment response is assessed, using a single question: "Overall, how would you rate your response to the study medication?". Responses options are namely, about the actual day: "poor", "fair", "good", "very good" and "excellent".

7.3 Analysis population

- Safety Population: all subjects included in the study
- Rollover Safety Population: subjects who participated in DX-2930-03 study
- Non-rollover Safety Population: subjects who entered DX-2930-04 study directly

7.4 General principles

7.4.1 Description of variables

Continuous variables were described by their frequency, mean, standard deviation (SD), standard error of the mean (SEM), median, first and third quartiles, extreme values (minimum and maximum values), and number of missing values.

Categorical variables were described by the frequency and percentage of each response choice, with missing data being included in the calculation of percentage.

7.4.2 Level of significance

All p-values are considered descriptive. Their interpretation are performed using a level of significance set to 5% (two-sided test). No method to control for multiple testing was applied.

7.5 Missing data handling

For the score calculations, the missing items of the PRO questionnaires were handled as proposed by the authors of the questionnaires.

No missing PRO assessment was imputed in the analyses.

7.6 Software

Data analysis were performed using SAS version 9.4.

7.7 Analysis plan

The detailed analysis plan is available in Appendix 1. The analyses conducted on the PRO data of the DX-2930-04 study are summarized below:

- Description of AE-QoL scores over the study: description of the AE-QoL scores in the Rollover Safety population and in the Non-Rollover Safety population at each visit from Day 0 to end of study visit; description of change in AE-QoL scores from Day 0 to each scheduled visit in the Rollover Safety population and in the Non-Rollover Safety population; description of change in AE-QoL scores from Day 0 to each scheduled visit in the Rollover Safety population by treatment received during the DX-2930-03 study

- Description of other PRO scores over the study: description of the EQ-5D-5L index score, WPAI-GH scores, HADS scores, SF-12v2 scores and TSQM-9 scores in the Rollover Safety population and in the Non-Rollover Safety population at each visit from Day 0 to end of study visit; description of change in these PRO scores from Day 0 to each scheduled visit in the Rollover Safety population and in the Non-Rollover Safety population; description of change in these PRO scores from Day 0 to each scheduled visit in the Rollover Safety population by treatment received during the DX-2930-03 study

- Exploratory analysis of AE-QoL changes in scores: linear regressions with the change in AE-QoL score from Day 0 to the end of study visit as explained variable and the following explanatory variables: duration of 'regular' treatment period, AE-QoL score at baseline, AE-QoL score at baseline from the DX-2930-03 study, and treatment received in the DX-2930-03 study in the Rollover Safety population.

- Responder analysis and empirical cumulative distribution functions (CDFs): description of percentage of responders (i.e. change in score above a predefined threshold) at each scheduled post-baseline visit in the Rollover Safety population overall, as well as according to treatment received in the DX-2930-03 study; description of percentage of responders at each scheduled post-baseline visit in the Non-Rollover Safety population; CDFs of the change in scores from Day 0 to the end of study visit in the Rollover Safety population and in the Non-Rollover Safety population. Scores considered for the analysis were the AE-QoL scores, the WPAI-GH scores, the HADS scores and the SF-12v2 scores.

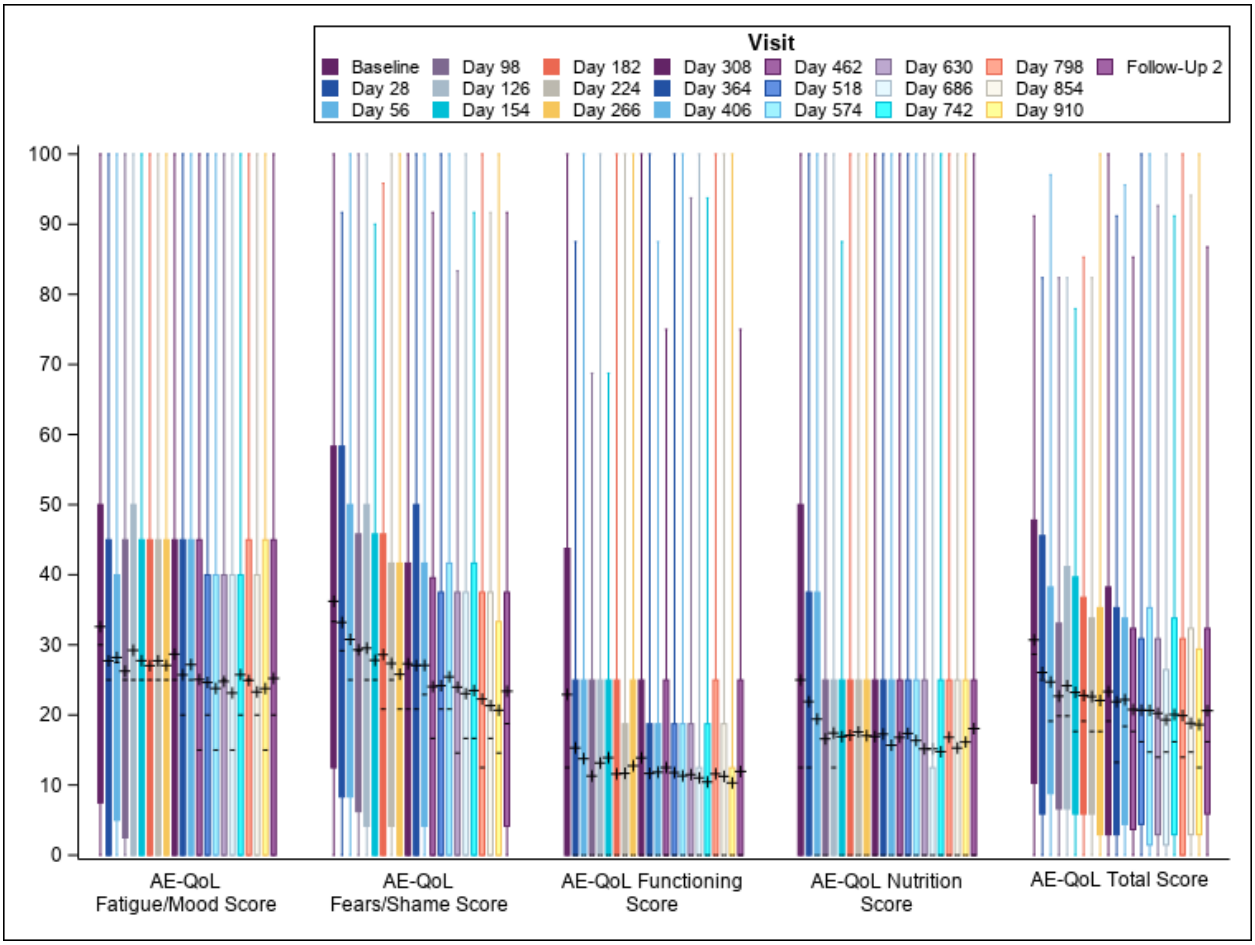
8. RESULTS

8.1 Description of AE-QoL scores over the study

8.1.1 Description of AE-QoL scores and change in AE-QoL scores in Rollover Safety Population

Figure 2 shows the distribution of AE-QoL scores in the Rollover Safety population at each visit from Day 0 to end of study visit. Mean AE-QoL scores were systematically lower than 40 (on a scale ranging from 0 to 100) at all visits, indicating no to moderate impairment due to angioedema. The first quartile was 0 at several visits for all AE-QoL domain scores, indicating a floor effect: a number of subjects (at least 25%) reported the best possible status measured by the AE-QoL in terms of Fatigue/Mood, Functioning, Nutrition and even, for more recent visits, Fears/Shame. Mean AE-QoL domain and total scores decreased (indicating improvement) in the early follow-up (schematically from Day 0 to Day 56) before reaching a plateau. The Fears/Shame score was the AE-QoL domain score showing the greatest decrease (indicating improvement) between Day 0 and end of study visit, with a mean (SD) change of -12.87 (19.20). Other AE-QoL scores also showed improvement with mean changes from Day 0 to end of study visit of -7.39 (23.79) for the Fatigue/Mood score, -11.11 (24.27) for the Functioning score, -7.22 (26.10) for the Nutrition score, and -10.18 (17.90) for the Total score. A full description of the AE-QoL scores is available in Appendix 1, Output 1.

Figure 2 Description of AE-QoL scores at each visit from Day 0 to end of study visit in the Rollover Safety population (N=109)



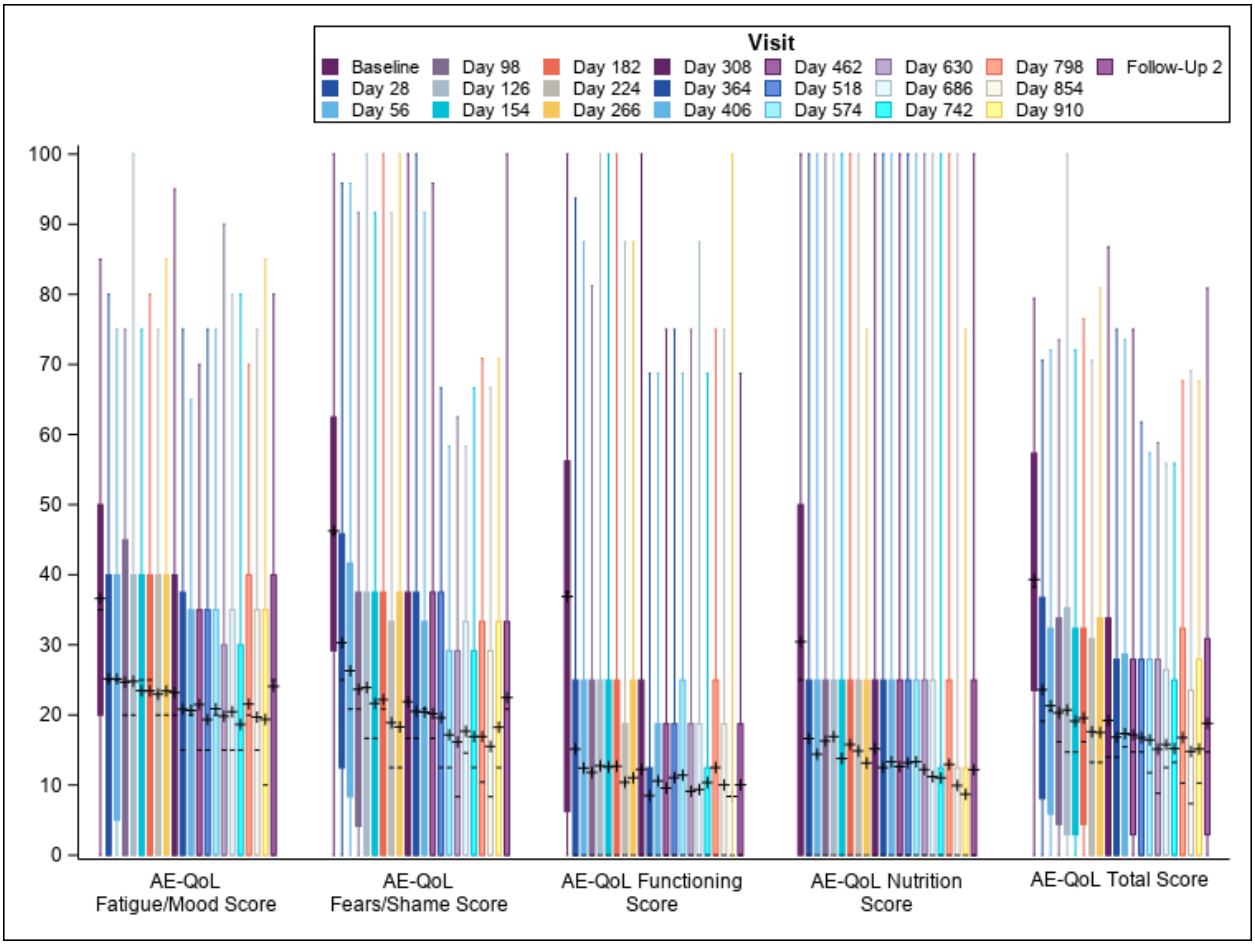
AE-QoL=Angioedema Quality of Life; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
Lower scores indicate lower impairment and higher scores indicate greater QoL impairment.
Source: Appendix 2, Output 1, Table 1.1.1, Table 1.1.2, Table 1.1.3, Table 1.1.4, Table 1.1.5, Table 1.1.6, Table 1.1.7, Table 1.1.8, Table 1.1.9, Table 1.1.10, Table 1.1.11, Table 1.1.12, Table 1.1.13, Table 1.1.14, Table 1.1.15, Table 1.1.16, Table 1.1.17, Table 1.1.18, Table 1.1.19, Table 1.1.20, Table 1.1.21 and Table 1.1.22

8.1.2 Description of AE-QoL scores and change in AE-QoL scores in the Non-Rollover Safety population

Figure 3 shows the distribution of AE-QoL scores in the Non-Rollover Safety population at each visit from Day 0 to end of study visit. AE-QoL scores went from markedly higher values, distributed around means (SD) of 36.62 (22.56) for Fatigue/Mood, 46.24 (22.95) for Fear/Shame, 36.89 (27.21) for functioning, 30.45 (26.60) for Nutrition and 39.31 (20.46) for the Total score at Day 0, to lower values distributed around means between 8 and 30 (on a scale ranging from 0 to 100) depending on the scores and the visits. The greatest decrease in AE-QoL domain and total scores was mostly observed between Day 0 and Day 28 (or Day 56, for Fear/Shame). The Functioning score was the AE-QoL domain showing the greatest decrease (indicating improvement) between Day 0 and end of study visit, with a mean (SD) change of -26.16 (27.71). Other AE-QoL scores also showed improvement over the follow-up, with mean changes from

Day 0 to end of study visit of -22.22 (24.31) for Fears/Shame, -11.60 (25.83) for Fatigue/Mood, -18.28 (24.35) for Nutrition, and -19.53 (21.31) for the Total score. Again, the first quartile was 0 at several visits for all AE-QoL domain scores, indicating a floor effect for these measures; a number of subjects (at least 25%) reported the best possible status measured by the AE-QoL in terms of Fatigue/Mood, Fear/Shame, Functioning, and Nutrition. Full AE-QoL domain and total score descriptions are available in Appendix 2, Output 2.

Figure 3 Description of AE-QoL scores at each visit from Day 0 to end of study visit in the Non-Rollover Safety population (N=103)



AE-QoL=Angioedema Quality of Life; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
Lower scores indicate lower impairment and higher scores indicate greater QoL impairment.
Source: Appendix 2, Output 2, Table 2.1.1, Table 2.1.2, Table 2.1.3, Table 2.1.4, Table 2.1.5, Table 2.1.6, Table 2.1.7, Table 2.1.8, Table 2.1.9, Table 2.1.10, Table 2.1.11, Table 2.1.12, Table 2.1.13, Table 2.1.14, Table 2.1.15, Table 2.1.16, Table 2.1.17, Table 2.1.18, Table 2.1.19, Table 2.1.20, Table 2.1.21 and Table 2.1.22

8.1.3 Description of change in AE-QoL scores in the Rollover Safety population by treatment received during DX-2930-03

Table 2 describes the change in AE-QoL scores from Day 0 to the end of study visit in the Rollover Safety Population according to the treatment previously received in the DX-2930-03 trial. Mean change between Day 0 and end of study visit showed greater improvement for

subjects previously treated with placebo than for subjects previously treated with lanadelumab in all AE-QoL scores. Full results are available in Appendix 2, Output 3.

