BIOCRYST PHARMACEUTICALS INC.
STATISTICAL ANALYSIS PLAN
PHASE III

VERSION: 1.0

DATE OF PLAN:

29 January 2019

BASED ON:

Protocol Version 2.0: 11 October 2018

CRF Version 22.0, 9 January 2019

STUDY DRUG:

BCX7353

PROTOCOL NUMBER:

BCX7353-302

IND No. 135,058

EudraCT No. 2017-003966-29

STUDY TITLE:

A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema

SPONSOR:

BioCryst Pharmaceuticals, Inc.
4505 Emperor Blvd., Suite 200
Durham, NC 27703
Phone: (919) 859-1302
Fax: (919) 851-1416

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

Sharon C. Murray, PhD
Author
Director, Biostatistics
BioCryst Pharmaceuticals, Inc.

Sharon C. Murray
Signature

29 Jan 2019
Date

Jennifer A. Elder, PhD
Reviewer
Chief Scientific Officer
PharPoint Research, Inc.

DocuSigned by:
Signer Name: Jenna Elder
Signing Reason: I approve this document
Signing Time: 29-Jan-2019 | 15:15 EST
0C6DF25C6D2E4441A51A3F798A29BD1C
Signature

29-Jan-2019 | 15:15 PM EST
Date

This document has been reviewed and accepted by:

Sylvia Dobo, MD
Vice President, Medical and Safety
BioCryst Pharmaceuticals, Inc.

Signature

29 JAN 2019
Date

Elliott Berger, PhD
Senior Vice President, Regulatory Affairs
BioCryst Pharmaceuticals, Inc.

Nicole M Yale for
Signature

29 Jan 2019
Date

Melanie Cornpropst, PhD
Vice President, Clinical Development
BioCryst Pharmaceuticals, Inc.

Melanie Cornpropst
Signature

29 Jan 19
Date

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company BioCryst Pharmaceuticals, Inc	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: BCX7353	**Page:**	
Name of Active Ingredient: (R)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride		
Title of Study: A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema (Study BCX7353-302)		
Investigators: **Study Centers:** Multiple study centers in North America and Europe		
Studied Period (years): **Approximately 2 years 11 months** (approximately a 9-month enrollment period plus approximately 2 months of screening and 2 years of treatment)		

Objectives:

Part 1 Primary Objective

- To determine the efficacy of prophylactic BCX7353 110 mg and 150 mg administered once daily (QD) for 24 weeks compared to placebo in subjects with hereditary angioedema (HAE)

Part 1 Secondary Objectives

- To assess the safety and tolerability of BCX7353 110 mg and 150 mg administered QD for 24 weeks
- To assess the effects of BCX7353 on HAE disease activity and HAE attack characteristics
- To evaluate the effects of BCX7353 on quality of life (QoL)
- To characterize the pharmacodynamic effects of BCX7353

Part 2 Primary Objective

- To evaluate the long-term safety and tolerability of BCX7353 110 mg and 150 mg administered QD over a 24- to 48-week administration period in subjects with HAE

Part 2 Secondary Objectives

- To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 24- to 48-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 24- to 48-week administration period
- To evaluate subject satisfaction with BCX7353 over a 24- to 48-week administration period

Part 3 Primary Objectives

- To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 48- to 96-week administration period in subjects with HAE

Part 3 Secondary Objectives

- To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 48- to 96-week administration period

- To evaluate QoL and HAE disease activity of BCX7353 over a 48- to 96-week administration period
- To evaluate subject satisfaction with BCX7353 over a 48- to 96-week administration period

Methodology:

This is a randomized, placebo-controlled, double-blind, parallel-group, 3-part study. Part 1 is designed to test the hypothesis that the HAE attack rate during 24 weeks of prophylactic BCX7353 treatment at each of 2 dosage levels will be less than that observed during 24 weeks of placebo. The primary efficacy endpoint will be assessed after the last subject completes Part 1 (through Week 24). Part 2 is designed to primarily evaluate the long-term safety of BCX7353 at 2 dosage levels. Part 3 is open-label and designed to primarily evaluate the long-term safety of BCX7353. Parts 1, 2, and 3 will be conducted in sequence, with Parts 2 and 3 conducted as continuous rollovers from Parts 1 and 2, respectively. All subjects will receive BCX7353 in Parts 2 and 3, including those randomized to receive placebo in Part 1.

Part 1 (24-week evaluation of blinded efficacy and safety)

Subjects with HAE Type 1 or 2 will be eligible for the study following assessment of data obtained from screening procedures, including demonstration of a minimum number of attacks documented during a prospective run-in period of 2 to 8 weeks from the date of the screening visit.

Treatment-eligible subjects will receive study drug (BCX7353 or placebo) in Part 1 of the study based on randomization in a 1:1:1 ratio into 1 of 3 treatment groups:

- Group 1: BCX7353 110 mg administered orally QD for 24 weeks
- Group 2: BCX7353 150 mg administered orally QD for 24 weeks
- Group 3: Placebo administered orally QD for 24 weeks

Enrollment into treatment groups will be stratified by the baseline HAE attack rate ($\geq$ 2 attacks/month vs. $<$ 2 attacks/month).

Details of acute attacks of angioedema will be recorded in an electronic diary (e-diary). Attacks will be treated in accordance with the subject's normal standard of care. Treatment medications for angioedema attacks will not be provided by the Sponsor.

Within approximately 2 business days of the end of each attack that occurs beginning at the screening visit through the follow-up visit after Part 2, subjects will be contacted by the Investigator to discuss the clinical characteristics of the attack, any questions the Investigator has on the entered data or to gain additional attack details not included in the e-diary that the Investigator deems important to clinically evaluate the event, as applicable. This information, in conjunction with the e-diary record, will be used by the Investigator to verify or reject the event recorded in the diary as an HAE attack. All Investigator-confirmed attacks of HAE must include symptoms of swelling; prodromal symptoms in the absence of swelling are not considered HAE attacks, regardless of treatment. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling.

The main study will be comprised of adult subjects ($\geq$ 18 years of age); a substudy in participating regions will allow adolescent subjects $\geq$ 12 to 17 years of age to participate. Main study and substudy subjects will be randomized via a separate randomization scheme; however, study-mandated procedures will be identical, and analyses will include all subjects who participate in the study.

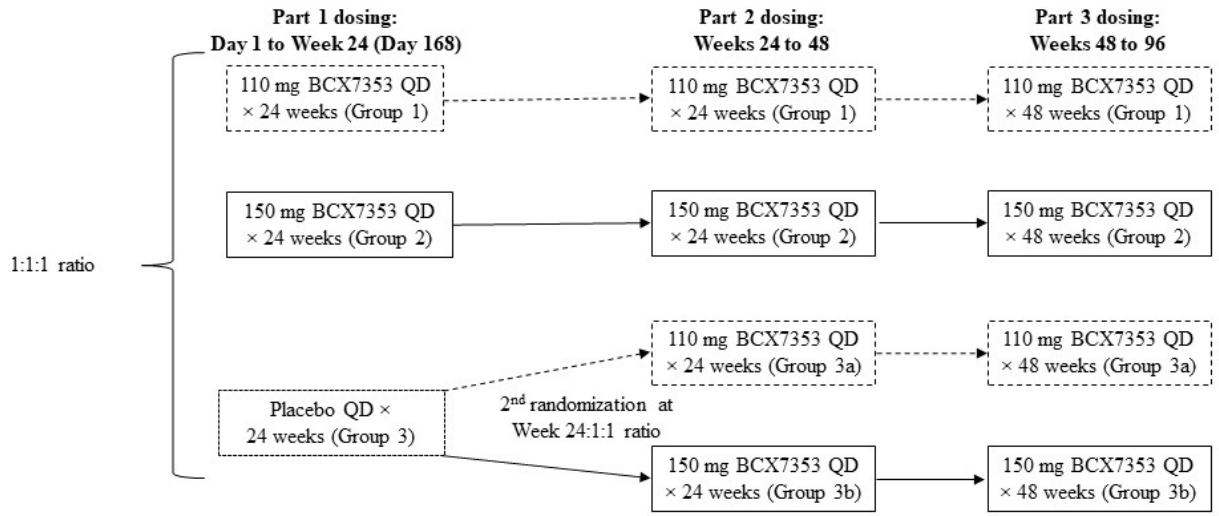
Safety and tolerability will be evaluated through assessments of treatment-adverse events (TEAEs), laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, electrocardiograms, and physical examinations.

Study visits in Part 1 will occur at screening, baseline and Weeks 2, 4, 8, 12, 18, and 24. The primary efficacy analysis will occur after the last subject completes the Week 24 visit and will include all data through Week 24. Subject treatment will remain blinded to the subject, site, and Sponsor staff who interact with sites during Part 2.

Part 2 (24-week evaluation of safety of blinded BCX7353)

Part 2 of the study will start with the administration of study drug dispensed at the Week 24 visit. Subjects in Groups 1 and 2 will continue to receive the same BCX7353 dose to which they were randomized in Part 1 of the study in a blinded manner. Subjects randomized to Group 3 will undergo a second randomization in a 1:1 ratio to receive either a 110 mg or 150 mg dose in a blinded manner beginning at the Week 24 visit (see figure below).

The active dose a subject receives in Part 2 will be blinded for all subjects; subjects will be informed that they will receive an active dose of BCX7353 in Part 2.



Study visits during Part 2 will occur during Weeks 26, 28, 32, 36, and 48 with telephone contacts at Weeks 40 and 44. Subjects will continue to document all angioedema attacks that occur while on study drug in their e-diary and will have regular visits to assess safety and tolerability; Investigator confirmation of angioedema attacks will continue to be required for Part 2. Interim safety analyses will be conducted while Part 2 is ongoing to support regulatory filings.

Part 3 (48-week evaluation of safety of open-label BCX7353)

Part 3 of the study will start with the administration of the study drug dispensed at the Week 48 visit. Subjects will continue to receive the same BCX7353 dose in Part 3 as received in Part 2 but in an open-label manner. Once results from the Part 1 analysis, are available, all subjects in Part 3 may be moved to a single dose level of BCX7353, based on the data from Part 1, if appropriate.

Study visits during Part 3 will occur during Weeks 60, 72, 84, and 96, with telephone contact at Weeks 52, 56, 64, 68, 76, 80, 88, and 92. A final study follow-up visit will be scheduled approximately 3 weeks following the last administration of study drug (Week 99). Investigator confirmation of attacks will not be required in Part 3. All attacks recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in the effectiveness analyses. These rules are outlined in this Statistical Analysis Plan.

Number of Subjects (planned and analyzed):

Approximately 120 subjects will be enrolled in this study (n = 40 per Part 1 dose group). This includes any adolescent subjects enrolled in the substudy.

Diagnosis and main criteria for inclusion:

See Protocol Section 8.2.

Test product, dose and mode of administration:

BCX7353 capsules, to be administered orally.

BCX7353 capsules contain 55 and 75 mg of the active ingredient (free base equivalents). Subjects will take the following orally QD at approximately the same time each day, with whichever meal is typically the largest of the day:

Treatment Group 1 (110 mg QD) Parts 1 and 2: two 55-mg capsules of BCX7353
Treatment Group 2 (150 mg QD) Parts 1 and 2: two 75-mg capsules of BCX7353

Subjects randomized to Treatment Group 1 or 2 will receive the same dose in both Parts 1 and 2, for a total duration of 48 weeks of treatment during Parts 1 and 2 (24 weeks of treatment in each study part for Parts 1 and 2).