Table 2 Description of Change in AE-QoL Scores from Day 0 to the End of Study Visit for Rollover Subjects (Rollover Safety Population)

	Double-Blind Actual Treatment				
Variable	Placebo N=32	DX-2930 150 mg every 4 weeks N=22	DX-2930 300 mg every 4 weeks N=21	DX-2930 300 mg every 2 weeks N=22	Rollover Safety Population N=97
AE-QoL Fatigue/Mood Score					
n (missing)	30 (2)	19 (3)	20 (1)	21 (1)	90 (7)
Mean (SD)	-15.50 (25.06)	-8.16 (23.35)	-4.50 (15.30)	2.14 (26.30)	-7.39 (23.79)
AE-QoL Fears/Shame Score					
n (missing)	30 (2)	19 (3)	20 (1)	21 (1)	90 (7)
Mean (SD)	-20.00 (17.21)	-7.02 (20.41)	-9.17 (18.37)	-11.51 (19.76)	-12.87 (19.20)
AE-QoL Functioning Score					
n (missing)	30 (2)	19 (3)	20 (1)	21 (1)	90 (7)
Mean (SD)	-30.63 (22.10)	-1.32 (15.11)	-5.31 (10.19)	2.38 (26.84)	-11.11 (24.27)
AE-QoL Nutrition Score					
n (missing)	30 (2)	19 (3)	20 (1)	21 (1)	90 (7)
Mean (SD)	-25.42 (25.95)	2.63 (14.78)	1.25 (18.98)	1.79 (27.75)	-7.22 (26.10)
AE-QoL Total Score					
n (missing)	30 (2)	19 (3)	20 (1)	21 (1)	90 (7)
Mean (SD)	-21.81 (17.96)	-4.88 (16.09)	-5.66 (10.17)	-2.66 (17.82)	-10.18 (17.90)

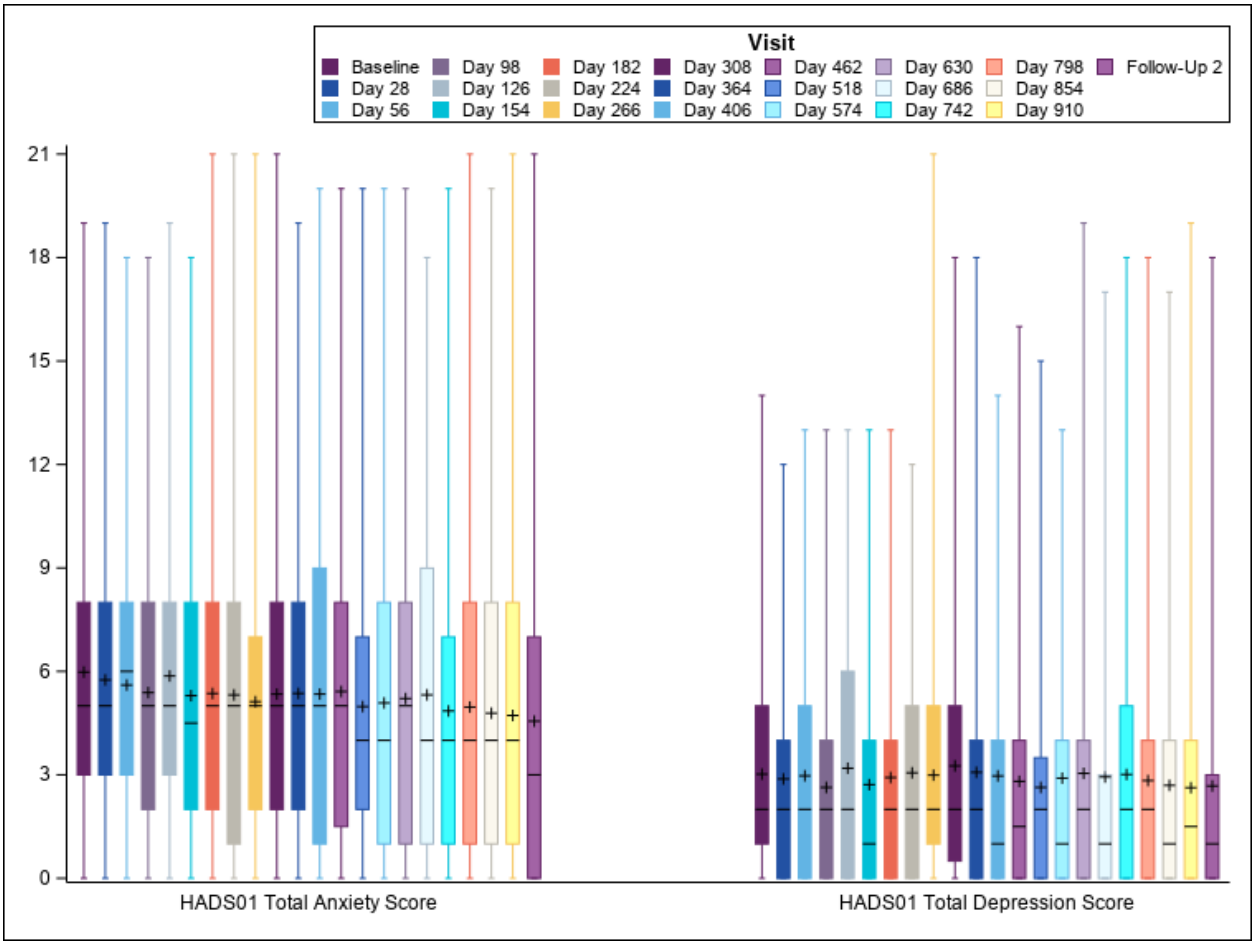
AE-QoL=Angioedema Quality of Life Questionnaire
Negative values indicate improvement and positive values indicate worsening
Source: Appendix 2, Output 3, Table 3.1

8.2 Description of other PRO scores over the study

8.2.1 Description of PRO scores and change in PRO scores in Rollover Safety Population

Figure 4 shows the distribution of HADS domain scores in the Rollover Safety population at each visit from Day 0 to end of study visit. HADS Anxiety and Depression scores remained stable over the course of the study, with mean scores lower than 6, indicating normal levels of anxiety and depression. A full description of the HADS scores is available in Appendix 2, Output 4.

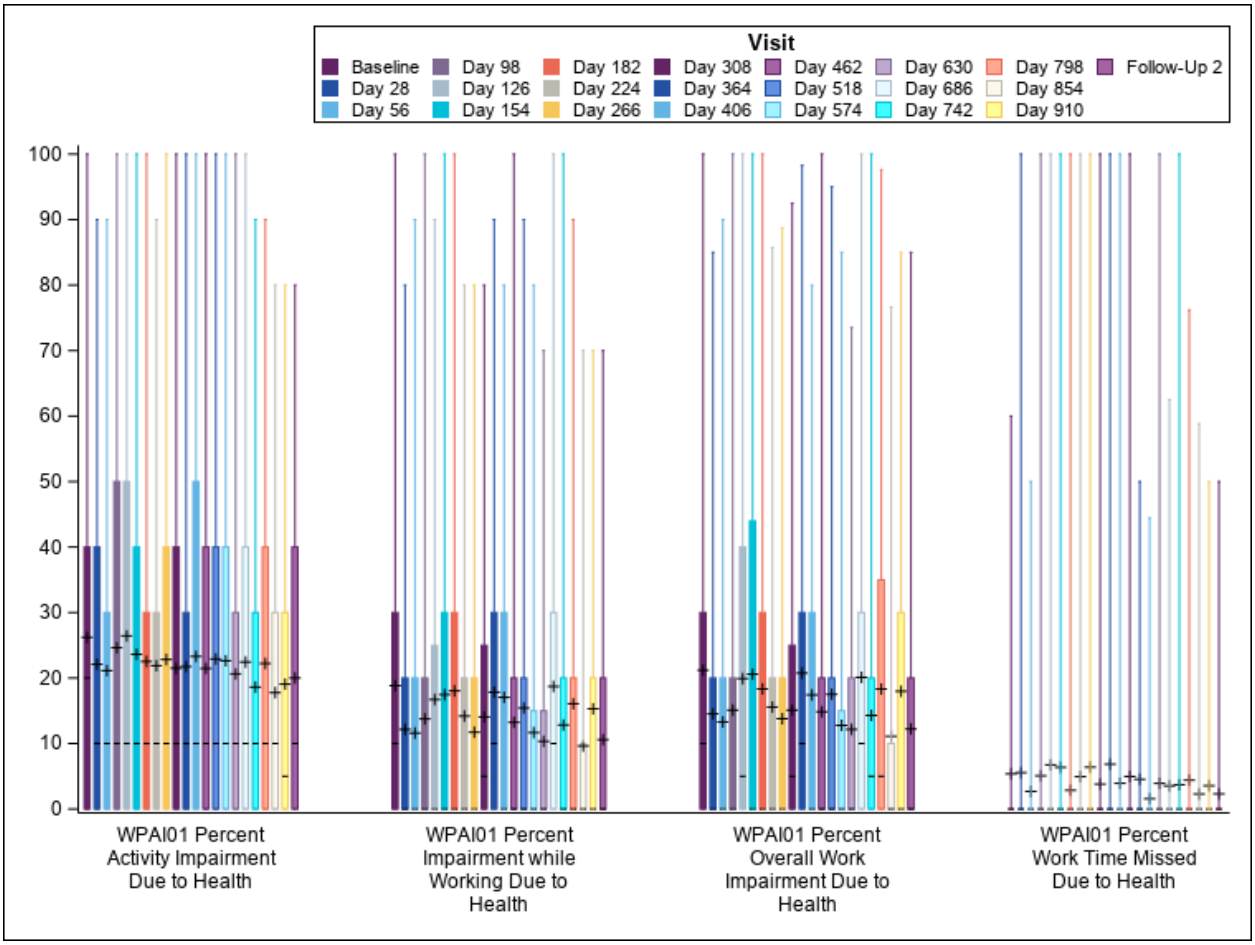
Figure 4 Description of HADS domain scores at each visit from Day 0 to end of study visit in the Rollover Safety population (N=109)



HADS=Hospital Anxiety and Depression Scale; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
0-7: normal anxiety/depression; 8-10: mild anxiety/depression; 11-14: moderate anxiety/depression; 15-21: severe anxiety/depression
Source: Appendix 2, Output 4, Table 4.1.1, Table 4.1.2, Table 4.1.3, Table 4.1.4, Table 4.1.5, Table 4.1.6, Table 4.1.7, Table 4.1.8, Table 4.1.9, Table 4.1.10, Table 4.1.11, Table 4.1.12, Table 4.1.13, Table 4.1.14, Table 4.1.15, Table 4.1.16, Table 4.1.17, Table 4.1.18, Table 4.1.19, Table 4.1.20, Table 4.1.21 and Table 4.1.22

Figure 5 shows the distribution of WPAI-GH domain scores in the Rollover Safety population at each visit from Day 0 to end of study visit. WPAI-GH domain scores remained stable over the follow-up, with mean percent activity impairment due to health between 17.76 (22.06) and 26.44 (30.94); mean percent impairment while working due to health between 9.62 (14.93) and 18.82 (26.46); mean percent overall work impairment due to health between 11.10 (18.27) and 21.19 (29.27); and mean Percent work time missed due to health between 1.57 (6.66) and 6.84 (19.40). All scores showed a clear floor effect with several subjects reporting the smallest possible impact on productivity at all visits. A full description of the WPAI-GH is available in Appendix 2, Output 4.

Figure 5 Description of WPAI-GH scores at each visit from Day 0 to end of study visit in the Rollover Safety population (N=109)



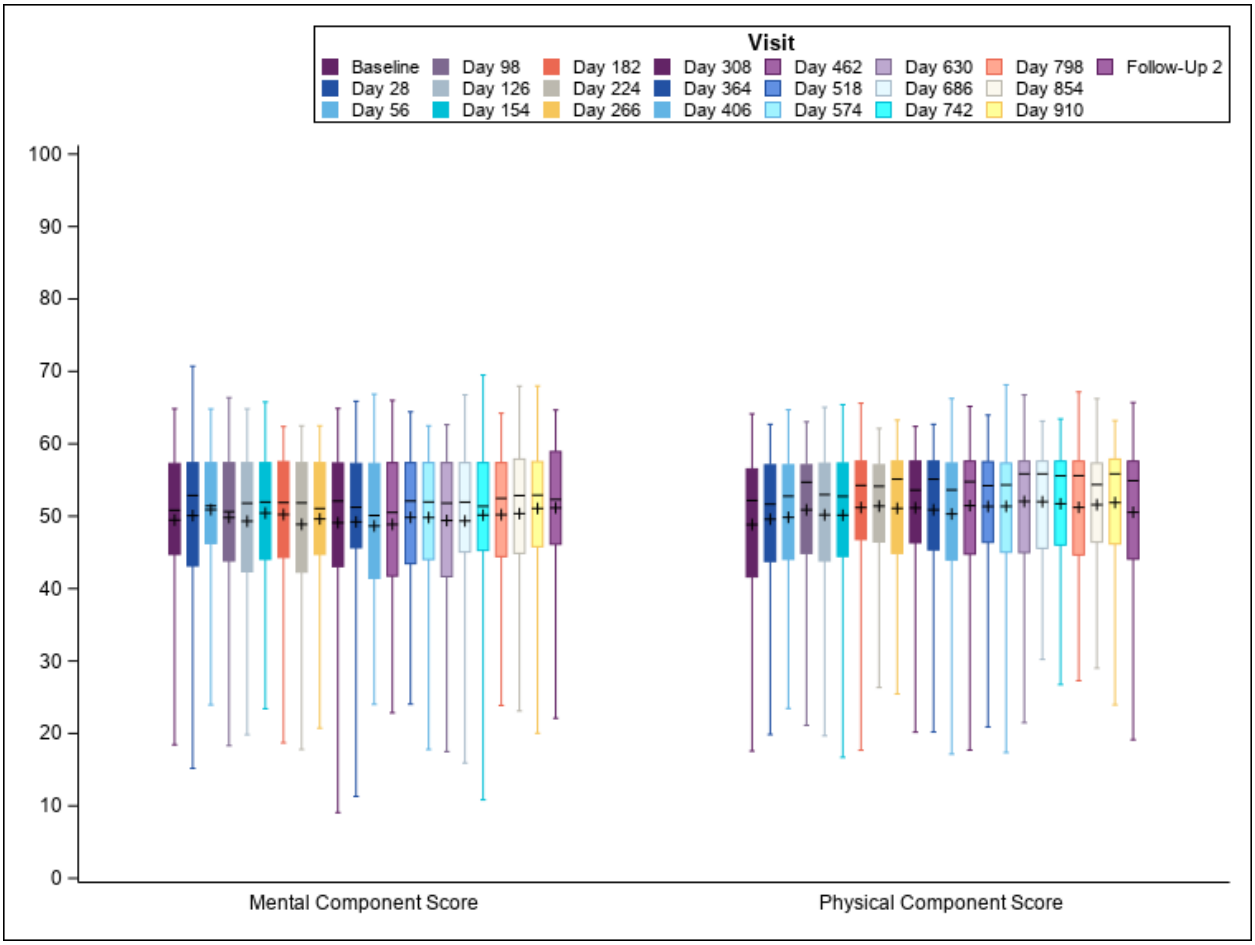
WPAI-GH=Work and Productivity Activity Impairment – General Health questionnaire; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET

Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
Higher values indicate greater impairment and less work productivity

Source: Appendix 2, Output 4, Table 4.1.1, Table 4.1.2, Table 4.1.3, Table 4.1.4, Table 4.1.5, Table 4.1.6, Table 4.1.7, Table 4.1.8, Table 4.1.9, Table 4.1.10, Table 4.1.11, Table 4.1.12, Table 4.1.13, Table 4.1.14, Table 4.1.15, Table 4.1.16, Table 4.1.17, Table 4.1.18, Table 4.1.19, Table 4.1.20, Table 4.1.21 and Table 4.1.22

Figure 6 shows the distribution of the SF-12v2 Mental and Physical Component scores in the Rollover Safety population at each visit from Day 0 to end of study visit. SF-12v2 Mental Component score (MCS) and Physical Component score (PCS) remained stable over the course of the study, with mean scores between 48.65 (10.08) and 51.15 (9.82) for the MCS score and between 48.84 (10.31) and 52.04 (8.81) for the PCS score. All the SF-12v2 scores were stable over the course of the study, except the General Health score that showed a slight increase from 65.19 (24.59) at Day 0 to 71.17 (25.33) at the end of study visit. A full description of the SF-12v2 scores is available in Appendix 2, Output 4.

Figure 6 Description of SF-12v2 Mental Components and Physical Component scores at each visit from Day 0 to end of study visit in the Rollover Safety population (N=109)



SF-12v2=12 Item Short Form v2 Health Survey; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values 0 indicates the lowest health level as measured by the scales and 100 the highest*
Source: Appendix 2, Output 4, Table 4.1.1, Table 4.1.2, Table 4.1.3, Table 4.1.4, Table 4.1.5, Table 4.1.6, Table 4.1.7, Table 4.1.8, Table 4.1.9, Table 4.1.10, Table 4.1.11, Table 4.1.12, Table 4.1.13, Table 4.1.14, Table 4.1.15, Table 4.1.16, Table 4.1.17, Table 4.1.18, Table 4.1.19, Table 4.1.20, Table 4.1.21 and Table 4.1.22

EQ-5D-5L was completed by the Rollover Safety population at each visit from Day 0 to end of study visit. Mean (± SD) EQ-5D-5L index score was 0.85 (±0.19) at Day 0 in the Rollover Safety population. It was stable over the study, going slightly up to 0.87 (±0.17) at Day 742 and down to 0.83 (±0.22) at Day 364. Mean (± SD) EQ-5D-5L at end of study visit was 0.86 (±0.18) (data not shown, see Appendix 2, Output 4).