Subjects randomized to Treatment Group 3 (placebo) in Part 1 will be re-randomized to receive active study drug from the Week 24 visit (Part 2):

Treatment Group 3a (110 mg QD) Part 2: two 55-mg capsules of BCX7353
Treatment Group 3b (150 mg QD) Part 2: two 75-mg capsules of BCX7353

Part 3

BCX7353 capsules contain 110 and 150 mg of the active ingredient (free base equivalents). Subjects will take a single capsule orally once daily at approximately the same time each day, with whichever meal is typically the largest of the day.

Treatment Groups 1 and 3a (110 mg QD) Part 3: one 110-mg capsule of BCX7353
Treatment Groups 2 and 3b (150 mg QD) Part 3: one 150-mg capsule of BCX7353

Subjects randomized to Treatment Groups 1 and 2 will receive a total of up to 96 weeks of active BCX7353 treatment. Subjects randomized to Treatment Group 3 will receive a total of up to 72 weeks of active BCX7353 treatment.

Duration of treatment:

Subjects will take capsules of BCX7353 or placebo orally for 24 weeks in Part 1 and capsule(s) of BCX7353 in Parts 2 and 3 orally for 72 weeks (24 weeks in Part 2 and 48 weeks in Part 3), for a total duration of study drug treatment of 96 weeks.

Reference therapy, dose and mode of administration:

Placebo-to-match BCX7353 capsules. Subjects randomized to Treatment Group 3 will take 2 capsules of placebo orally QD for 24 weeks during Part 1 with their largest meal of the day.

Criteria for evaluation (see protocol section 7.1):

Part 1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is as follows:

- The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to Day 168)

Part 1 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- Change from baseline in Angioedema Quality of Life (AE-QoL) questionnaire at Week 24 (total score)
- Number and proportion of days with angioedema symptoms through 24 weeks
- Rate of investigator-confirmed HAE attacks during dosing in the effective treatment period (beginning on Day 8 through 24 weeks)

Part 1 Exploratory Efficacy Endpoints

- Number and proportion of subjects with no attacks over 24 weeks
- Use of HAE attack medications over 24 weeks
- The proportion of responders to study drug, defined as at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks during treatment compared with the baseline attack rate

Part 1 Safety Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a treatment-emergent serious adverse event (TESAE)
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality

Part 1 Health Outcome Endpoints

- EuroQoL 5-dimensional, 5-level questionnaire (EQ-5D-5L) scores
- Treatment Satisfaction Questionnaire for Medication (TSQM) scores
- Work productivity and activity impairment questionnaire (WPAI) scores

Part 2 Primary Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality
- The proportion of subjects with a treatment-emergent, treatment-related adverse event consistent with a drug rash

Part 2 Secondary Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of HAE attack medications
- Discontinuations due to lack of efficacy
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

Part 3 Primary Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality
- The proportion of subjects with a treatment-emergent, treatment-related AE consistent with a drug rash

Part 3 Secondary Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms

- Use of HAE attack medications
- Discontinuations due to lack of efficacy
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

Statistical methods:

The primary endpoint is the rate of investigator-confirmed HAE attacks during dosing in the entire treatment period of Part 1, expressed as attacks per month where 1 month is defined as 28 days. Comparisons of the rate of investigator-confirmed HAE attacks between each BCX7353 dose and placebo during the entire dosing period for Part 1 will be conducted using a Poisson regression model. The number of investigator-confirmed attacks will be included as the dependent variable, the treatment will be included as a fixed effect, baseline attack rate will be included as a covariate and the logarithm of duration on treatment will be included as an offset variable. The estimated monthly rate of attacks for each treatment group, the treatment differences expressed as the attack rate ratio (BCX7353 over placebo rate ratio) and their associated 95% confidence intervals (CIs) will be provided from the Poisson regression model.

Missing data sensitivity will be conducted for the analysis of the primary endpoint using data collected post treatment discontinuation and using multiple imputation for missing data, In addition, a a tipping point analysis will be conducted. A separate analysis using only data from subjects who completed Part 1 will also be conducted.

Analysis of secondary endpoints for Part 1 will be as follows:

Treatment comparisons in the AE-QoL total score change from baseline will be analyzed using a mixed model for repeated measures (MMRM) with fixed effects for treatment, baseline attack rate, baseline AE-QoL, visit, a visit by treatment interaction, and a random effect for subject. An unstructured covariance structure will be used. The estimated treatment difference for each BCX7353 dose vs. placebo at each visit will be displayed together with the 95% CI and the associated p-value. Primary inferences will be drawn from treatment differences for the changes from baseline derived from the MMRM model at Week 24. The change from baseline in the AE-QoL domain scores (function, fatigue, nutrition, and fear/shame) will also be analyzed using the MMRM model.

The number and proportion of days with angioedema symptoms through Week 24 will be computed. The proportion of days with angioedema symptoms through Week 24 will be analyzed using an analysis of covariance model with baseline attack rate as a covariate and treatment included as a fixed effect. The estimated treatment difference comparing each active treatment to placebo will be displayed together with the 95% CI and the associated p-value. Least squares means (LSM) will be presented with the standard error and the number of subjects who contribute to the LSM.

For the Investigator-confirmed HAE attacks during the effective treatment period, between-treatment comparisons will be performed using a Poisson regression model similar to that used for the primary endpoint analysis.

A combination of hierarchical testing and the Hochberg step-up procedure will be used to control the Type I error rate for testing of primary and secondary endpoints in Part 1.

Analysis of safety data for Parts 1, 2, and 3 and of effectiveness data for Parts 2 and 3 will primarily be descriptive.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations and Definitions of Terms

Abbreviation	Term
AE	Adverse Event
AE-QoL	Angioedema Quality of Life Questionnaire
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
C1-INH	C1 Esterase Inhibitor
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
EC_{50}	Half-Maximal Effective Concentration
eCRF	Electronic Case Report Form
e-diary	Electronic Diary
EQ-5D-5L	EuroQoL 5-dimensional, 5-level questionnaire
EQ VAS	EuroQoL Visual Analogue Scale
GI	Gastrointestinal
HAE	Hereditary Angioedema
HLGT	High-Level Group Term
ICH	International Council for Harmonization
ITT	Intent-to-Treat Population
IXRS	Interactive Response System
%KKI	Percent Kallikrein Inhibition
LSM	Least Squares Mean
MCID	Minimum Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MMRM	Mixed Model of Repeated Measures
N	Total Sample Size

PBMC	Peripheral Blood Mononuclear Count
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol Population
PT	Preferred Term
QD	Once Daily
QoL	Quality of Life
QTcF	QT Interval Corrected Using Fridericia's Method
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Classification
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TSQM	Treatment Satisfaction Questionnaire for Medication
TTO	Time Trade-Off
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Questionnaire

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Study BCX7353-302.

Protocol Revision Chronology:		
Protocol	21 November 2017	Version 1
Protocol	11 October 2018	Version 2 – added Part 3 to extend the study to 96 weeks to allow for collection of long-term safety and effectiveness data.

This SAP was developed in accordance with the International Council for Harmonisation (ICH) E9 guideline. The purpose of this document is to provide details on the statistical methodology used to analyze the safety and efficacy data for Study BCX7353-302. Study population definitions, derivations of variables, handling of missing data, and other information necessary for analysis of study data are provided. Planned tables, figures, and listings are specified. All decisions regarding final analysis will be made, the SAP will be finalized, approved by the Sponsor, and placed on file before the database is locked for interim analysis.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Part 1 Primary Objective

- To determine the efficacy of prophylactic BCX7353 110 mg and 150 mg administered once daily (QD) for 24 weeks compared to placebo in subjects with hereditary angioedema (HAE)

3.1.2. Part 1 Secondary Objectives

- To assess the safety and tolerability of BCX7353 110 mg and 150 mg administered QD for 24 weeks
- To assess the effects of BCX7353 on HAE disease activity and HAE attack characteristics
- To evaluate the effects of BCX7353 on quality of life (QoL)
- To characterize the pharmacodynamic (PD) effects of BCX7353

3.1.3. Part 2 Primary Objective

- To evaluate the long-term safety and tolerability of BCX7353 110 mg and 150 mg administered QD over a 24- to 48-week administration period in subjects with HAE

3.1.4. Part 2 Secondary Objectives

- To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 24- to 48-week administration period

- To evaluate QoL and HAE disease activity of BCX7353 over a 24- to 48-week administration period
- To evaluate subject's satisfaction with BCX7353 over a 24- to 48-week administration period

3.1.5. Part 3 Primary Objectives

- To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 48- to 96-week administration period in subjects with HAE

3.1.6. Part 3 Secondary Objectives

- To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 48- to 96-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 48- to 96-week administration period
- To evaluate subject satisfaction with BCX7353 over a 48- to 96-week administration period

3.2. Study Endpoints

3.2.1. Part 1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is as follows:

- The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to Day 168)

3.2.2. Part 1 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- Change from baseline in Angioedema Quality of Life questionnaire (AE-QoL) at Week 24 (total score)
- Number and proportion of days with angioedema symptoms through 24 weeks
- Rate of investigator-confirmed HAE attacks during dosing in the effective treatment period (beginning on Day 8 through 24 weeks)

3.2.3. Part 1 Exploratory Efficacy Endpoints

- Number and proportion of subjects with no attacks over 24 weeks
- Use of HAE attack medications over 24 weeks
- The proportion of responders to study drug, defined as at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks during treatment, compared with the baseline attack rate

3.2.4. Part 1 Safety Endpoints

- Number and proportion of subjects with a treatment-emergent adverse event (TEAE)
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a treatment-emergent serious adverse event (TESAE)
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality

3.2.5. Part 1 Health Outcome Endpoints

- EuroQoL 5-dimensional, 5-level questionnaire (EQ-5D-5L) scores
- Treatment Satisfaction Questionnaire for Medication (TSQM) scores
- Work productivity and activity impairment questionnaire (WPAI) scores

3.2.6. Part 2 Primary Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality
- The proportion of subjects with a treatment-emergent, treatment-related adverse event (AE) consistent with a drug rash

3.2.7. Part 2 Secondary Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of HAE attack medications
- Discontinuations due to lack of efficacy
- Durability in angioedema QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

3.2.8. Part 3 Primary Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality
- The proportion of subjects with a treatment-emergent, treatment-related AE consistent with a drug rash

3.2.9. Part 3 Secondary Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of HAE attack medications
- Discontinuations due to lack of efficacy
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

4. STUDY DESIGN

4.1. Summary of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 3-part study. Part 1 is designed to test the hypothesis that the HAE attack rate during 24 weeks of prophylactic BCX7353 will be less than that observed during 24 weeks of placebo. The primary efficacy endpoint will be assessed after the last subject completes Part 1 (through Week 24). Part 2 is designed to primarily evaluate the long-term safety of BCX7353 at 2 dosage levels. Part 3 is open-label and designed to primarily evaluate the long-term safety of BCX7353. Parts 1, 2, and 3 will be conducted in sequence, with Parts 2 and 3 conducted as continuous roll-overs from Parts 1 and 2, respectively. All subjects will receive BCX7353 in Parts 2 and 3, including those randomized to receive placebo in Part 1.

Part 1 (24-week evaluation of blinded efficacy and safety data)

Subjects with HAE Type 1 or 2 will be eligible for the study following assessment of data obtained from screening procedures, including demonstration of a minimum number of attacks

documented during a prospective run-in period of 2 to 8 weeks from the date of the screening visit.