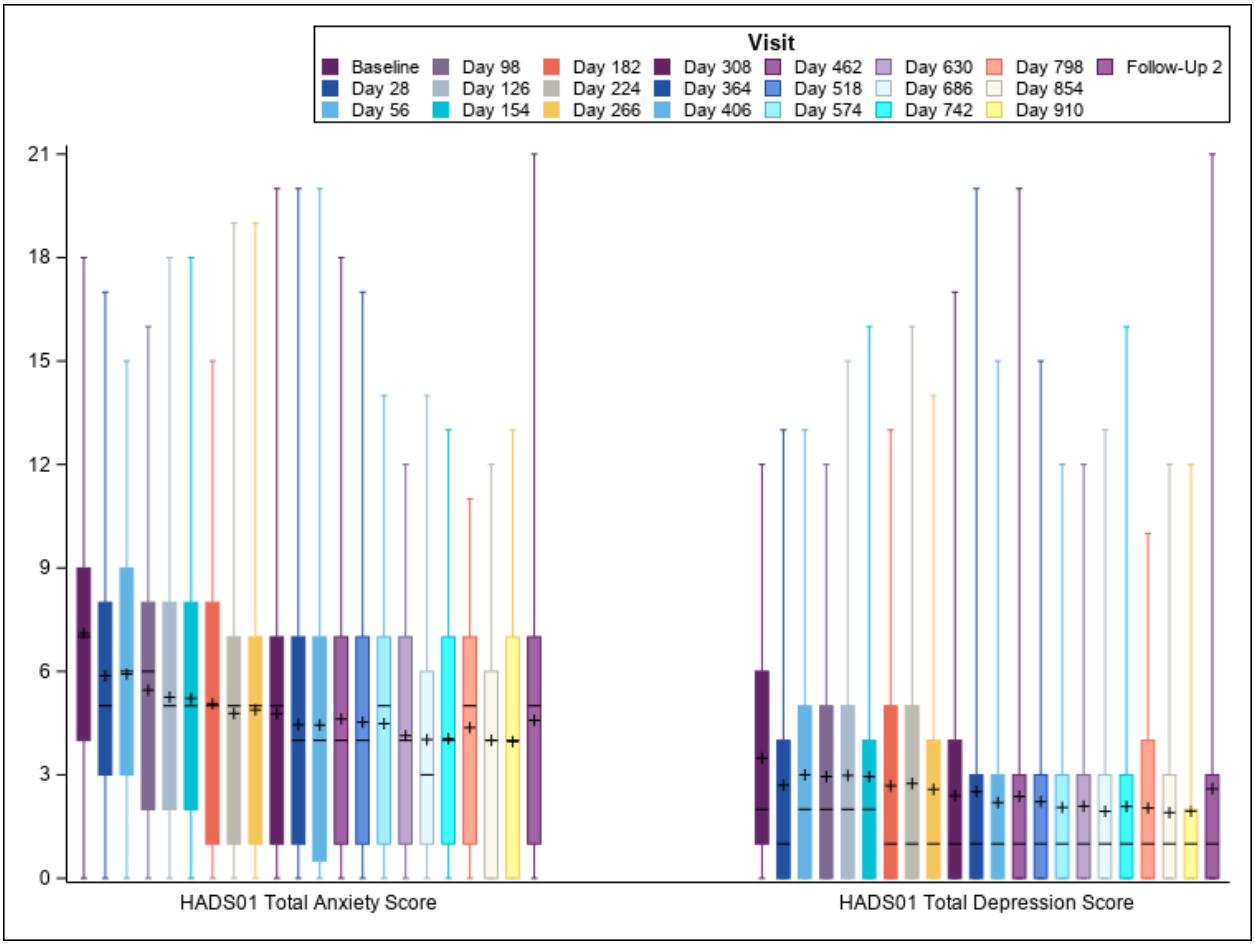
The TSQM-9 was completed by the subjects at Day 364, Day 574 and end of study visit only. Mean (±SD) Effectiveness score fluctuated between 90.30 (±18.17) and 94.26 (±10.87) indicating that Rollover subjects were very satisfied with their treatment effectiveness. Mean (±SD) Convenience score fluctuated between 83.92 (±15.70) and 86.48 (±17.69) indicating subjects reported their treatment was convenient. Mean (±SD) Satisfaction score ranged from

87.97 (±15.14) to 91.51 (±13.54) indicating that subjects were very satisfied with their medication. A full description of the TSQM-9 scores is available in Appendix 2, Output 4.

8.2.2 Description of PRO scores and change in PRO scores in the Non-Rollover Safety population

Figure 7 shows the distribution of HADS domain scores in the Non-Rollover Safety population at each visit from Day 0 to end of study visit. The mean (SD) HADS Anxiety score was 7.10 (4.06) at Day 0, indicating normal to mild anxiety. The mean HADS Depression score was 3.48 (3.09) at Day 0, indicating normal depression. At each post-baseline visit, mean HADS Anxiety scores and mean HADS Depression scores were lower than 6 on a scale ranging from 0 to 21, indicating normal anxiety and normal depression. A full description of HADS scores is available in Appendix 2, Output 5.

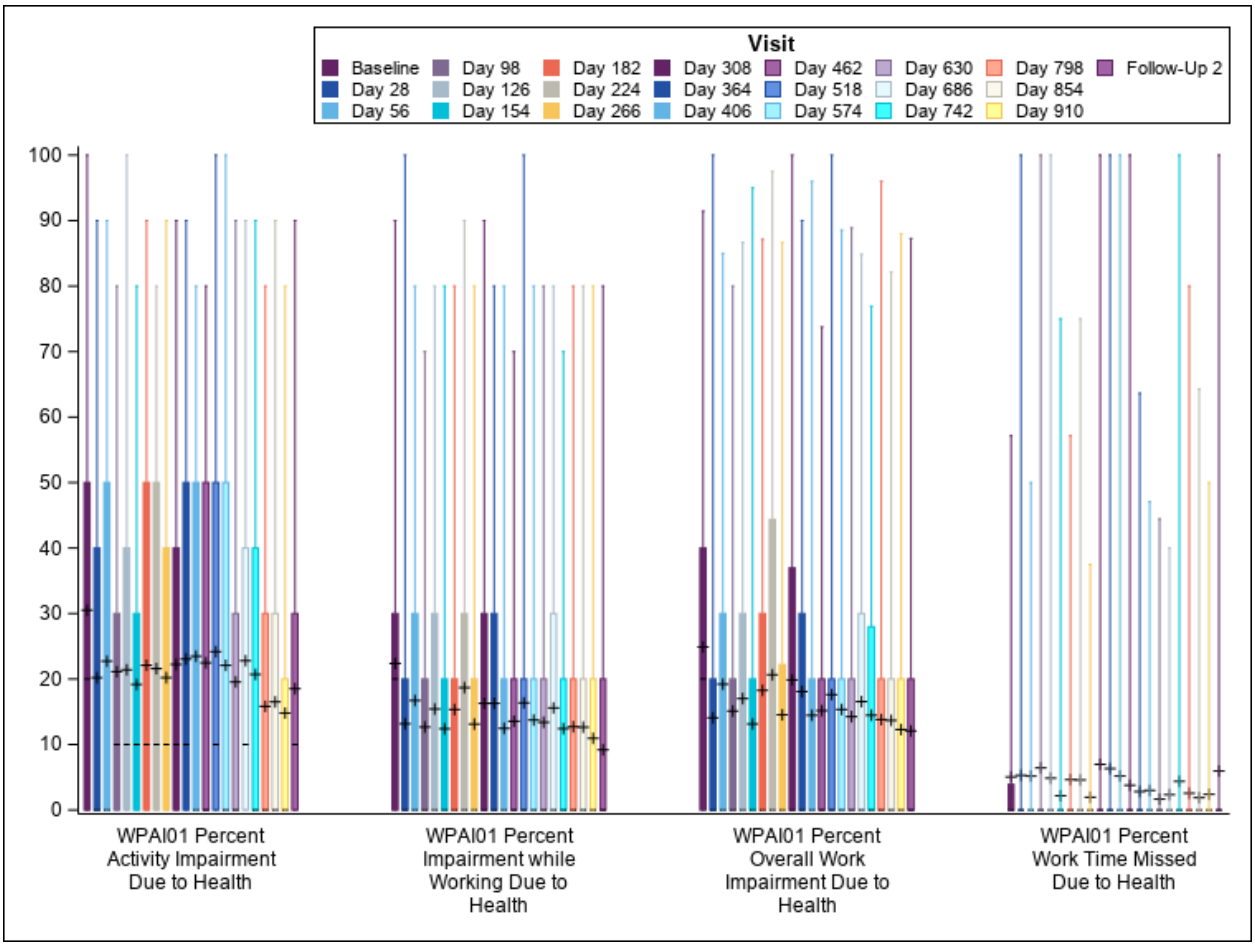
Figure 7 Description of HADS domain scores at each visit from Day 0 to end of study visit in the Non-Rollover Safety population (N=103)



HADS=Hospital Anxiety and Depression Scale; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
0-7: normal anxiety/depression; 8-10: mild anxiety/depression; 11-14: moderate anxiety/depression; 15-21: severe anxiety/depression
Source: Appendix 2, Output 5, Table 5.1.1, Table 5.1.2, Table 5.1.3, Table 5.1.4, Table 5.1.5, Table 5.1.6, Table 5.1.7, Table 5.1.8, Table 5.1.9, Table 5.1.10, Table 5.1.11, Table 5.1.12, Table 5.1.13, Table 5.1.14, Table 5.1.15, Table 5.1.16, Table 5.1.17, Table 5.1.18, Table 5.1.19, Table 5.1.20, Table 5.1.21 and Table 5.1.22

Figure 8 shows the distribution of WPAI-GH domain scores in the Non-Rollover Safety population at each visit from Day 0 to end of study visit. Mean (SD) Percent activity impairment due to health score was 30.52 (27.29) at Day 0 and between 14.81 (22.06) and 24.18 (30.88) at each post-baseline visit. Mean (SD) Percent impairment while working due to health was 22.38 (23.12) at Day 0 and mean (SD) Percent overall work impairment due to health was 24.90 (25.62) at Day 0; these scores were between 9 and 21 at each post-baseline visit. Mean (SD) Percent work time missed due to health was below 7 at each visit. Full WPAI-GH score descriptions are available in Appendix 2, Output 5.

Figure 8 Description of WPAI scores at each visit from Day 0 to end of study visit in the Non-Rollover Safety population (N=103)

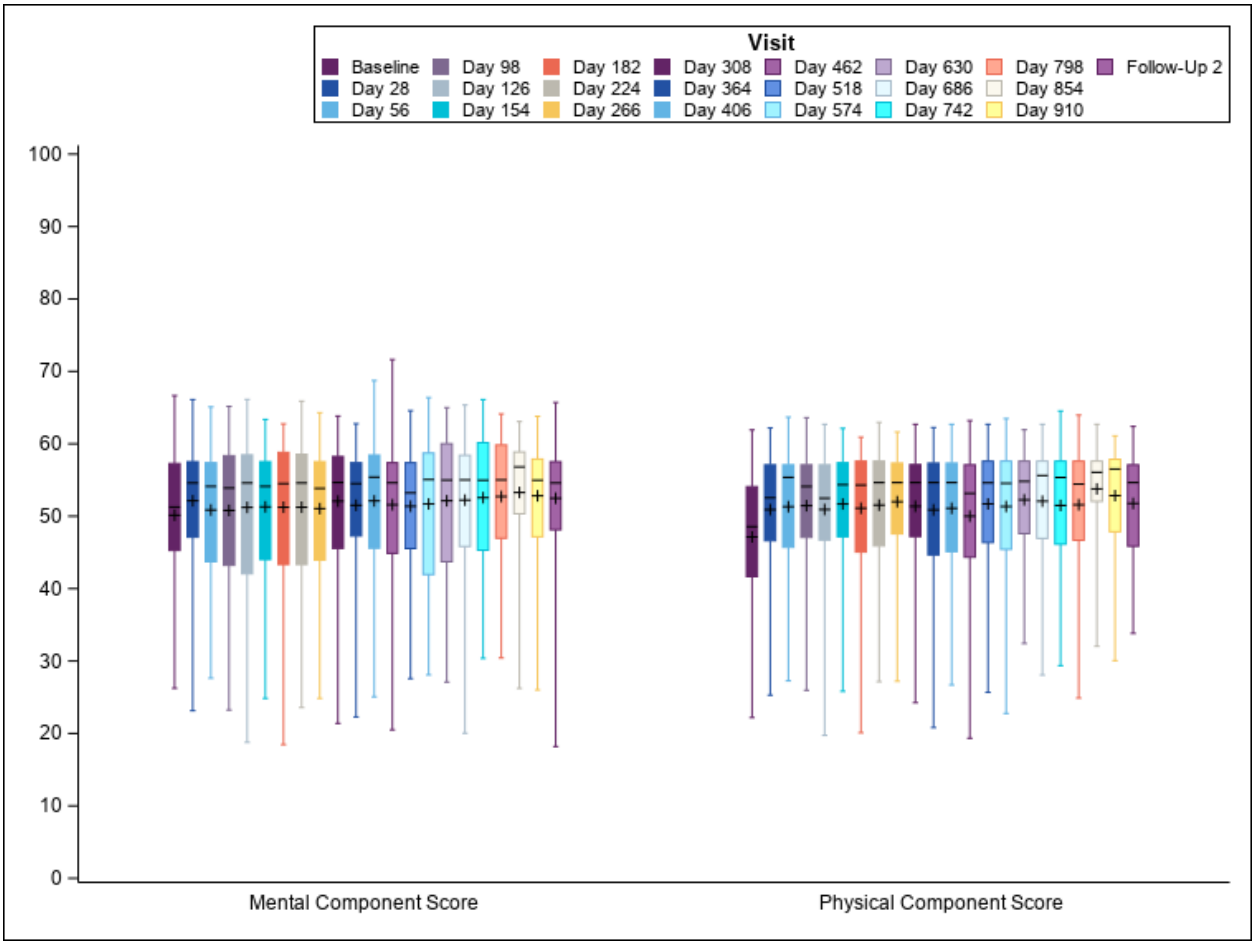


WPAI-GH=Work and Productivity Activity Impairment – General Health questionnaire; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
Higher values indicate greater impairment and less work productivity
Source: Appendix 2, Output 5, Table 5.1.1, Table 5.1.2, Table 5.1.3, Table 5.1.4, Table 5.1.5, Table 5.1.6, Table 5.1.7, Table 5.1.8, Table 5.1.9, Table 5.1.10, Table 5.1.11, Table 5.1.12, Table 5.1.13, Table 5.1.14, Table 5.1.15, Table 5.1.16, Table 5.1.17, Table 5.1.18, Table 5.1.19, Table 5.1.20, Table 5.1.21 and Table 5.1.22

Figure 9 shows the distribution of the SF-12v2 Mental and Physical Component scores in the Non-Rollover Safety population at each visit from Day 0 to end of study visit. SF-12v2 Mental Component scores and Physical Component scores increased slightly (i.e. improvement) at the

first post-Baseline visit and then remained stable over the course of the study, with mean (SD) scores ranging from 50.14 (8.88) to 53.27 (8.76) for the Mental Component score and 47.13 (8.62) to 53.77 (5.80) for the Physical Component score. All SF-12v2 domain scores were stable over the course of the study. A full description of the SF-12v2 scores is available in Appendix 2, Output 5.

Figure 9 Description of SF-12v2 Mental Component and Physical Component scores at each visit from Day 0 to end of study visit in the Non-Rollover Safety population (N=103)



SF-12v2=12 Item Short Form v2 Health Survey; EOS=end of study; ET=early termination; Follow-up 2=EOS visit/ET
Legend: *Box for each score: interquartile range (Q1-Q3); +: mean; —: median; bottom and top bars: observed minimum and maximum values*
0 indicates the lowest health level as measured by the scales and 100 the highest
Source: Appendix 2, Output 5, Table 5.1.1, Table 5.1.2, Table 5.1.3, Table 5.1.4, Table 5.1.5, Table 5.1.6, Table 5.1.7, Table 5.1.8, Table 5.1.9, Table 5.1.10, Table 5.1.11, Table 5.1.12, Table 5.1.13, Table 5.1.14, Table 5.1.15, Table 5.1.16, Table 5.1.17, Table 5.1.18, Table 5.1.19, Table 5.1.20, Table 5.1.21 and Table 5.1.22

EQ-5D-5L was completed by the Non-Rollover Safety population at each visit from Day 0 to end of study visit. Mean (± SD) EQ-5D-5L index score was 0.85 (±0.16) at Day 0 in the Non-Rollover Safety population. It very slightly increased to 0.89 (±0.15) at end of study visit (data not shown, see Appendix 2, Output 5).

The TSQM-9 was completed by the subjects at Day 364, Day 574 and end of study visit only. Mean (±SD) Effectiveness score fluctuated between 90.29 (±15.15) and 91.70 (±14.68) indicating that Non-Rollover subjects were very satisfied with their treatment effectiveness. Mean (±SD) Convenience score fluctuated between 81.14 (±17.59) and 83.46 (±16.81) indicating subjects reported their treatment was convenient. Mean (±SD) Satisfaction score ranged from 87.68 (±13.93) to 89.00 (±16.75) indicating that subjects were very satisfied with their medication. A full description of the TSQM-9 scores is available in Appendix 2, Output 5.

8.2.3 Description of change in PRO scores in the Rollover Safety population by treatment received during DX-2930-03

Mean change in PRO scores were described in the Rollover Safety Population from Day 0 to end of study visit according to the treatment previously received in the DX-2930-03 trial.

Mean change between Day 0 and end of study visit showed greater improvement for subjects previously treated with placebo than for subjects previously treated with lanadelumab in WPAI-GH scores and SF-12v2 Mental Component and Physical Component scores. Mean changes in HADS and EQ-5D-5L scores were similar regardless of the treatment received during Study DX-2930-03. Full results are available in Appendix 2, Output 6.

8.3 Exploratory analysis of AE-QoL score changes in the Rollover Safety Population

Linear regressions were conducted with the change in AE-QoL scores from Day 0 to end of study visit as explained variable, and the following explanatory variables: duration of 'regular' treatment period, AE-QoL score at baseline, treatment received in the DX-2930-03 study and baseline AE-QoL score in the DX-2930-03 study, in the Rollover Safety population. Detailed results are available in Appendix 2, Output 7.

Table 3 presents the percentage of variance (R^2) explained by the linear regressions conducted on the change in each AE-QoL score from Day 0 to end of study visit in the Rollover Safety population.

The linear regressions explained respectively 34%, 35%, 57%, 36% and 41% of the variance of the change from Day 0 to end of study visit in the AE-QoL Fatigue/Mood, Fear/Shame, Functioning, Nutrition and Total scores, respectively.