Approximately 96 treatment-eligible subjects will receive study drug (BCX7353 or placebo) in Part 1 of the study based on randomization in a 1:1:1 ratio into 1 of 3 treatment groups:

Group 1 (N = 32): BCX7353 110 mg administered orally QD for 24 weeks

Group 2 (N = 32): BCX7353 150 mg administered orally QD for 24 weeks

Group 3 (N = 32): Placebo administered orally QD for 24 weeks

Enrollment into treatment groups will be stratified by the baseline HAE attack rate ($\geq$ 2 attacks/month vs. < 2 attacks/month).

Qualifying attacks for eligibility determination are characterized as follows:

- The attacks must occur during the run-in period of 56 consecutive days, starting on the day of the screening visit
- The attacks are unique, defined as an attack that does not begin within 48 hours of the end of a previous attack.
- The attacks must have either been treated, required medical attention, or be documented to cause functional impairment, based on the subject's entry in the electronic diary (e-diary). Functional impairment is defined as the subject not being able to perform his or her daily activities without restriction (ie, subject records that he/she is at least slightly restricted in daily activities during the HAE attack).
- The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions, which are indicative of internal swelling.
- The attacks are otherwise confirmed by the Investigator to be HAE attacks.

Once the subject records 2 such attacks, he or she may be randomized to study drug beginning on or after Day 28 of the run-in period; subjects who have at least 3 such attacks may be randomized to study drug beginning on or after Day 14 of the run-in period. A study schematic can be found in Figure 1.

Beginning at screening and through the Week 48 visit, details of acute attacks of angioedema will be recorded in an electronic diary (e-diary). Attacks will be treated in accordance with the subject's normal standard of care. Within approximately 2 business days of the end of each attack that occurs from the screening visit through the Week 48 visit, subjects will be contacted by the Investigator (or appropriately trained designee) to discuss the clinical characteristics of the attack, any questions on the entered data or to gain additional attack details not included in the e-diary that the Investigator deems important to clinically evaluate the event, as applicable. This information, in conjunction with the e-diary record, will be used by the Investigator to verify or reject the event recorded in the diary as an HAE attack. All Investigator-confirmed attacks of HAE must include symptoms of swelling; prodromal symptoms in the absence of swelling are not considered HAE attacks, regardless of treatment. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions, which are indicative of internal swelling.

The main study will be comprised of adult subjects (≥ 18 years of age); a substudy in participating regions will allow adolescent subjects (≥ 12 to 17 years of age) to enroll. Main study and substudy subjects will be randomized via a separate randomization scheme; however, study-mandated procedures will be identical, and the analyses will include all subjects who participate in the study.

Study visits in Part 1 will occur at screening, baseline and Weeks 2, 4, 8, 12, 18 and 24. The primary efficacy analysis will occur after the last subject completes the Week 24 visit and will include all data through Week 24. Subject treatment will remain blinded to the subjects, site staff, and Sponsor staff who interact with sites on a regular basis during Part 2.

Part 2 (24-week evaluation of safety of blinded BCX7353)

Part 2 of the study will start with the administration of study drug dispensed at the Week 24 visit. Subjects in Groups 1 and 2 will continue to receive the same BCX7353 dose to which they were randomized in Part 1 of the study in a blinded manner. Subjects randomized to Group 3 will undergo a second randomization in a 1:1 ratio to receive either a 110 mg QD dose or 150 mg QD dose of BCX7353 in a blinded manner beginning at the Week 24 visit (see Figure 1). The active dose a subject receives in Part 2 will be blinded for all subjects; subjects will be informed that they will receive an active dose of BCX7353 in Part 2.

Study visits in Part 2 will occur during Weeks 26, 28, 32, 36, and 48 with telephone contact at Weeks 40 and 44. Subjects will continue to document all angioedema attacks that occur while on study drug in their e-diary. Investigator confirmation of attacks will continue to be required for Part 2. Interim safety analyses will be conducted while Part 2 is ongoing to support regulatory filings.

Part 3 (48-week evaluation of safety of open-label BCX7353)