Table 3 Fit statistics of the linear regressions conducted on the change in AE-QoL scores from Day 0 to end of study visit in the Rollover Safety population

	Model with change in score from Day 0 to end of study visit	
Score	**N**	**R^2**
AE-QoL Fatigue/Mood score	90	**0.336**
AE-QoL Fears/Shame score	90	**0.354**
AE-QoL Functioning	89	**0.572**
AE-QoL Nutrition score	90	**0.358**
AE-QoL Total score	90	**0.413**

In bold, R^2>0.020
AE-QoL: Angioedema Quality of Life Questionnaire
Source: Appendix 2, Output 7, Table 7.1.1, Table 7.1.2, Table 7.2.1, Table 7.2.2, Table 7.3.1, Table 7.3.2, Table 7.4.1, Table 7.4.2, Table 7.5.1 and Table 7.5.2

Table 4 presents the estimates obtained on the linear regressions on the change in AE-QoL scores from Day 0 to end of study visit in the Rollover Safety population; results are presented for all 5 models as their percentage of explained variance is greater than 15%. The only variable that was significant at the threshold of 5% in each model was the Baseline AE-QoL score. The negative parameter estimates indicated that the decrease in the AE-QoL scores (i.e. improvement) from Day 0 to end of study visit was slightly higher for subjects who had higher Baseline AE-QoL scores. The treatment received during Study DX-2930-03 was also significant at the threshold of 5% in the AE-QoL Nutrition score model. The positive parameter estimates for all DX-2930 groups indicated that the decrease in the AE-QoL Nutrition score (i.e. improvement) from Day 0 to end of study visit was lower for subjects previously treated with DX-2930 than for subjects previously treated with placebo. This was in line with the raw description of change in score (see 8.1.3).

Table 4 Results of the linear regressions on change in AE-QoL scores from Day 0 to end of study visit in the Rollover Safety population

					Treatment received in DX-2930-03 study (Reference: Placebo)		
Score	Intercept	Baseline score	Baseline score in the DX-2930-03 study	Regular treatment period duration (in months)	DX-2930 150 mg every 4 weeks	DX-2930 300 mg every 2 weeks	DX-2930 300 mg every 4 weeks
AE-QoL Fatigue/Mood score	5.399	**-0.586**	0.223	-0.190	1.647	4.516	1.223
Ae-QoL Fears/Shame score	3.570	**-0.436**	0.118	-0.427	8.550	3.023	6.651
AE-QoL Functioning score	-8.436	**-0.581**	0.095	-0.053	13.234	11.579	10.619
AE-QoL Nutrition score	-16.569	**-0.400**	0.093	0.150	**17.138**	**17.449**	**20.663**
AE-QoL Total score	-2.764	**-0.440**	0.091	-0.172	10.094	9.233	9.098

In bold, significant variables ($p<0.05$); for treatment received in DX-2930-03 study, p-values are in bold only if the omnibus p-value was significant in the model.
AE-QoL: Angioedema Quality of Life Questionnaire
Source: Appendix 2, Output 7, Table 7.1.4, Table 7.2.4, Table 7.3.4, Table 7.4.4 and Table 7.5.4

8.4 Responder analysis and empirical cumulative distribution functions

The percentage of PRO responders between Day 0 and end of study visit was calculated for all PRO scores and CDFs of the change in all available scores between Day 0 and end of study visit were plotted (Appendix 2, Output 8). A subject was considered a PRO responder if the change in score was greater than a predefined threshold that was considered clinically meaningful. The thresholds used for these analyses were a 6-point change for all AE-QoL scores; a 2-point change for HADS scores; a 5-point change for SF-12v2 scores; and changes of 14, 11, 10 and 7 points for the WPAI-GH Percent activity impairment, Percent impairment while working, Percent overall work impairment, and Percent work time missed scores respectively. CDFs and percentage of responders were also obtained for the Non-Rollover Safety population, i.e., subjects who were not previously treated with lanadelumab (see Appendix 2, Output 9).

The CDFs showed a consistent greater improvement in AE-QoL scores from Day 0 to end of study visit for subjects previously treated with placebo in the Rollover Safety population. No clear pattern was observed in the CDFs of the WPAI-GH, HADS and SF-12v2 scores. A higher percentage of responders in AE-QoL scores between Day 0 and end of study visit was observed in the Non-Rollover Safety population than in the Rollover Safety population. The percentage of responders in HADS Depression and Total scores, the WPAI-GH scores and the SF-12v2 (except for the Role Physical score, the Vitality score, the Mental Health score, and the Mental Component score) was also higher in the Non-Rollover Safety population than in the Rollover Safety population.

Full results and CDFs are provided in Appendix 2, Output 8 (for the Rollover Safety population) and Output 9 (for the Non-Rollover Safety population).

9. DISCUSSION OF RESULTS

The analyses presented in this report aimed to describe the AE-QoL and other PRO scores (EQ-5D-5L, WPAI-GH, HADS, SF-12v2 and TSQM-9) until end of study visit of Study DX-2930-04 and to investigate change in PRO scores between baseline and end of study according to previous exposure to lanadelumab in Study DX-2930-03. Study DX-2930-04 was an open-label, long term safety and efficacy extension of Study DX-2930-03, which aimed to evaluate lanadelumab for prevention of acute angioedema attacks in subjects with Type I or Type II HAE. Two types of subjects were enrolled in this study: Rollover subjects, who completed the double-blind treatment period at Day 182 of Study DX-2930-03 and consented to enter Study DX-2930-04, and Non-Rollover subjects who did not participate in Study DX-2930-03 and entered directly in Study DX-2930-04.

Overall, improvements in all AE-QoL scores were observed between Day 0 and end of study visit of DX-2930-04 in both subjects who participated in Study DX-2930-03 (Rollover) and subjects who did not (Non-Rollover). Most of the improvement in AE-QoL scores was observed during the early follow-up (before Day 56). Subjects not previously treated with lanadelumab (either Non-Rollover subjects, or Rollover subjects treated with placebo in Study DX-2930-03) showed a greater improvement in all AE-QoL domains in DX-2930-04 study than subjects who had been treated with lanadelumab in Study DX-2930-03. This indicates a possible benefit due to treatment with lanadelumab. The overall improvement in AE-QoL scores observed in the Rollover Safety population may have been mainly driven by the improvement in subjects who switched from placebo to lanadelumab in Study DX-2930-04. These subjects showed greater change in AE-QoL scores in Study DX-2930-04. An improvement was observed during Study DX-2930-04 in the AE-QoL Fears/Shame score in subjects who had received lanadelumab 300mg in Study DX-2930-03, but not in all other AE-QoL domain scores (Functioning, Nutrition and Fatigue/Mood) in which scores were maintained from baseline to end of study visit as expected. This may explain why the AE-QoL Fears/Shame score was the AE-QoL domain of the Rollover Safety population showing the greatest improvement overall in Study DX-2930-04. A longer follow-up may be needed for subjects to perceive improvement in distal concepts such as Fears and Shame, compared to Fatigue or Functioning. The longer follow-up offered by the open-label extension may have allowed this benefit to be captured.

HADS Anxiety and Depression scores remained stable over the course of the study, with mean scores lower than 6, indicating normal levels of anxiety and depression in subjects who participated in Study DX-2930-03 (Rollover). In the Non-Rollover Safety population, the mean HADS anxiety score was 7 at baseline indicating normal to mild anxiety and the mean HADS depression score was 3 indicating no depression. At each post-baseline visit, HADS Anxiety and Depression scores were lower than 6, indicating normal level of anxiety and depression over the course of the study in the Non-Rollover safety population. No change in productivity as measured by the WPAI-GH was observed in subjects who participated in Study DX-2930-03 (Rollover) except for those who received placebo in Study DX-2930-03 as their WPAI-GH scores decreased slightly, indicating an improvement in work productivity and impairment for those patients. A slight improvement in productivity was observed in subjects who did not participate in Study DX-2930-03 (Non-Rollover) at the beginning of Study DX-2930-04 then the WPAI-GH scores stabilized. The SF-12v2 scores were stable in the Rollover Safety population

during Study DX-2930-04, and subjects previously treated with placebo showed a slight increase (i.e. improvement) in SF-12 Physical and Mental Component scores; SF-12v2 scores were stable in the Non-Rollover Safety population. No change in health status was seen in Rollover and Non-Rollover subjects, who already had good health status at Day 0 (mean score=0.85 in both populations) as measured by the EQ-5D-5L.

The benefit of the treatment was seen in the level of TSQM-9 scores at Day 364, Day 574 and end of study visit in both the Rollover and Non-Rollover Safety populations, showing that the subjects were very satisfied with their treatment effectiveness (mean Effectiveness score > 90), found their treatment convenient (mean Convenience score > 81) and were very satisfied with their medication (mean Satisfaction score > 87).

Linear regressions of change in AE-QoL scores in the regular treatment period in the Rollover Safety population showed that the baseline AE-QoL scores statistically significantly explained the change in all AE-QoL scores, with subjects having higher baseline AE-QoL scores (i.e. greater QoL impairment) in Study DX-2930-04 having a higher decrease in AE-QoL scores (indicating a higher improvement). The treatment received during the DX-2930-03 study also statistically significantly explained the change in AE-QoL Nutrition score, with a lower decrease in the AE-QoL Nutrition score (i.e. improvement) from Day 0 to end of study visit for subjects previously treated with DX-2930 than for subjects previously treated with placebo. This result was confirmed by the CDFs on the AE-QoL Nutrition score and also observed for the other AE-QoL scores, as they showed a greater improvement from Day 0 to end of study visit for subjects previously treated with placebo in the Rollover Safety population. No clear pattern was observed for the other scores. The percentage of responders to change in PRO scores from Day 0 to end of study visit was higher in the Non-Rollover Safety population than in the Rollover Safety population except for the HADS Anxiety score, SF-12v2 Role Physical, Vitality, Mental Health and Mental Component scores. The highest difference in percentage of responders to change between Rollover and Non-Rollover Safety population was observed in the AE-QoL scores. These results consistently support the benefit of lanadelumab, as subjects who had not been previously treated by lanadelumab reported greater improvement in all PROs when they initiate a treatment with lanadelumab than subjects remaining on lanadelumab.

A few limitations were observed in the analyses of PRO data from Study DX-2930-04. Especially, the generic instruments (EQ-5D-5L, HADS and SF-12v2) showed little to no impairment at baseline making it difficult to show improvements. In addition,, some PRO scores showed floor effects that may have impacted the ability to demonstrate higher improvement during follow-up of Study DX-2930-04; a number of subjects (typically at least 25%) systematically reported the lowest possible score(s), preventing any further improvement in the corresponding concept to be demonstrated.

10. CONCLUSION

These analyses of PRO data collected in Study DX-2930-04 showed improvements in all AE-QoL scores between Day 0 and end of study visit of DX-2930-04 in both subjects who participated in Study DX-2930-03 (Rollover) and subjects who did not (Non-Rollover). Subjects not previously treated with lanadelumab (either Non-Rollover subjects, or Rollover subjects treated with placebo in Study DX-2930-03) showed a greater improvement in all AE-QoL domains in DX-2930-04 study than subjects who had been treated with lanadelumab in Study DX-2930-03, supporting the benefit of lanadelumab treatment.

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12. LIST OF APPENDICES

Appendix 1 DX-2930-04 PRO Statistical Analysis Plan v1.0 10 December 2019

Patient-reported Outcomes Statistical Analysis Plan

Phase 3

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

Protocol Identifier: DX-2930-04

Study Sponsor(s):	Dyax Corp., (an indirect, wholly-owned subsidiary of Shire plc) 300 Shire Way, Lexington, MA 02421 USA
Author:	[redacted]
Protocol:	Amendment 3.0 29 June 2017
Drug:	Lanadelumab (TAK-743, formerly SHP643, formerly DX-2930)
SAP Type:	Assessment of Patient Reported Outcomes Data
SAP Version #:	Version 1.0
SAP Date:	10 December 2019
Status:	Final

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ABBREVIATIONS

Abbreviation	Definition
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
ACT	Asthma Control Test
CDF	Cumulative distribution function
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level Measure
HAE	Hereditary angioedema
HADS	Hospital Anxiety and Depression Scale
MCID	Minimal clinically important difference
PRO	Patient-reported outcome
HRQoL	Health-related quality of life
PRO-SAP	Patient-reported outcomes-specific statistical analysis plan
SEM	Standard error of the mean
SF-12v2	12 Item Short Form v2 Health Survey
TSQM	Treatment Satisfaction Questionnaire for Medication
UCT	Urticaria Control Test
VAS	Visual Analogue Scale
WPAI-GH	Work Productivity and Activity Impairment – General Health

1. BACKGROUND

The DX-2930-04 open-label study will be conducted in subjects with Type I or Type II hereditary angioedema (HAE) to evaluate the long-term safety and efficacy of DX-2930. The primary objective of the DX-2930-04 study is to evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930; the secondary objectives of the study are to evaluate the long-term efficacy of DX-2930 in preventing acute HAE attacks and to characterize the outer bounds of dosing frequency for DX-2930. The DX-2930-04 study is an open-label extension of the DX-2930-03 study.

Patient-reported outcomes (PROs) were assessed in the DX-2930-04 study to investigate tertiary objectives, namely: to evaluate the effect of DX-2930 on health-related quality of life (HRQoL), to assess treatment satisfaction, and to assess global impression of treatment response. PRO instruments collected in the study included the angioedema quality of life questionnaire (AE-QOL), the 12-item short-form version 2 health survey (SF-12v2), the hospital anxiety and depression scale (HADS), the work productivity and activity impairment – general health (WPAI-GH) questionnaire, the angioedema control test (AECT), the treatment satisfaction questionnaire for medication – 9 items (TSQM-9), the EuroQol group 5 dimension-5 levels (EQ-5D-5L) questionnaire, and a subject global impression of treatment response.

This PRO-specific statistical analysis plan (PRO-SAP) describes the statistical analyses to be performed on the PRO data collected in the DX-2930-04 study to address the PRO objectives of the study. This PRO-SAP is being developed after review of the DX-2930-04 protocol amendment 3.0, but before the final database cut.

2. OBJECTIVES

The objectives of the PRO analyses performed using the PRO data collected in the DX-2390-04 study will be:

- To describe PRO scores over the course of the DX-2930-04 study separately for patients who participated in the DX-2930-03 study ("rollover patients") and patients who did not participate in the DX-2930-03 study ("non-rollover patients"):
  - Functioning, fatigue/mood, fear/shame, nutrition as assessed by the AE-QOL
  - Work productivity and activity impairment, as assessed by the WPAI-GH
  - Anxiety and depression, as assessed by the HADS
  - Generic HRQoL, as assessed by the SF-12v2
  - Treatment satisfaction, as assessed by the TSQM-9
  - Health status, as assessed by EQ-5D-5L
- To investigate change in PRO scores between baseline and end of study according to previous exposure to DX-2930 in the DX-2930-03 study

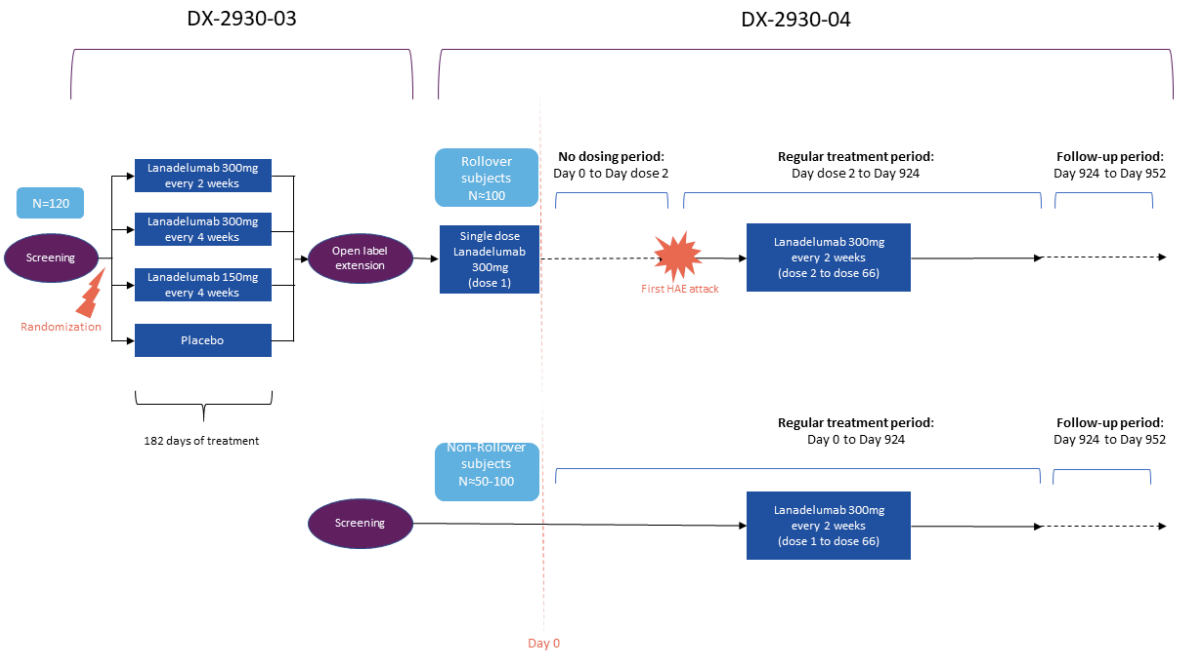
3. MATERIAL

3.1 DX2930-04 Study

3.1.1 Study Design

DX-2930-04 is an open-label, long term safety and efficacy extension study of DX-2930-03, which aims to evaluate DX-2930 for prevention of acute angioedema attacks in subjects with Type I or Type II HAE. A schematic study design of the DX-2930-04 study is provided in Figure 1.

Figure 1. Schematic DX-2930-04 Study Design



Two types of subjects were to be enrolled into this study: rollover and non-rollover subjects. Rollover subjects were subjects who completed the double-blind treatment period at Day 182 of the DX-2930-03 study and consented to enter the DX-2930-04 study. They received a single open-label dose of 300 mg DX-2930 administered SC on Day 0. Subjects did not receive any additional DX-2930 doses until their first reported and investigator-confirmed HAE attack. They then continued to receive repeated SC administrations of open-label 300mg DX-2930 every 2 weeks for the remaining duration of the treatment period.

Non-rollover subject did not participate in the DX-2930-03 study. They received an open-label dose of 300 mg DX-2930 administered SC on Day 0, then continued to receive a 300 mg SC dose every 2 weeks throughout the duration of the treatment period.

The study duration was planned to be 34 months (952 days), including a 4-week follow up period, after the treatment period. The study was expected to enroll at least 100 rollover subjects, and at least 50 (to approximately 100) non-rollover subjects, to achieve a total enrollment of at least 150 (maximum of 250) subjects.

3.1.2 PROs Data

Subjects enrolled in the DX-2930-04 study were asked to complete the following PRO instruments:

- AE-QoL
- EQ-5D-5L
- WPAI-GH Questionnaire
- HADS
- SF-12v2
- AECT
- TSQM-9
- Global Impression of Treatment Response

The PRO assessment schedule is presented in Table 1. Of those PRO instruments, only the AE-QOL and EQ-5D-5L were administered in the previous DX-2930-03 study.

All PRO instruments are described below.

Table 1. PROs recording Schedule in DX2390-04 Study

Day	0	28	56	98	126	154	182	224	266	308	364	406	462	518	574	630	686	742	798	854	910	952[1]
AE-QoL	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WPAI-GH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HADS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SF-12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AECT											✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TSQM											✓				✓							✓
Global Impression of Treatment Response											✓											✓

[1] Records at Day 952 correspond to the end of the study and of the 4-week follow-up period (Day 924 to 952)

3.2 PRO Instruments

3.2.1 AE-QoL

The AE-QoL is a self-administered instrument developed to assess HRQoL impairment in subjects with recurrent angioedema. (Weller et al. 2012) It consists of 17 items divided into 4 domains: functioning, fatigue/mood, fear/shame, and nutrition. Items are scored in 5-point Likert-scales ranging from "Never" to "Very Often", asking for patient ratings over the last four weeks. Scores for each domain and a total score can be obtained by taking the mean of the item scores within the scale (or mean item scores of all items, for the total score) and transforming it linearly on a 0-100 scale. The AE-QOL scores range between 0 to 100, with a higher score indicating greater QoL impairment.

A 6-point difference has been reported to be the minimal clinically important difference (MCID) for the AE-QOL total score. (Weller et al. 2016) This value will be used as threshold for PRO response in the PRO responder analyses, for all AE-QOL scores (in the absence of specific value for the domain scores).

3.2.2 EQ-5D-5L

The EQ-5D-5L is a self-administered standardized measure of health status comprising a descriptive system and a Visual Analogue Scale (VAS). (Herdman et al. 2011) The descriptive systems assess five dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. (Herdman et al. 2011) Each dimension is rated on a 5-point scale to describe subject health for the current day, with 1 being "no problems" and 5 "extreme problems". An index score can be derived using "value sets" that reflect the preferences of a population between the various health states defined by the five items. The index score is a utility measure that ranges between 0 and 1, with 1 corresponding to a perfect health. The UK value set will be used to calculate the EQ-5D-5L index scores in this study.

Separately from the descriptive part, the VAS is a measure of overall self-rated health status. The subject assesses his or her health using a 20-cm vertical VAS, between "the best health you can imagine" and "the worst health you can imagine." Scores ranges from 0 to 100, with a higher score indicating better health.

3.2.3 WPAI-GH Questionnaire

The WPAI-GH is a 6-item self-assessment of the effect of health problems on the subject's ability to work and perform regular activities, during the past seven days. (Reilly et al. 1993) WPAI-GH scoring guidelines lead to the creation of the following scores: percent work time missed due to health, percent impairment while working due to health, percent overall work impairment due to health, and percent activity impairment due to health.

The MCID for the WPAI-GH has been suggested in other conditions to be 7.2 for absenteeism, 11.1 for presenteeism, 9.8 for overall work productivity, and 14.3 for activity impairment. (Bolge et al. 2009) Based on these values, the following values will be used as threshold for PRO response in the PRO responder analyses: 7 for absenteeism, 11 for presenteeism, 10 for overall work productivity, and 14 for activity impairment.

3.2.4 HADS

The HADS is a self-assessed instrument developed to detect subjects states of depression, anxiety, and emotional distress. (Zigmond and Snaith 1983) From its 14 items, 7 relate to anxiety and 7 to depression during the past week. Responses are scored on a scale ranging from 0 to 3, with 3 indicating the highest symptom frequency. For each domain, scores range from 0 to 21, and can be categorized as normal (0 to 7), mild (8 to 10), moderate (11 to 14), and severe (15 to 21). Additionally, a total score can be calculated from the full set of items, ranging from 0 to 42, with a higher score indicating more distress.

The MCID has been estimated in other conditions to be in the range 1.5-2.5. (Chan et al. 2016; Puhan et al. 2008) Based on these values, a 2-point value will be used as threshold for PRO response in the PRO responder analyses for the HADS scores.

3.2.5 SF-12v2

The SF-12v2 is a validated instrument designed to measure functional health and well-being. It consists of 12 question, divided into 8 health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. (Ware Jr. et al. 1996) Questions are asked of subjects regarding their health for the last 4 weeks. Physical and Mental Health Composite, as well as raw and norm-based domain scores can be calculated. All scores range from 0 to 100, with 0 indicating the lowest health level as measured by the scales and 100 the highest. Norm-based scores are obtained using t-scores based on a general US population mean of 50.0, with a standard deviation of 10.0, allowing direct comparisons to the US general population.

The MCID has been estimated in other conditions to be in the range 4.9-5.2. (Schwab et al. 2008; Skolasky et al. 2015) Based on these values, a 5-point value will be used as threshold for PRO response in the PRO responder analyses for the SF-12v2 scores.

3.2.6 AECT

The AECT is a 10-question instrument designed to assess the control of angioedema among subjects with recurrent angioedema (including HAE). Only the four first items (frequency of symptoms, impact on HRQoL, impact of unpredictability, and perceived disease control) were used in the study. This is a useful measure specially to drive treatment decisions. Its concept is

similar to the previously developed and established Asthma Control Test (ACT) and Urticaria Control Test (UCT). (Nathan et al. 2004; Weller et al. 2014) Questions have 5 answer options (verbal rating scale), scored from 0 to 4 points. A total AECT score can be obtained from the ten items but will not be computed in this study as only four of them will be available.

3.2.7 TSQM-9

The TSQM-9 is a generic measure of treatment satisfaction that allows for comparison across medication types and subjects conditions. (Bharmal et al. 2009) It assesses the subject's perception of treatment effectiveness, convenience, and global satisfaction during the last two to three weeks or when the treatment was last used. Scores for each of the 3 domains, as well as a combined score are calculated separately. Scores are transformed to a 0 to 100 scale, with a higher score indicating higher satisfaction with treatment.

3.2.8 Global Impression of Treatment Response

The subject global impression of treatment response is assessed using a single question: "Overall, how would you rate your response to the study medication?". Responses options are namely, about the actual day: "poor", "fair", "good", "very good," and "excellent".

4. GENERAL ANALYTICAL CONSIDERATIONS

4.1 Analysis Population

The PRO analyses will be conducted in the Safety population, Rollover Safety population and Non-rollover Safety populations, as defined in the main statistical analysis plan of the DX-2930-04 study.

4.2 General Principles

4.2.1 Description of Variables

Quantitative variables will be described by their frequency, mean, standard deviation (SD), standard error of the mean (SEM), median, first and third quartiles, extreme values (minimum and maximum values), and number of missing values.

Qualitative variables will be described by the frequency and percentage of each response choice, with missing data being included in the calculation of percentage.

4.2.2 Level of Significance

No formal statistical hypothesis testing will be performed. All p-values will be considered descriptive.

4.3 Missing Data Handling

For the score calculations, the missing items of the PRO questionnaires will be handled as proposed by the authors of the questionnaires.

No missing PRO assessment will be imputed in the analyses.

4.4 Software

Data analysis will be performed using SAS version 9.4 (SAS Institute; Cary, North Carolina, USA).

5. ANALYSIS PLAN

5.1 Description of AE-QoL Scores over the Study

5.1.1 Description of AE-QoL Scores and Change in AE-QoL Score in Rollover Subjects

The AE-QoL scores will be described at baseline and all scheduled assessment visits in the rollover safety population.

The change in AE-QoL scores from baseline (Day 0) to each scheduled AE-QoL assessment visit will be described in the rollover safety population.

5.1.2 Description of AE-QoL Scores and Change in Score in Non-rollover Subjects

The AE-QoL scores will be described at baseline and all scheduled assessment visits in the non-rollover safety population.

The change in AE-QoL scores from baseline (Day 0) to each scheduled assessment visit will be described in the non-rollover safety population.

5.1.3 Description of Change in AE-QoL Score in Rollover Subjects by Treatment Received During DX-2930-03

The change from baseline (Day 0, Dose 1) to the end-of-study visit will be described in the rollover safety population by treatment received in the DX-2930-03 study (placebo and each of the 3 DX-2930 treatment arms).

5.2 Description of Other PRO Scores over the Study

The analyses specified in this section will be applied to the following PRO scores:

- EQ-5D-5L index score
- WPAI-GH scores
- HADS domain scores
- SF-12v2 raw and norm-based domains and composites scores
- TSQM domain scores

5.2.1 Description of PRO Scores and Change in PRO Score in Rollover Subjects

The PRO scores will be described at baseline and all scheduled assessment visits in the rollover safety population.

The change in PRO scores from baseline (Day 0) to each scheduled PRO assessment visit will be described in the rollover safety population.

5.2.2 Description of PRO Scores and Change in Score in Non-rollover Subjects

The PRO scores will be described at baseline and all scheduled assessment visits in the non-rollover safety population.

The change in PRO scores from baseline (Day 0) to each scheduled assessment visit will be described in the non-rollover safety population.

5.2.3 Description of Change in PRO Score in Rollover Subjects by Treatment Received During DX-2930-03

The change from baseline (Day 0, Dose 1) to the end-of-study visit will be described in the rollover safety population by treatment received in the DX-2930-03 study (placebo and each of the 3 DX-2930 treatment arms).

5.3 Exploratory Analysis of AE-QoL Changes in Scores

5.3.1 Exploratory Analysis of AE-QoL Score Changes in Rollover Subjects

This section describes exploratory explanatory analyses of the change in the AE-QoL domain and total scores over the treatment period and over the regular treatment period in rollover subjects. These changes may depend on various simple factors: baseline AE-QoL score, time of treatment exposure (eg, duration of "regular" treatment period), treatment received in the DX-2930-03 study, and baseline AE-QoL score in the DX-2930-03 study.

The change in AE-QoL scores from baseline (Day 0) to the end-of-study visit will be analyzed using linear regressions with the change in AE-QoL score as explained variable and the following explanatory variables: duration of "regular" treatment period, AE-QoL score at baseline, AE-QoL score at baseline from the DX-2930-03 study, and treatment received in the DX-2930-03 study.

The change in AE-QoL scores from the Dose 2 PRO visit to end-of-study visit will be analyzed using linear regressions with the change in AE-QoL score as explained variable and the following explanatory variables: duration of "regular" treatment period, AE-QoL score at baseline, AE-QoL score at baseline from the DX-2930-03 study, and treatment received in the DX-2930-03 study.

These analyses will be performed in the rollover safety population.

5.4 Responder Analysis and Empirical Cumulative Distribution Functions

The analyses specified in this section will be applied to the following PRO scores that have a value at baseline (Day 0) of the study DX-2930-04, and predefined responder thresholds (*see description of the instruments above*):

- AE-QoL domain and total scores
- WPAI-GH scores
- HADS domain scores
- SF-12v2 domain and composites scores

5.4.1 Responder Analysis and Cumulative Distribution Function in Rollover Subjects

For each PRO score, subjects whose change in score from baseline (Day 0, Dose 1) to the end-of-study visit is greater than the predefined responder threshold will be categorized as responders. The percentage of responders will be calculated in the rollover safety population overall, and according to the treatment received in DX-2930-03.

Empirical cumulative distribution functions (CDF) of the change in score between baseline (Day 0, Dose 1) and the end-of-study visit will be plotted in the rollover safety population overall, and according to the treatment received in DX-2930-03.

5.4.2 Responder Analysis and Cumulative Distribution Function in Non-rollover Subjects

For each PRO score, subjects whose change in score from baseline (Day 0) to the end-of-study visit is greater than the predefined responder threshold will be categorized as responders. The percentage of responders will be calculated in the non-rollover safety population.

Empirical cumulative distribution functions (CDF) of the change in score between baseline (Day 0) and the end-of-study visit will be plotted in the non-rollover safety population.

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1 TITLE PAGE

Analysis Plan

Pharmacokinetic, Pharmacodynamic, HAE and Anti-Drug Antibody Data Summarization of Lanadelumab in Study DX-2930-04

Final Analysis (Part 3)

Investigational Medicinal Product:	Lanadelumab (SHP643, DX-2930)
Study Number:	DX-2930-04
Sponsor:	Takeda (Shire)
Reference No.:	SHIR-CSC-134
Date of Analysis Plan:	January 29, 2020
Version:	Final

2 SIGNATURE PAGE

Approval

The undersigned have reviewed the planned PK, PD, HAE and ADA data summarization plan.

[redacted], MSc
[redacted]
Certara Strategic Consulting

[redacted]
Date

[redacted], PhD, FCP
[redacted]
Certara Strategic Consulting

[redacted]
Date

2 SIGNATURE PAGE (CONT'D)

Sponsor Review and Approval

The undersigned have reviewed the planned PK, PD, HAE and ADA data summarization plan.

[redacted], MPH, PhD

[redacted]

Date

[redacted] Global Clinical Pharmacology & Pharmacokinetics
Clinical Research & Development
Takeda

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
BLQ	Below the limit of quantification
cHMWK	2-Chain of high molecular weight kininogen
CSC	Certara Strategic Consulting
CV	Coefficient of variability
EDT	Electronic data transmission
HAE	Hereditary angioedema
NAb	Neutralizing antibody
OLE	Open-label extension
PD	Pharmacodynamics
PK	Pharmacokinetics
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QC	Quality control
SC	Subcutaneous
sFTP	Secure file transfer protocol
SOP	Standard Operating Procedure

5 BACKGROUND

Lanadelumab (SHP643, DX-2930) is a fully human IgG1 recombinant monoclonal antibody that binds specifically to active plasma kallikrein. Lanadelumab is approved for the prophylactic treatment of angioedema attacks in patients with hereditary angioedema (HAE), a serious and life-threatening disease.

6 OBJECTIVES

Protocol DX-2930-04 is an open-label study to evaluate the long-term safety and efficacy of DX-2930 for prevention against acute attacks of Hereditary Angioedema (HAE) (HELP Study Extension™). There are two types of subjects to be enrolled into this study: (1) Subjects who rollover from Study DX-2930-03; (2) Subjects who are non-rollovers (i.e., were not participants in Study DX-2930-03).

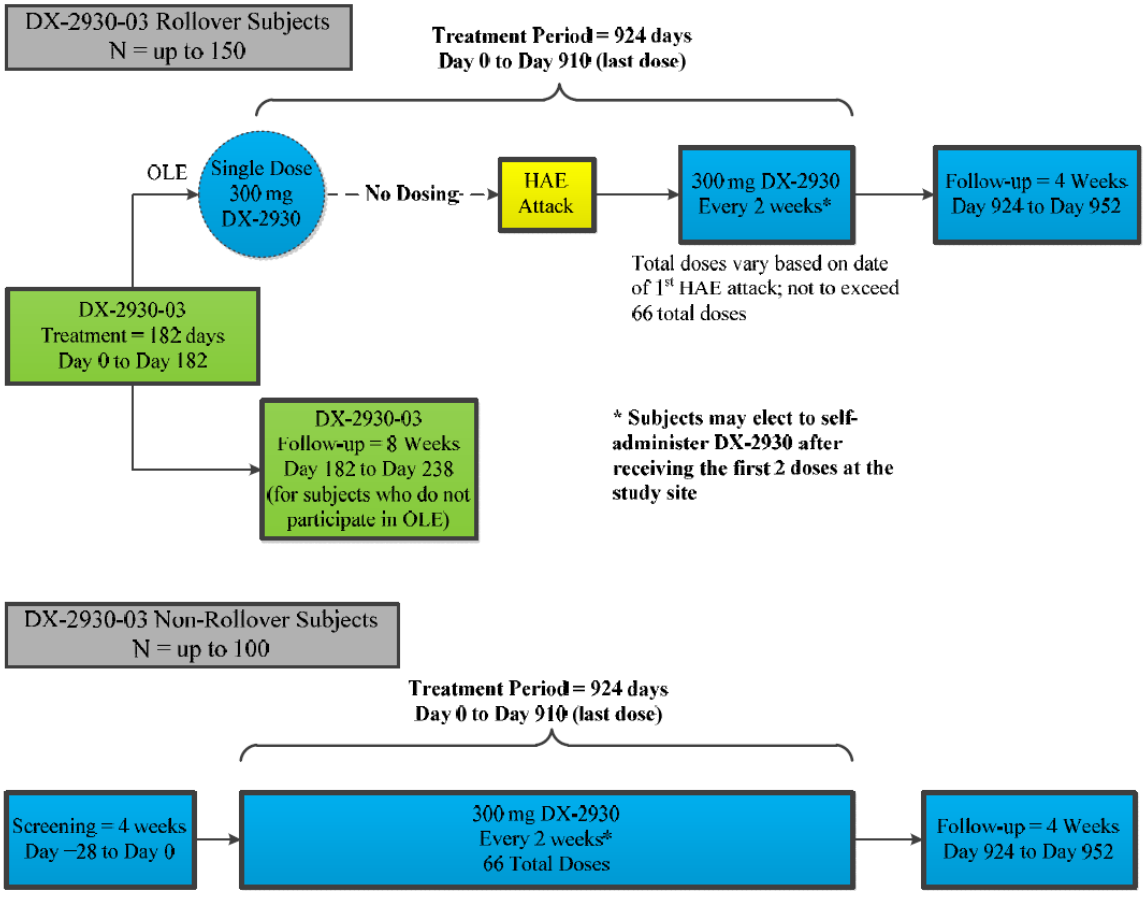
- For rollover subjects: Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of 300 mg SHP643 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional SHP643 doses until their first reported, and investigator-confirmed, HAE attack. As such, the total number of doses within the treatment period will vary between rollover subjects. The duration between the first open-label dose and first reported HAE attack will vary between rollover subjects. Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of SHP643 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit (i.e., Day 14, 28, 42, 56, 70, 84, 98…), this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit (i.e., an unscheduled visit). Similarly, if the second dose is administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra unscheduled study visit, (i.e., this visit will not replace any scheduled visit). Following the second open-label dose, rollover subjects will continue to receive repeated SC administrations of open label 300 mg SHP643 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedule.