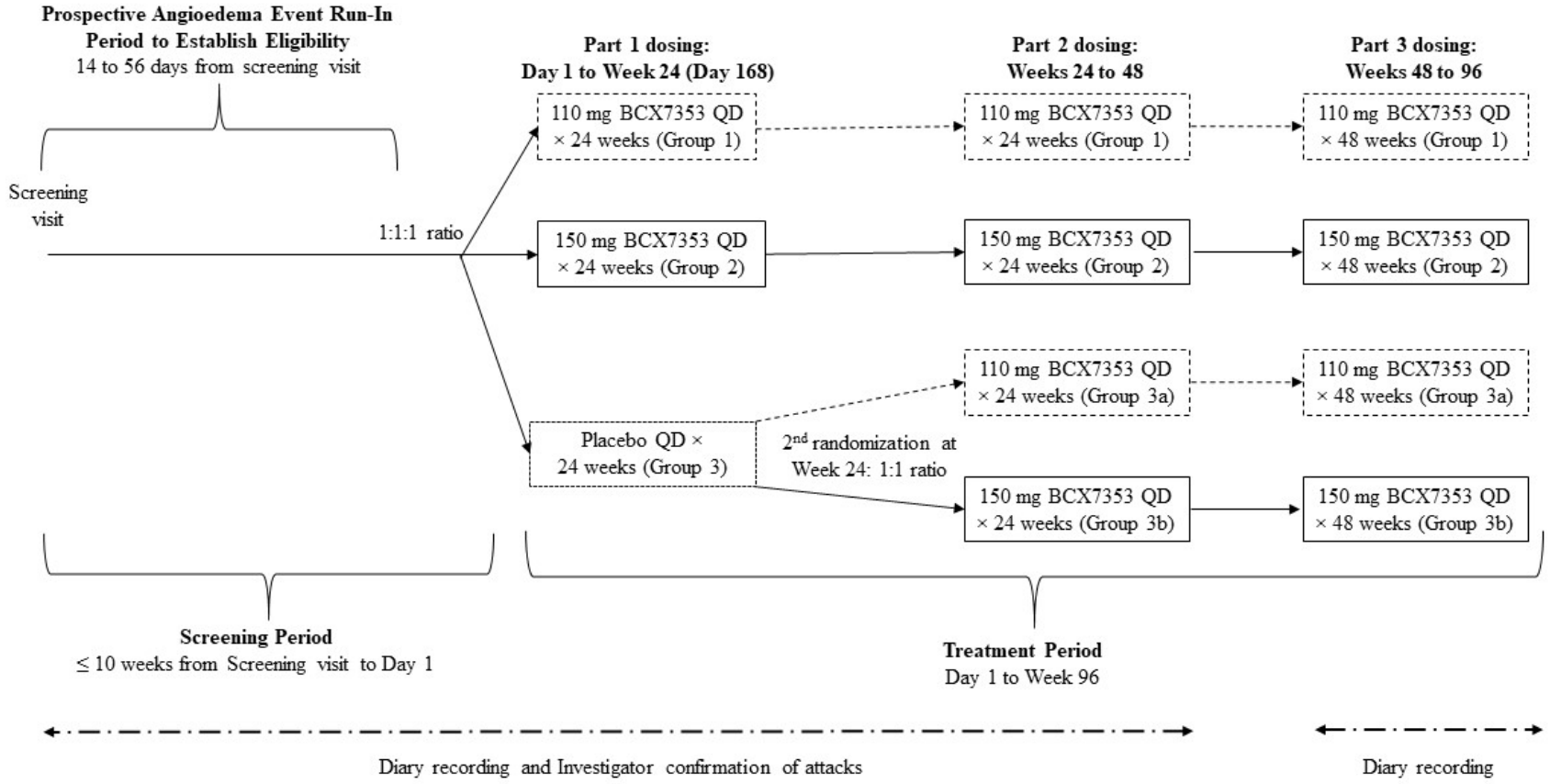
Part 3 of the study will start with the administration of the study drug dispensed at the Week 48 visit. Subjects will continue to receive the same BCX7353 dose in Part 3 to which they were randomized in Part 2 of the study in an open-label manner. Once Part 1 results are available, all subjects in Part 3 may be moved to a single dose level of BCX7353, based on the data from Part 1, if appropriate.

Study visits in Part 3 will occur during Weeks 60, 72, 84, and 96, with telephone contact at Weeks 52, 56, 64, 68, 76, 80, 88, and 92.

Subjects will continue to document all angioedema attacks that occur in a paper diary throughout Part 3 and will have regular visits to assess safety and tolerability. Investigator confirmation of attacks will not be required for Part 3. All attacks recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in effectiveness analyses. These rules, which were constructed in concert with HAE-treating physicians, will be outlined in this SAP.

A final study follow-up visit will be scheduled approximately 3 weeks following the last administration of study drug (Week 99).

Figure 1: Study Schema



Abbreviations: QD = once daily.

4.2. Definition of Study Drugs

BCX7353 110 mg QD is supplied as two 55-mg capsules of BCX7353 per dose for Parts 1 and 2 and as one 110-mg capsule of BCX7353 per dose for Part 3.

BCX7353 150 mg QD is supplied as two 75-mg capsules of BCX7353 per dose for Parts 1 and 2 and as one 150-mg capsule of BCX7353 per dose for Part 3.

Placebo QD is supplied as 2 capsules of matching placebo per dose.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

The pooled standard deviation (SD) of the attack rate during effective dosing period (Days 8 to 28) in Study BCX7353-203 was 0.55. The observed treatment difference between the BCX7353 125 mg dose with dihydrochloride salt (equivalent to the 110 mg free base dose for the current study) and placebo for the effective dosing period using the full analysis population was 0.70 attacks/week, which represented a 73.8% reduction in attack rate from the placebo group.

Assuming a normalized placebo attack rate of 1 unit and a common SD of 0.55 units for BCX7353 and placebo attack rates, a sample size of 32 subjects will have 94% power to detect a 50% attack rate reduction (a treatment difference of 0.5 units) between BCX7353 and placebo, based on a 2-sided test at significance level of 0.05.

Sample sizes were increased to approximately 40 subjects for each active treatment group and placebo, to conservatively account for a potential dropout rate of 20%. Initial sample size calculations at the time the protocol was written did not allow for dropout.

4.3.2. Sample Size Re-estimation

A blinded sample size re-estimation was originally planned to address uncertainty of the variability in the SD of the HAE attack rate. An interim analysis may have been performed after 50% subjects completed 24 weeks to provide the SD of the attack rate based on pooled data. Based on the pooled SD, the sample size may have been re-estimated to maintain at least 90% power to detect a 50% attack rate reduction. The study would have remained blinded, and the interim analysis would have been based on pooled data for sample size re-estimation. The final sample size was to be the maximum of either the initial sample size or the re-estimated sample size.

Due to rapid enrollment of study subjects, the sample size re-estimation was not performed.

4.4. Randomization

Subjects will be randomized via the interactive response system (IXRS). Details on the processes followed for randomization are provided in a separate manual.