- For non-rollover subjects: Following pre-dose assessments, non-rollover subjects will receive an open-label dose of 300 mg SHP643 administered SC on Day 0 and will continue to receive SC administrations of open-label 300 mg SHP643 every 2 weeks throughout the duration of the treatment period per the scheduled dosing in the Study Activities Schedule.

Subjects were to be 12 years of age or older experiencing at least one attack per 12 weeks. The total enrolment is expected to be at least 150, but not more than 250 subjects with a documented diagnosis of Type I or Type II HAE.

PK, PD, and anti-drug antibody (ADA) samples were drawn for all rollover and non-rollover. In addition to the schedule, an additional PK, PD and anti-drug antibody sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs. An overview of the study design is presented in Figure 1.

Figure 1. Overview of Study Design (Protocol DX-2930-04)



The DX-2930-04 protocol amendment 3.0 was finalized on 29 Jun 2017. The purpose of this amendment was to add new objectives and related measurements, quality of life (QoL) endpoints, and extend the study from 12 months to 30 months (Day 952) to continue to obtain data important for the assessment of SHP643 (i.e., safety and efficacy data).

7 OBJECTIVES

The specific objectives of this project are to summarize PK, PD, HAE attacks and ADA results. In addition, potential correlation between PK, PD and HAE attacks (average monthly HAE attack) in study DX-2930-04 will be explored.

This analysis plan provides general guidance on the extent, scope for the data summarization of PK, PD, HAE and ADA results. However, due to the uncertainty of the nature of the data *a priori*, deviations from this plan may occur. Due to the blinded nature of the data, effort will take place upon data base lock/unblinding to understand the data structure and nature of various variable. This analysis plan may be modified accordingly. These modifications/will be discussed with Shire before finalizing the data summarizations and will be noted in the footnotes of TFLs for full transparency with the scientific rationale.

8 DATA HANDLING

8.1 Data Transfer

Electronic files from Shire will be transferred to Certara Strategic Consulting (CSC) via a Secure File Transfer Protocol (sFTP) site provided by Shire. Electronic Data Transmission (EDT) contact at Shire will be:

[redacted], MPH, PhD
[redacted]
[redacted] Global Clinical Pharmacology & Pharmacokinetics
Clinical Research & Development
Takeda
Office: [redacted]
Mobile: [redacted]
Email: [redacted]

The following CSC designates will be the EDT contacts:

[redacted] PhD, FCP
[redacted]
Certara Strategic Consulting
Montréal, Québec, Canada H3A 2W5
Cell: [redacted]
Email: [redacted]

Data will be provided as .csv or SAS transport files by Shire.

8.2 Variables

The dataset to be used in the summarization steps (i.e. to produce tables, listings and figures for Study DX-2930-04) will include at a minimum the following variables:

Subject Information

- Study (STUDY)
- Unique patient ID (USUBJID)
- Nominal time of sample or observation (NTIME in hours)
- Visit day of sample or observation (VISIT)
- Visit number of sample of observation (VISITNUM)
- Study day (DAY)
- Indicator if the subject is a rollover from study DX-2930-03 or non-rollover (ROLL) where rollover from DX-2930-03 = ROLL and non-rollover = NONROLL
- Treatment indicator (ARM) – should be "Lanadelumab 300 mg every 2 weeks" for all subjects
- For subjects rolling over from DX-2930-03, indicator of which arm of DX-2930-03 the subject participated in (ARM03):
    - Placebo
    - Lanadelumab 300 mg every 2 weeks
    - Lanadelumab 300 mg every 4 weeks
    - Lanadelumab 150 mg every 4 weeks
- Dose administered (DOSE) in mg presented without units
- Location of dose administered (EXLOC) – abdomen = 0 and upper arm = 1 and thigh =2 (where applicable)
- Subject age (AGE)
- Subject age category (AGECATG)
    - ≥18 years (Adult)
    - <18 years (Pediatric)

Primary PK and PD variables

- Lanadelumab concentrations in ng/mL
- Baseline %2-chain high molecular weight kininogen by Western Blot using citrate samples (BLHMWK) in % units
- On treatment %2-chain high molecular weight kininogen by Western Blot using citrate samples (CHMWK) in % units
- Percent change from baseline %2-chain high molecular weight kininogen by Western Blot using citrate samples (PCFBHMWK) in % units calculated at [(CHMWK-BLHMWK)/(BLHMWK)]*100%

Anti-Drug Antibody (ADA)

In addition, the dataset will include measures of immunogenicity. As ADA testing is typically performed in a staged fashion, only samples which test presumably positive in a screening assay are submitted to a confirmatory assay. Similarly, only samples which are positive in a confirmatory assay are submitted to a neutralizing assay test. Datasets will contain the following ADA measurements with the possible results:

1. Screening assay (presumptive positive, negative or NA)
2. Confirmatory assay (positive, negative or NA)
3. Neutralizing assay (positive, negative or NA)
4. ADA titer level (value or NA if the sample was not submitted for a confirmatory assay)
5. Overall status (positive, negative or NA)

ADA samples coded as NA (or similar coding) imply the sample was not tested due the previous assay step result being non-positive.

The dataset for summarization will include whether a sample was positive or non-positive in the confirmatory assay (CONFIRM)

The dataset for summarization will include whether a sample was positive or non-positive in the neutralizing assay (NANTBD)

The dataset for summarization will include the titer of the confirmatory assay (TITRE). For subjects where at least two on treatment samples are positive in CONFIRM, the subject will include an indicator if the subject had persistently positive ADA (to be defined by Shire) or transient ADA (ADAPER). For subjects where at least two on treatment samples are positive in NANTBD assay, the subject will include an indicator if the subject had persistently positive ADA (to be defined by Shire) or transient ADA (NABPER)

HAE History at Baseline and On-Treatment

- Each investigator confirmed HAE attack (HAEATTACK) during the baseline (for non-rollover subjects) evaluation period and while on treatment (both rollover and non-rollover subject)
- Baseline number of HAE attacks over a 28-day period (THAERIN). NOTE: A month is defined as a 4 week period or 28 days;
    - Baseline for the rollover population is defined as the number of investigator-confirmed HAE attacks occurring during the run-in period of DX2930-03 divided by the total number of days in the run-in period multiplied by 28 days;
    - Baseline for the non-rollover population is defined as historical rate of HAE attacks in the last 3 months prior to screening divided by the number of days the subject contributed to the historical reporting period multiplied by 28 days.
- Monthly number of HAE attacks with lanadelumab (each month will be represented by a unique column (e.g. THAEMONTH1 to THAEMONTH13). NOTE: A month is defined as a 4 week period or 28 days.
- Total number of HAE attacks on treatment (THAETRT)
- Number of attack free days from the last dose of study drug in DX-2930-03 to the first dose in DX-2930-04 for rollover subjects (left blank for non-rollover subjects)
- Number of attack free days after the first dose (300 mg) for rollover subjects left blank for non-rollover subjects)

8.3 Subjects with Long Drug Interruptions

For subjects with extended drug interruptions (defined as missing ≥3 consecutive study medication doses), the time period and the corresponding PK, PD, ADA and efficacy (HAE) will be excluded from the analysis. A footnote indicating the numbers of subjects excluded will be included for each table and figure)

9 DATA SUMMARIZATION

9.1 PK, PD, HAE and ADA Data Summarization

Pharmacokinetics (Lanadelumab Concentrations)

For rollover subjects, blood samples for the measurement of lanadelumab concentrations were collected 1) prior to receiving a single open-label dose of 300 mg on Day 0, 2) after reporting a first HAE attack (second open label dose), and 3) at pre-specified scheduled visits following initiation of the Q2W 300 mg regimen(Visit 8, 14, 20, 27, 34, 42, 50, 58, 66 and 67; corresponding to Days 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924). Mean (+SD) lanadelumab concentrations will be presented for 1) the first open-label dose (day 0) by treatment assignment in study DX-2930-03, 2) for the second open-label dose at scheduled visits (±4 days) by treatment assignment in Study DX-2930-03. In addition, mean (+SD) lanadelumab concentrations will be presented after combining the second open-label dose at scheduled visits (±4 days) and time following initiation of Q2W 300 mg regimen (Day 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924). A footnote will be added to determine if any of the second open-label doses were administered at scheduled visits (Day 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924).

For non-rollover subjects, blood samples for the measurement of SHP643 concentrations were collected at baseline (Day 0) and at pre-specified scheduled visits (Visit 8, 14, 20, 27, 34, 42, 50, 58, 66 and 67; corresponding to Days 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) following initiation of Q2W 300 mg regimen. For non-rollover subjects, mean (+SD) concentrations of lanadelumab vs. Time (Day 0, 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) will be presented.

In addition, all the above analyses will be presented overall, and by age group (adult and pediatric population).

Individual data will be presented in tabular format by time (nominal visit day) and summarized with descriptive statistics (Arithmetic mean, standard deviation, arithmetic CV%, median, minimum and maximum). Any unscheduled results will be reported in subject listings.

Pharmacodynamics (cHMWK)

PD samples were collected at similar timepoint as PK (refer to section above). In rollover subjects, mean (+SD) of cHMWK levels (bar charts) will be presented for 1) the first open-label dose (day 0) by treatment assignment in study DX-2930-03, 2) for the second open-label dose at scheduled visits (±4 days) by treatment assignment in Study DX-2930-03 and 3) after combining the second open-label dose at scheduled visits (±4 days) and time (Day 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) following initiation of Q2W 300 mg Regimen.

For non-rollover subjects, mean (+SD) of cHMWK levels (bar charts) vs. Time (Day 0, 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) will be presented.

A similar presentation will be used for the percent (%) change from baseline cHMWK.

In addition, all the above analyses will be presented overall, and by age group (adult and pediatric population).

Individual data of cHMWK (raw and percent change from baseline) will be presented in tabular format by time (nominal visit day) and summarized with descriptive statistics (Arithmetic mean, standard deviation, arithmetic CV%, median, minimum and maximum). Any unscheduled results will be reported in subject listings.

HAE Attacks

The number of HAE attack by month with sample size will be presented for rollover and non-rollover subjects. In addition, the rate of HAE attack by month will be presented for rollover and non-rollover subjects.

For rollover subjects, the number of days without HAE attack will be summarized graphically and in tabular formats by treatment assignment in study DX-2930-03 (Placebo, 150 mg Q4W, 300 mg Q4W, and 150 mg Q2W).

All the above analyses will be presented overall, and by age group (adult and pediatric population).

Any unscheduled assay results will be reported in a subject listing.

9.2 PK, PD, ADA and HAE (Overlaid Information)

PK and PD Summary Figures

In rollover subjects, mean (+SD) concentrations of lanadelumab and cHMWK values (overlaid) will be presented for 1) the first open-label dose (day 0) by treatment assignment in study DX-2930-03, 2) for the second open-label dose at scheduled visits (±4 days) by treatment assignment in Study DX-2930-03 and 3) after combining the second open-label dose at scheduled visits (±4 days) and time (Day 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) following initiation of Q2W 300 mg regimen. For non-rollover subjects, mean (+SD) concentrations of lanadelumab and cHMWK values (overlaid) vs. Time (Day 0, 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) will be presented.

PK and ADA Summary Figures

In rollover subjects, mean (+SD) concentrations of lanadelumab and ADA status (confirmed ADA positive and non-positive) will be presented for the first open-label dose (day 0) by treatment assignment in study DX-2930-03 and for the second open-label dose at scheduled visits (±4 days) by treatment assignment in Study DX-2930-03 using bar charts. In addition, individual concentrations of lanadelumab in confirmed ADA positive and non-positive subjects will be presented after combining the second open-label dose at scheduled visits (±4 days) and time (Day 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) following initiation of Q2W 300 mg regimen.

In non-rollover subjects, individual concentrations of lanadelumab in confirmed ADA positive and non-positive subjects will be presented vs. Time (Day 0, 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) will be presented.

A similar presentation will be used for subjects with positive or non-positive neutralizing antibody (NAb). All the above analyses will be presented overall, and by age group (adult and pediatric population).

PD and ADA Summary Figures

A similar approach as described in "PK and ADA Summary Figures" will be used for PD and ADA figures.

PK, PD and HAE Attack Summary Figures

For rollover subjects, mean (+SD) lanadelumab concentrations vs. time following initiation of Q2W 300 mg regimen and monthly HAE attack rate (Day 98, 182, 266, 364, 462, 574, 686, 798, 910 and 924) will presented. For non-rollover subjects, mean (+SD) lanadelumab concentrations vs. time following initiation of Q2W 300 mg regimen and monthly HAE attack rate (run-in, Day 98, 182, 266, 364, 462, 574, 686, 798,

910 and 924) will presented.

In addition, a correlation figure for individual lanadelumab concentrations associated with the first open-label dose (day 0) and days without HAE attack by treatment assignment in Study DX-2930-03 will presented for rollover subjects. A similar analysis will be performed for the second open-label dose at scheduled visits (±4 days).

A similar approach as described above will be used for mean (+SD) and cHMWK levels.

PK, PD, and HAE Attack Individual Figures

Individual profiles of PK, PD and HAE will be presented graphically to explore potential correlations.

10 FORMATTING ELEMENTS FOR TABLES, LISTINGS AND FIGURES

- %2-Chain cHMWK will be abbreviated as cHMWK in plots
- Concentration vs. time plots (lanadelumab and/or cHMWK) will include a closed circle to represent the observation; sequential observations will be joined by a solid line.
- For descriptive figures and tables, where applicable, sample size will be noted either within the plot or as a caption/footnote associated with the plot
- Overlay plots of different observations types will be color coded such that closed circles and line colors are observation specific.
- Footnotes are not to be imbedded in images/plots and should be editable text outside of the embedded image

11 SOFTWARE

Dataset construction, exploration and figures will be performed using Phoenix NLME (Version 7.2 or higher), R® (Version 3.3.1 or higher) or SAS.

12 ELECTRONIC DATASETS

Consistent with FDA's requirements, datasets used for data summarization will be submitted as a SAS transport files (*.xpt). A description of each data item will be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis will be flagged and maintained in the datasets. Data definition documentation ("define.pdf" file) of the datasets used for the population PK analysis will be provided. The data definition documentation will include analysis-ready datasets used for

model development and validation in SAS transport file (*.xpt) format. A document describing the analysis-ready datasets and variables will be provided (that is, define.pdf file).

13 QUALITY CONTROL

Quality control of datasets will include high quality data visualizations, data driven exploratory analysis (e.g. concentration-time profiles, dosing history plots, time after dose analysis, and graphical display of goodness of fit such as distribution of weighted residuals, etc.), descriptive statistics, and stratification of information and/or code review. Random checks of the output dataset will be performed against the raw data to check programming logic where complex imputations/derivations are involved.

14 ARCHIVING

The project documentation (documents, report, records, and data) will be retained in hardcopy for a period of 3 years following project completion at CSC (Montreal, Quebec, Canada). During these retention periods, electronic versions of project documentation will be retained on CSC servers, with access limited to personnel assigned to the project. After completion of the retention period, sponsor approval will be requested and documented before destruction of documents.

15 REFERENCES

1. Study Number: DX-2930-04. HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) Amendment 3.0, 29 June 2017.

16 LIST OF TABLES, FIGURES AND LISTINGS

1- SUMMARY FIGURES - PK, PD, ADA, and HAE

Mean Concentration-Time Profiles of Lanadelumab

Mean Levels of cHMWK

Mean cHMWK Values (% Change from Baseline)

Summary of HAE Attacks over Time

Figure 14.13. Number of Hereditary Angioedema Attacks by Month with Sample Size - Rollover Subjects

Figure 14.14. Number of Hereditary Angioedema Attacks by Month with Sample Size- Non-Rollover Subjects

Figure 14.15. Rates of Hereditary Angioedema Attacks by Month - Rollover Subjects

Figure 14.16. Rates of Hereditary Angioedema Attacks by Month – Non-Rollover Subjects

Figure 14.17. Mean (+SD) Hereditary Angioedema Attack Free Days After the First Open Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

2- SUMMARY FIGURES– PK, PD, ADA, and HAE (Overlaid)

Summary PK and PD Figures

Figure 14.18. Mean (+SD) Lanadelumab Concentrations and cHMWK Levels Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.19. Mean (+SD) Lanadelumab Concentrations and cHMWK Levels Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.20. Individual Lanadelumab Concentrations and cHMWK Levels vs. Time (Starting from the First or Second Open-Label Dose) - Rollover Subjects

Figure 14.21. Individual and Mean (+SD) Lanadelumab Concentrations and cHMWK Levels vs. Time - Non-Rollover Subjects

Summary PK and ADA Figures

Figure 14.22. Mean (+SD) Lanadelumab Concentrations in Confirmed Anti-Drug Antibody Positive and Non-Positive Subjects Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.23. Mean (+SD) Lanadelumab Concentrations in Confirmed Anti-Drug Antibody Positive and Non-Positive Subjects Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.24. Individual Lanadelumab Concentrations vs. Time in Confirmed Anti-Drug Antibody Positive and Non-Positive Subjects (Starting from the First or Second Open-Label Dose) - Rollover Subjects

Figure 14.25. Individual and Mean (+SD) Lanadelumab Concentrations vs. Time in Confirmed Anti-Drug Antibody Positive and Non-Positive Subjects - Non-Rollover Subjects

Figure 14.26. Mean (+SD) Lanadelumab Concentrations in Neutralizing Positive and Non-Positive Subjects Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.27. Mean (+SD) Lanadelumab Concentrations in Neutralizing Positive and Non-Positive

Summary PD and ADA Figures

Summary PK, PD and HAE Attacks Figures

Figure 14.40. Individual cHMWK Levels and Monthly Hereditary Angioedema Attack Rates vs. Time From Initiation of the 300 mg every 2 weeks Regimen (Starting from the Second Open-Label Dose) - Rollover Subjects

Figure 14.41. Individual cHMWK Levels and Monthly Hereditary Angioedema Attack Rates vs. Time From Initiation of the 300 mg every 2 weeks Regimen (Starting from the Second Open-Label Dose) - Non-Rollover Subjects

Figure 14.42. Individual Lanadelumab Concentrations Prior to the First Open-Label Dose (Day 0) vs. Hereditary Angioedema Attack Free Days Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.43. Individual Lanadelumab Concentrations Prior to the Second Open-Label Dose vs. Hereditary Angioedema Attack Free Days Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.44. Individual cHMWK Levels Prior to the First Open-Label Dose (Day 0) vs. Hereditary Angioedema Attack Free Days Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Figure 14.45. Individual cHMWK Levels Prior to the Second Open-Label Dose vs. Hereditary Angioedema Attack Free Days Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Note: the above summary PK and PD/ADA/HAE Figures(14.1 to 14.45) will be presented overall and stratified by age categories (<18 and ≥ 18 years)

3- SUMMARY TABLES

Summary Tables of Lanadelumab Concentrations

Table 14.1. Descriptive Statistics of Lanadelumab Concentrations Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.2. Descriptive Statistics of Lanadelumab Concentrations - Rollover Subjects

Table 14.3. Descriptive Statistics of Lanadelumab Concentrations vs. Time - Non-Rollover Subjects

Summary Tables of cHMWK Levels (%)

Table 14.4. Descriptive Statistics of cHMWK Levels Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.5. Descriptive Statistics of cHMWK Levels - Rollover Subjects

Table 14.6. Descriptive Statistics of cHMWK Levels vs. Time - Non-Rollover Subjects

Summary Tables of cHMWK Percent Change from Baseline Levels (%)

Table 14.7. Descriptive Statistics of cHMWK Percent Change from Baseline Levels Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.8. Descriptive Statistics of cHMWK Percent Change from Baseline Levels - Rollover Subjects

Table 14.9. Descriptive Statistics of cHMWK Percent Change from Baseline Levels vs. Time - Non-Rollover Subjects

Summary Measurements Tables (ADA)

Table 14.10. Descriptive Statistics of Confirmed Positive Anti-Drug Antibody Samples Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.11. Descriptive Statistics of Confirmed Positive Anti-Drug Antibody Samples Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.12. Descriptive Statistics of All Confirmed Positive Anti-Drug Antibody Samples From Initiation of the 300 mg every 2 weeks Regimen (Starting from the Second Open-Label Dose) - Rollover Subjects

Table 14.13. Descriptive Statistics of Confirmed Positive Anti-Drug Antibody Samples vs. Time - Non-Rollover Subjects

Table 14.14. Descriptive Statistics of Neutralizing Positive Samples Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.15. Descriptive Statistics of Neutralizing Positive Samples Prior to the Second Open-Label Dose by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.16. Descriptive Statistics of All Neutralizing Positive Samples From Initiation of the 300 mg every 2 weeks Regimen (Starting from the Second Open-Label Dose) - Rollover Subjects

Table 14.17. Descriptive Statistics of Neutralizing Positive Samples vs. Time - Non-Rollover Subjects

Summary Measurements Tables (HAE Attacks)

Table 14.18. Summary of Time to First Hereditary Angioedema Attack (after First Open-Label Dose) by Study DX-2930-03 Treatment Assignment - Rollover Subjects

Table 14.19. Summary of Hereditary Angioedema Attacks by Month, Total Number of Attacks on Treatment and Average Attack Rate - Rollover Subjects

Table 14.20. Summary of Hereditary Angioedema Attacks by Month, Total Number of Attacks on Treatment and Average Attack Rate - Non-Rollover Subjects

Note: the above summary PK, PD, ADA and HAE Tables(14.1 to 14.20) will be presented overall and stratified by age categories (<18 and ≥ 18 years)

4- INDIVIDUAL PROFILES

Individual PK, PD and Efficacy Figures

Figure 16.1. Individual Lanadelumab Concentrations, cHMWK Levels and Hereditary Angioedema Attacks vs. Time

Figure 16.2. Individual Lanadelumab Concentrations, Percent Change from Baseline cHMWK Levels and Hereditary Angioedema Attacks vs. Time

Individual PK, ADA and Efficacy Figures

Figure 16.3. Individual Lanadelumab Concentrations, Confirmed Anti-Drug Antibody and Hereditary Angioedema Attacks vs. Time

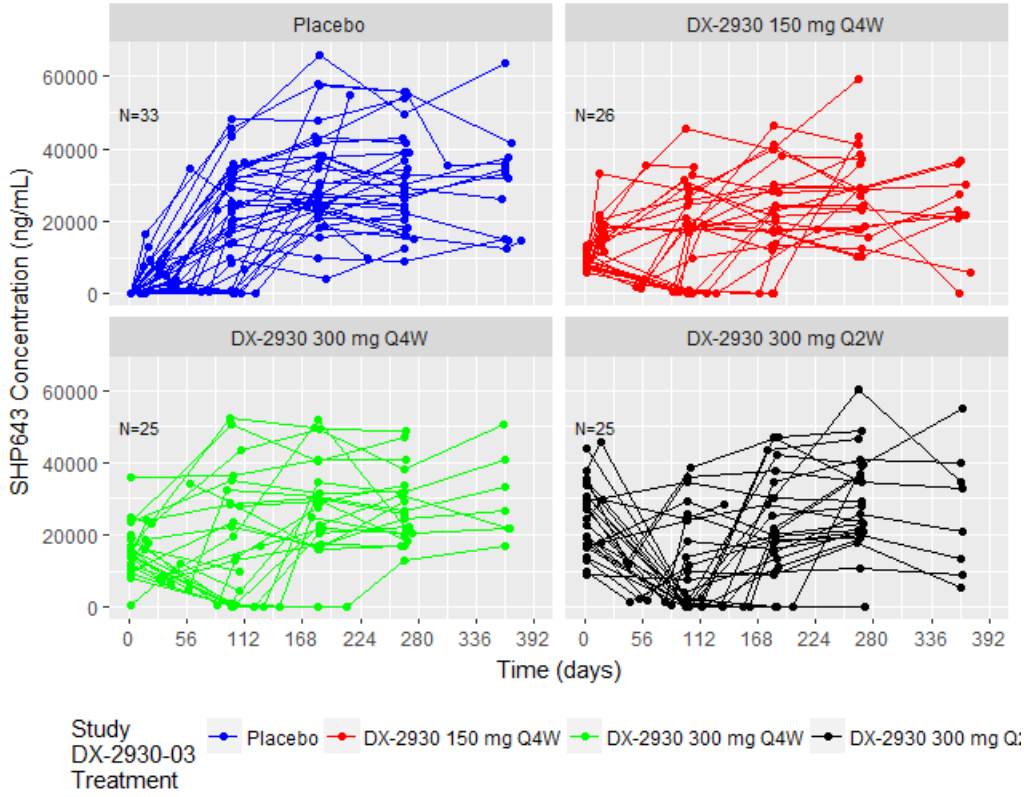
Figure 16.4. Individual Lanadelumab Concentrations, Neutralizing Antibody and Hereditary Angioedema Attacks vs. Time

5- LISTINGS OF INDIVIDUAL MEASUREMENTS

Figure 16.5. Individual Pharmacokinetics, Pharmacodynamics (cHMWK), Anti-Drug Antibody Values and Hereditary Angioedema Attacks vs. Time

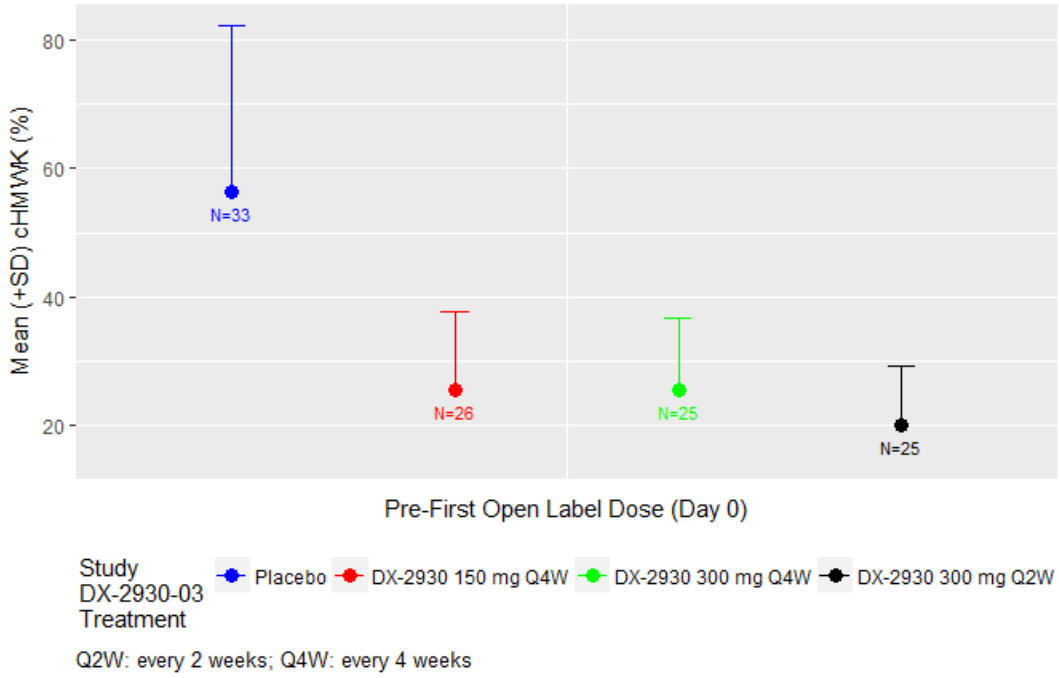
17 TABLE AND FIGURE SHELLS

Figure 14.3. Individual Lanadelumab Concentrations vs. Time (Starting from the First Open-Label Dose) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)



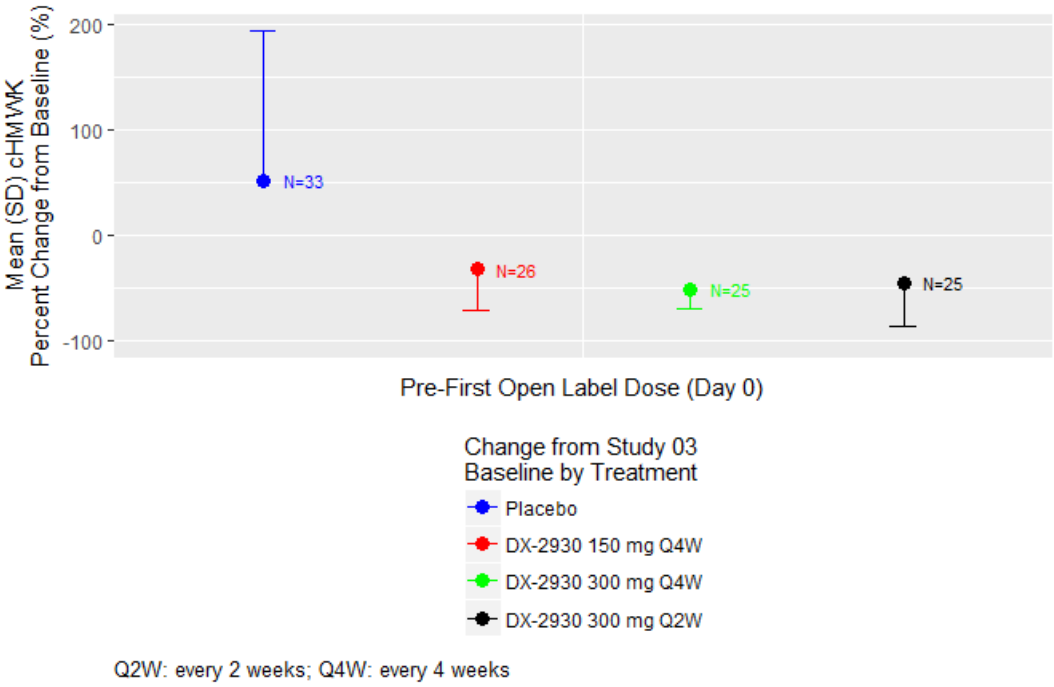
Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.5. Mean (+SD) cHMWK Levels Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)



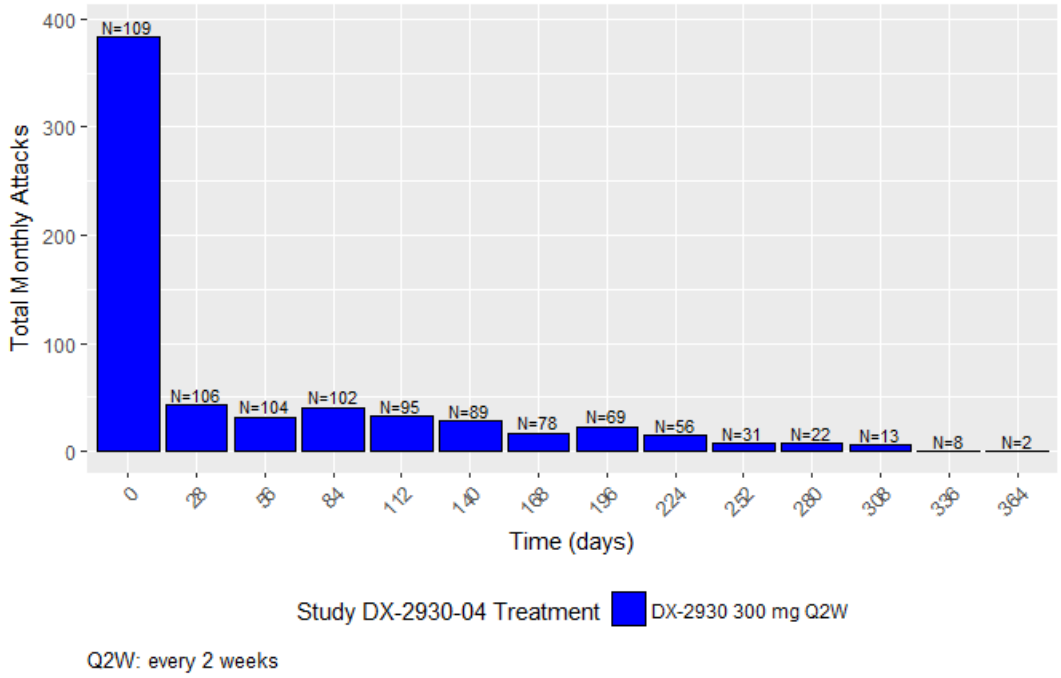
Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.9 Mean (SD) Percent Change of cHMWK from Study 03 Baseline Levels Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)