4.4.1. Part 1 Randomization

Approximately 96 subjects will be randomized in a 1:1:1 (active:active:placebo) ratio to 1 of the following treatments in Part 1:

- Group 1: BCX7353 110 mg administered orally QD for 24 weeks
- Group 2: BCX7353 150 mg administered orally QD for 24 weeks
- Group 3: Placebo administered orally QD for 24 weeks

Enrollment into treatment groups will be stratified by the site-calculated baseline HAE attack rate (≥ 2 attacks/month vs. < 2 attacks/month). The site-calculated baseline attack rate must have been provided during randomization and was to be calculated as:

$$\frac{\text{Number of HAE attacks meeting baseline criteria from Screening to Randomization} \times 28}{\text{Randomization Date} - \text{Screening Date} + 1}$$

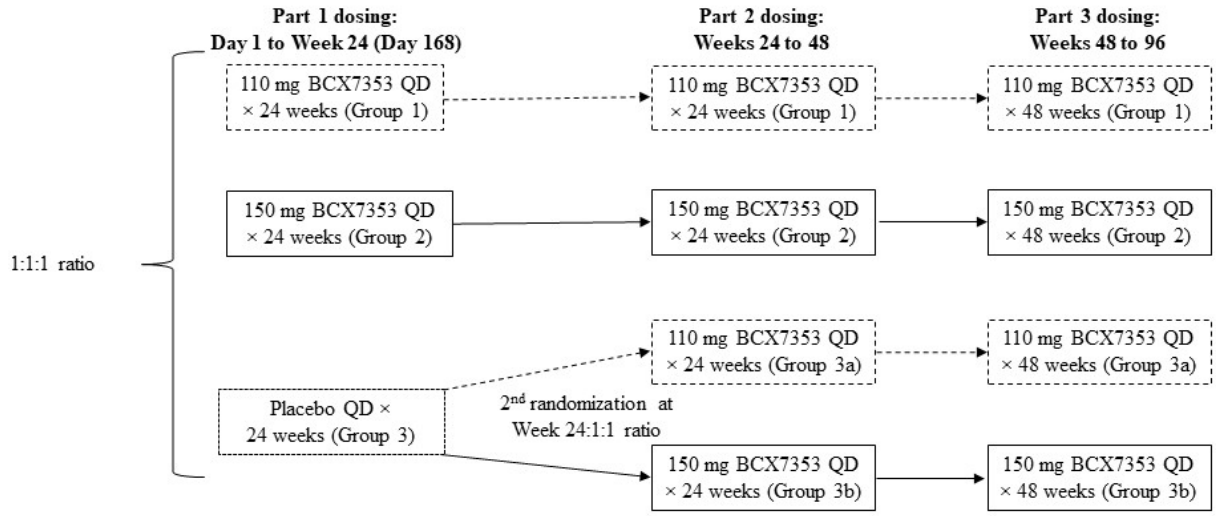
HAE attacks to be utilized in calculation of the baseline attack rate must meet the following criteria:

- The attacks must be unique, which is defined as an attack that does not begin within 48 hours of the end of the previous attack.
- The attacks must have either been treated, required medical attention, or have been documented to cause functional impairment based on subject entry in the e-diary. Functional impairment is defined as the subject being unable to perform daily activities without restriction (ie, subject records that he/she is at least slightly restricted in daily activities during the HAE attack).
- The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions, which are indicative of internal swelling.
- The attacks must be confirmed by the Investigator to be HAE attacks. Subjects will be contacted within 2 business days of the attack to discuss the attack and to resolve any Investigator queries on the entered data in the e-diary, as applicable.

4.4.2. Part 2 Randomization

At the Week 24 visit, subjects originally randomized to placebo in Part 1 will be randomized in a 1:1 (active:active) ratio to receive a 110 mg QD or 150 mg QD dose of BCX7353 in Part 2 (see Figure 2). Subjects will continue to receive the same dosing regimen received in Part 2 during Part 3. Once Part 1 results are available, all subjects in Part 3 may be moved to a single dose level of BCX7353, based on the data from Part 1, if appropriate.

Figure 2: Study Randomization



Abbreviations: QD = once daily.

4.5. Clinical Assessments

The schedule of assessments for Parts 1, 2 and 3, are provided in Table 2, Table 3, and Table 4, respectively.

Table 2. Schedule of Assessments: Part 1 of Study BCX7353-302

Assessment	Screening Period		Baseline	Part 1 Double-Blind, Placebo-Controlled Study Drug Administration					Week 24 Day 169[d]
	Screening Visit[a,b] (up to Week -10)	Run-in Period[a]	Day 1[a]	Week 2[c] Day 15 ± 2 days	Week 4 Day 29 ±2 days	Week 8 Day 57 ± 2 days	Week 12 Day 85 ± 2 days	Week 18 Day 127 ± 2 days	
Informed consent[b]	X								
In-clinic evaluations	X		X	X[c]	X	X	X	X	X
Telephone contact[e]	◄							►	
Inclusion-exclusion criteria	X	X	X						
Medical history[f]	X		X						
HAE medical and medication history[f]	X		X						
Weight/height/BMI[g]	X		X		X	X	X	X	X
Drugs of abuse screen[h]	X								
Physical examination[i]	X		X		X	X	X	X	X
Pregnancy test[j]	X		X		X	X	X	X	X
Vital signs[k]	X		X		X	X	X	X	X
FSH[l]	X								
HIV, HCV, HBV serology	X								
Diagnosis of HAE established[m]	X								
Attack qualification confirmation[n]		X							
Safety laboratory evaluations[h]	X		X	X[c]	X	X	X	X	X
Troponin I, Troponin T			X		X	X	X	X	X
C3 and C1-INH antigenic level			X						
HLA typing[o]			X						
Optional sample for possible exploratory PG testing[p]			X						
NGAL			X		X	X	X	X	X
CK-MB			X		X	X	X	X	X
Urinalysis[h]	X		X	X[c]	X	X	X	X	X
12-lead ECG[q]	X		X		X	X	X	X	X
EQ-5D-5L[r,s]			X		X	X	X	X	X
AE-QoL, TSQM, WPAI[s]			X		X	X	X	X	X