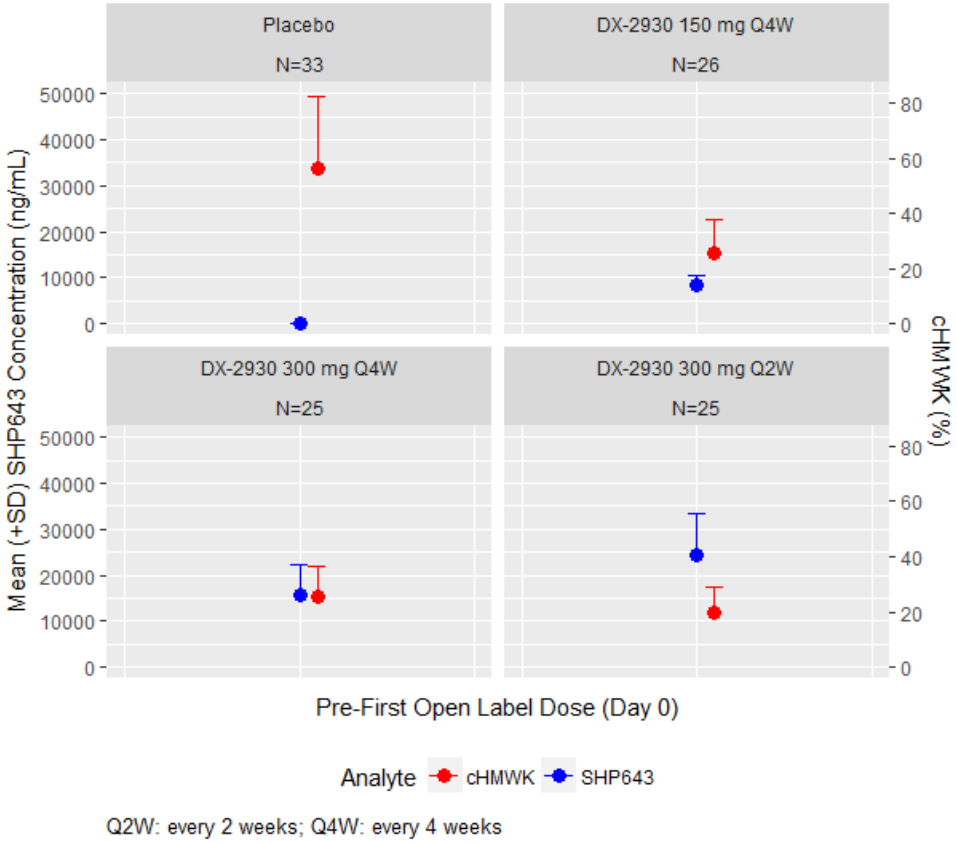
Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.13. Number of Hereditary Angioedema Attacks by Month with Sample Size - Rollover Subjects (Overall)



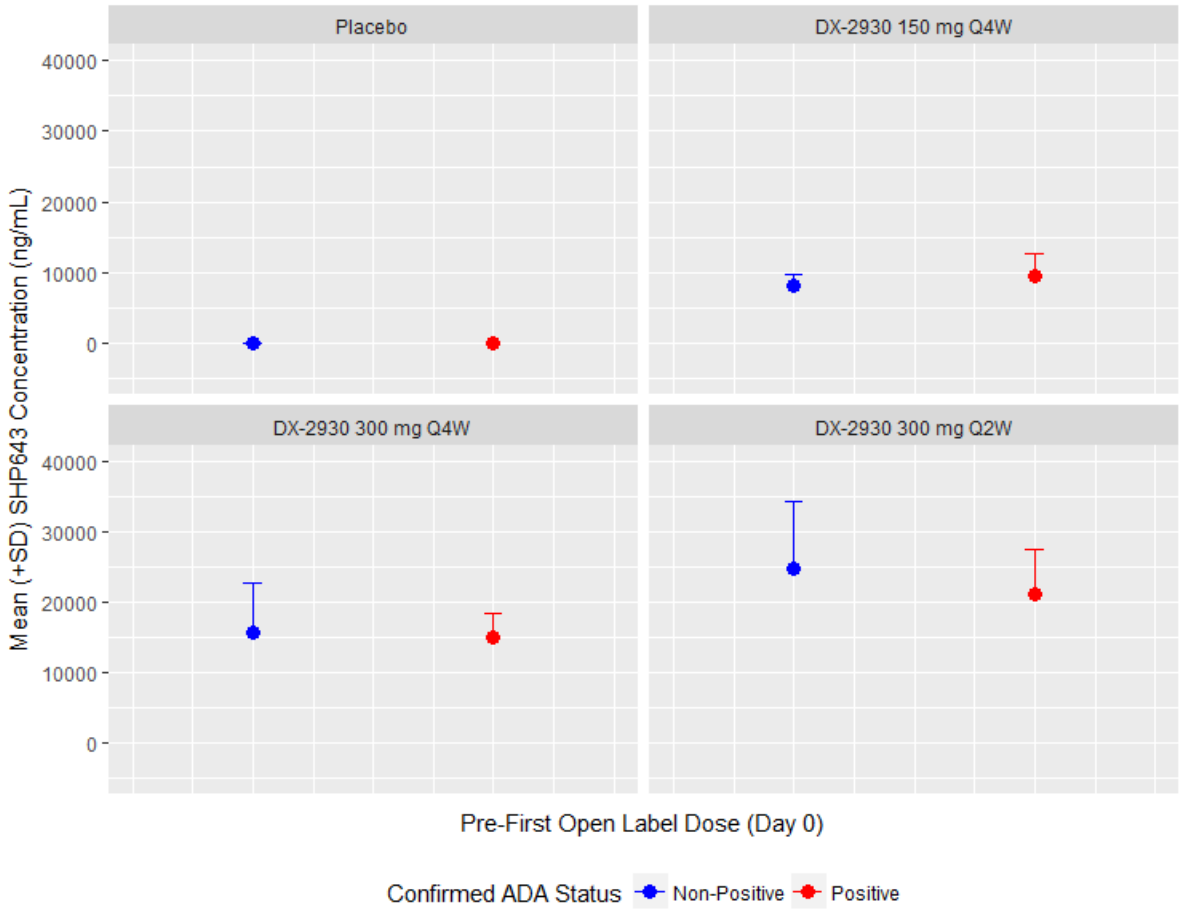
Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.18. Mean (+SD) Lanadelumab Concentrations and cHMWK Levels Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)



Note: These are for presentation purpose, axis titles and range will be set accordingly.

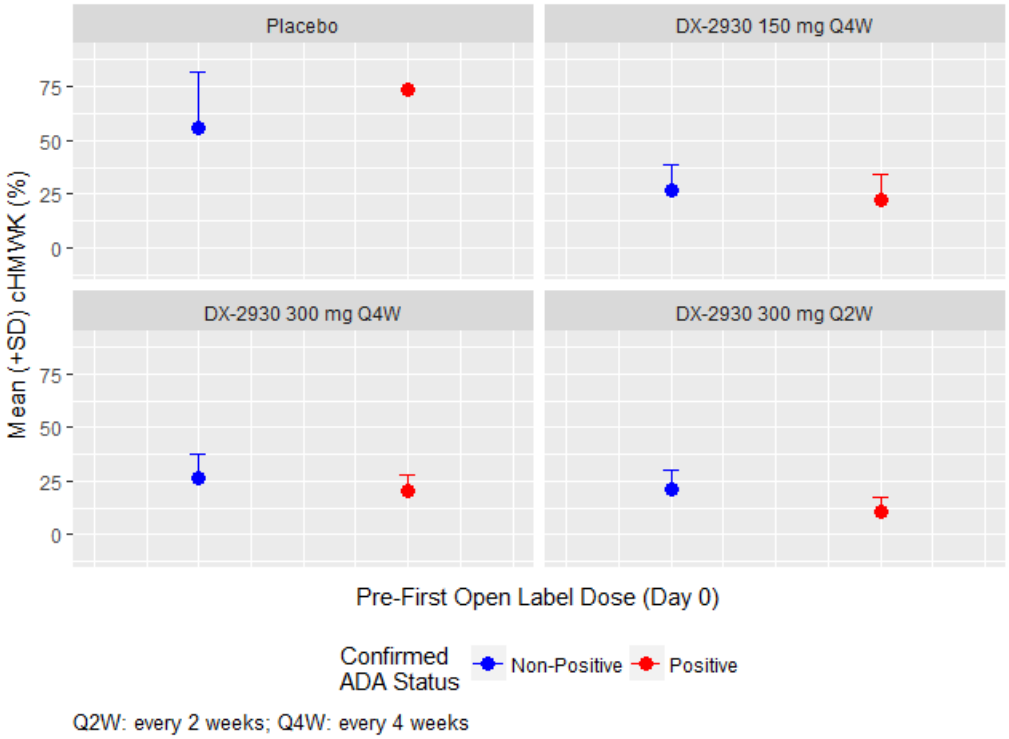
Figure 14.22. Mean (+SD) Lanadelumab Concentrations in Confirmed Anti-Drug Antibody Positive and Non-Positive Subjects Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)



Q2W: every 2 weeks; Q4W: every 4 weeks

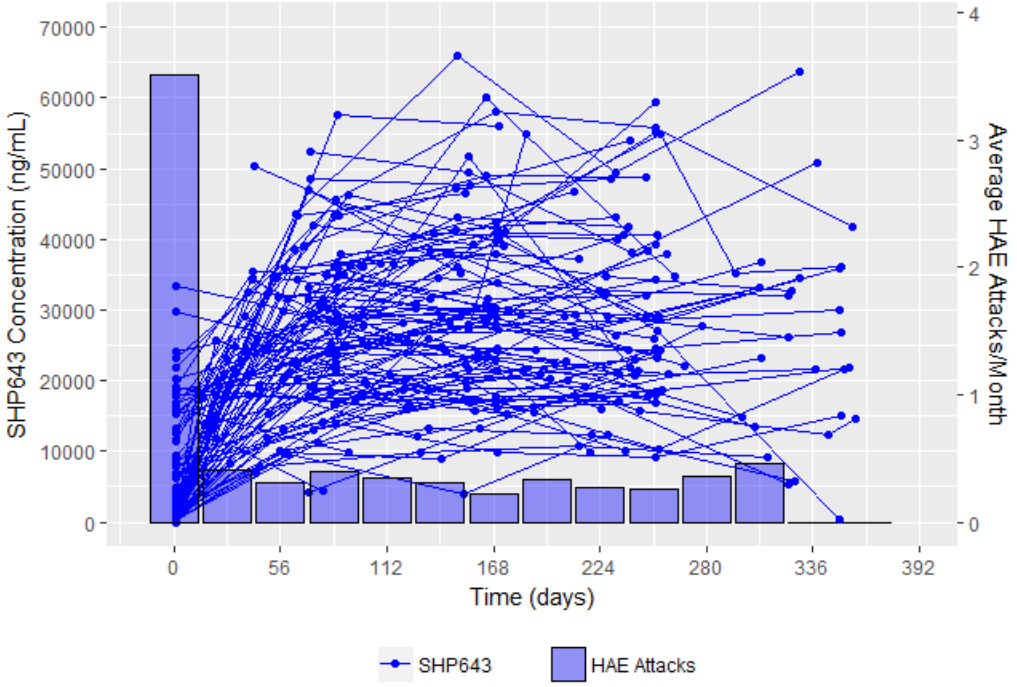
Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.30. Mean (+SD) cHMWK Levels in Confirmed Anti-Drug Antibody Positive and Non-Positive Subjects Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)



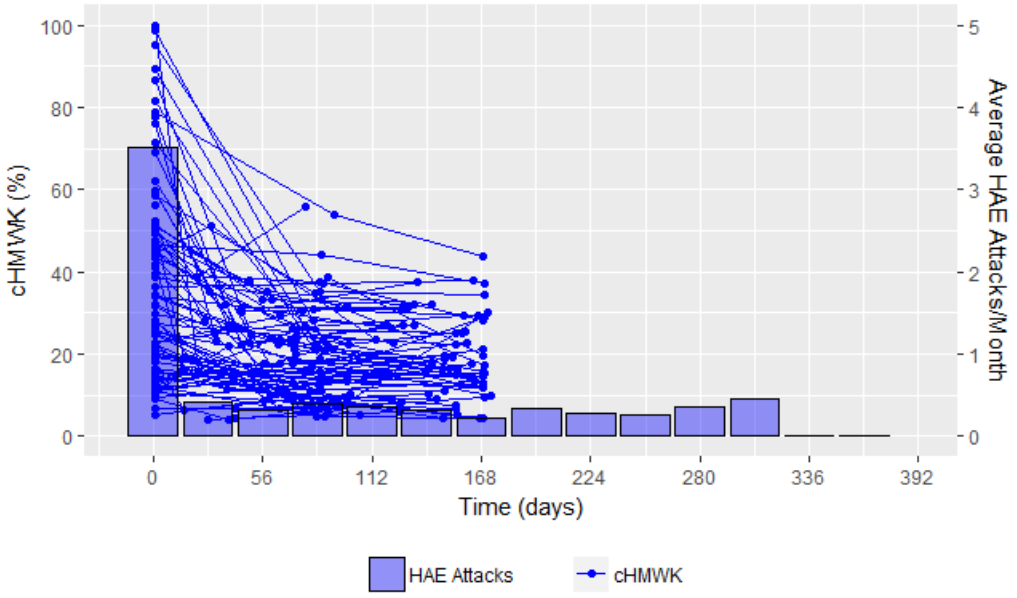
Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.38. Individual Lanadelumab Concentrations and Monthly Hereditary Angioedema Attack Rates vs. Time From Initiation of the 300 mg every 2 weeks Regimen (Starting from the Second Open-Label Dose) - Rollover Subjects (Overall)



Note: These are for presentation purpose, axis titles and range will be set accordingly.

Figure 14.40 Individual cHMWK Levels and Monthly Hereditary Angioedema Attack Rates vs. Time From Initiation of the 300 mg every 2 weeks Regimen (Starting from the Second Open-Label Dose) - Rollover Subjects (Overall)



Note: These are for presentation purpose, axis titles and range will be set accordingly.

Summary Measurements Tables (PK, ADA, and HAE)

Table 14.2 Descriptive Statistics of Lanadelumab Concentrations Following Study Initiation and After the Second Open-Label Dose - Rollover Subjects (Overall)

Lanadelumab (ng/mL)	DAY 98 WEEK 14 (n=xx)	DAY 182 WEEK 26 (n=xx)	DAY 266 WEEK 38 (n=xx)	DAY 364 WEEK 52 (n=xx)	DAY … WEEK ... (n=…)
Mean					
SD					
SE					
CV%					
GeoMean					
GeoCV%					
Median					
Min					
Max					

Note: similar tables will be used to summarize cHMWK raw and change from baseline concentrations

Table 14.10 Descriptive Statistics of Confirmed Positive Anti-Drug Antibody Samples Prior to the First Open-Label Dose (Day 0) by Study DX-2930-03 Treatment Assignment - Rollover Subjects (Overall)

Treatment	Day	Not Positive	Positive	Total	Percent Positive

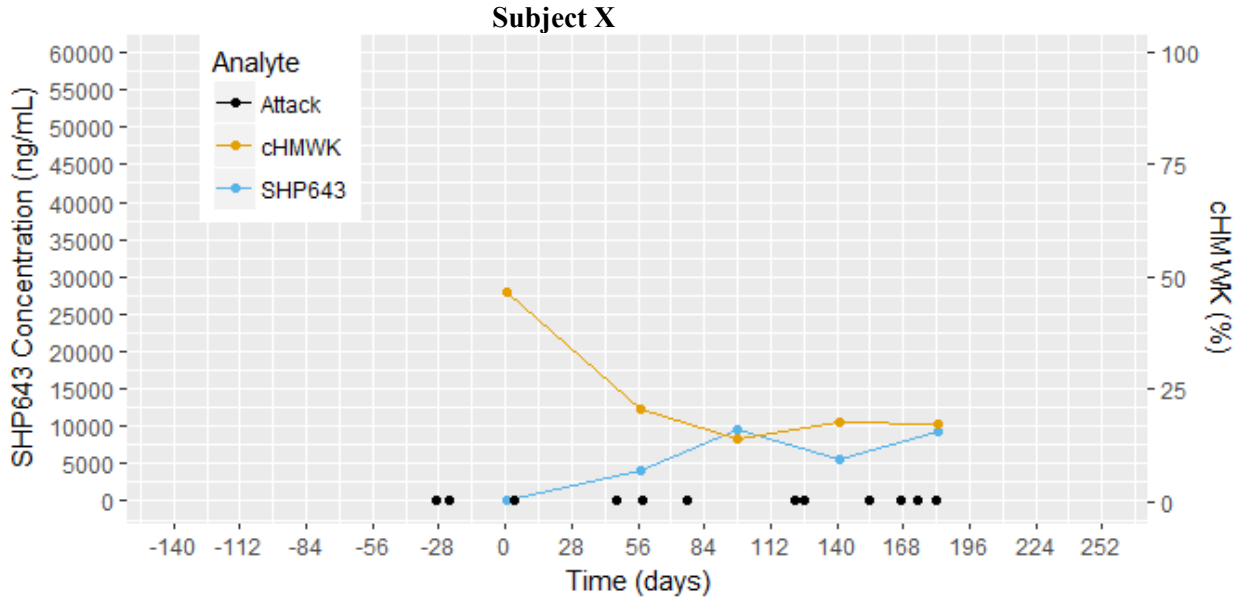
Note: Similar tables will be used to summarize positive NAb

Table 14.19 Summary of Hereditary Angioedema Attacks by Month, Total Number of Attacks on Treatment and Average Attack Rate - Rollover Subjects (Overall)

Subject	Treatment	1	2	3	4	5	6	7	8	9	Total	Description
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
…												

Individual PK, PD (cHMWK) and Efficacy Figures

Figure 16.11: Individual Lanadelumab Concentration, PD (cHMWK) and HAE Attacks vs. Time by Treatment



cHMWK: cleaved high molecular weight kininogen;
HAE: hereditary angioedema;
HAE attacks were investigator-confirmed.
Source: SHP643 from ADPC, cHMWK from ADLB and HAE from AE and SUPPAE SDTM

Listings of Individual Measurements

Listing 16.1 Individual Pharmacokinetics, Pharmacodynamics (cHMWK), Anti-Drug Antibody Values and Hereditary Angioedema Attacks vs. Time

Subject	Day	Cohort	Treatment	Study 03 Treatment	Visit	Age Category	Lanadelumab (ng/mL)	cHMWK (%)	% CFB cHMWK (%)	Confirm	NAb	Titer (ng/mL)	HAE Attack
1													
1													
1													
1													
1													
2													
2													
2													
2													
2													
2													

Confirm: Confirmatory ADA results; Nab: Neutralizing antibody result; NS: No sample