Assessment	**Screening Period**		**Baseline**	**Part 1 Double-Blind, Placebo-Controlled Study Drug Administration**					Week 24 Day 169[d]
	Screening Visit[a,b] (up to Week -10)	Run-in Period[a]	Day 1[a]	Week 2[c] Day 15 ± 2 days	Week 4 Day 29 ±2 days	Week 8 Day 57 ± 2 days	Week 12 Day 85 ± 2 days	Week 18 Day 127 ± 2 days	
Concomitant medications	←	←	←	←	←	←	←	←	→
AEs	←	←	←	←	←	←	←	←	→
Randomization[t]			X						X
e-diary instruction/review/ set-up[u]	X	X	X		X	X	X	X	X
e-diary daily completion[v]	←	←	←	←	←	←	←	←	→
Study drug dosing[w]			←	←	←	←	←	←	→
Investigator confirmation of attacks[x]	←	←	←	←	←	←	←	←	→
Study drug accountability/ dispensing			X		X	X	X	X	X
Plasma for PK analysis[y]			X		X	X	X	X	X
Plasma for kallikrein inhibition[y]			X		X	X	X	X	X

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; C1-INH = C1 esterase inhibitor; C3 = complement 3; C4 = complement 4; CK-MB = creatine kinase MB isoenzyme; CRF = case report form; ECG = electrocardiogram; e-diary = electronic diary; EQ-5D-5L = EuroQoL 5-dimensional, 5-level questionnaire; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; HAE = hereditary angioedema ; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IXRS = interactive (voice/web) response system; LLN = lower limit of normal; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic; PG = pharmacogenomic; PK = pharmacokinetic; QTcF = QT interval corrected using Fridericia's method; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI = Work Productivity and Activity Index.

[a] The baseline visit must be held within 10 weeks (70 days) of the Screening visit, accommodating a run-in period of 14 days (minimum) to up to 56 days (maximum). The Investigator must gain Sponsor approval to enroll subjects who are not randomized within 10 weeks of the Screening visit; this may require screening labs to be redrawn. Subjects will not be permitted to rescreen if they did not meet the HAE attack requirements during the run-in period.

[b] Signing of informed consent may occur in advance of the Screening visit, which is defined as the visit where site-conducted screening procedures, including e-diary dispensing, are performed.

[c] The Week 2 visit will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, ALP); urine and additional tubes of blood may be required to accommodate possible reflex testing for abnormal GGT, AST or ALT. If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

[d] The last visit in Part 1 (Week 24) must occur the day following 24 weeks of study drug dosing in Part 1.

[e] The Investigator (or designee) must call and talk to the subject at least weekly in between the Screening and Baseline visits and on-treatment during through Week 24; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the

investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of attack details (if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an attack as the Investigator must call and confirm or reject the attack (see Footnote 'x').

[f] An HAE medical history form will be completed by the subject at screening. Medical and medication history will be taken at screening and updated at baseline.

[g] BMI calculation and height at screening; weight is to be recorded at each scheduled in-clinic visit during Part 1 except at Week 2.

[h] The protocol lists parameters to be assessed.

[i] Full physical examinations will be performed at Screening, Baseline and Week 24; abbreviated physical examinations targeted to signs and symptoms will be performed at all post-baseline visits except for Week 2.

[j] For women of childbearing potential (including adolescents), regardless of contraception or lifestyle, a serum pregnancy test will be administered at screening, urinary pregnancy tests will be assessed at all subsequent visits as indicated in the table. Demonstration of a negative urine pregnancy test will be required prior to the subject taking study drug on Day 1. In addition to urine pregnancy tests at study visits, women of childbearing potential who enroll at sites in Europe will be dispensed urinary pregnancy tests to be completed at home at Weeks 16 and 22. Sites will confirm negative test results by telephone and record the results in source documents.

[k] To include blood pressure and pulse rate. Temperature and respiratory rate will be captured at Screening, Baseline and Week 24 only. Prior to obtaining vital signs, subjects should rest in a supine position for at least 5 minutes.

[l] For women who declare that they have been post-menopausal ≤ 2 years.

[m] A clinical diagnosis of HAE Type I or II, defined as having a C1-INH functional level below 50% and a C4 level below the lower LLN reference range, as assessed during the screening period. In the absence of a low C4 value drawn during the intercritical period, 1 of the following is acceptable to confirm the diagnosis of HAE assessed during the Screening period: 1) a SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or 2; 2) a confirmed family history of C1-INH deficiency; 3) a C4 redrawn and retested during an attack with the results below the LLN reference range. For subjects with C1-INH function ≥ 50% but less than the assay LLN, a SERPING-1 gene mutation known or likely to be associated with HAE Type I or II assessed during the screening period or a repeat C1-INH functional level < 50% will be considered acceptable for enrollment.

[n] The subject will be determined as eligible for the study based upon screening evaluations and the prospective recording of HAE attacks during the run-in period. The subject must have at least 2 HAE attacks during the run-in period which meet all of the following requirements: 1) the attacks must occur during the run-in period (period between Screening and Baseline; minimum of 14 days and maximum of 56 days); 2) the attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack; 3) the attacks must have either been treated, required medical attention or be documented to cause functional impairment based on subject entry in the diary; 4) the attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling and; 5) the attacks are otherwise confirmed by the Investigator to be HAE attacks (see Footnote 'x').

[o] A blood sample for HLA typing will be drawn at the baseline/Day 1 visit; if a blood sample is not obtained at baseline, the sample may be drawn at any time during the study.

[p] A blood sample for possible exploratory PG testing will be drawn at the Baseline/Day 1 visit only if consent/assent is obtained for this optional testing; if a blood sample is not obtained at baseline, the sample may be drawn at any time during the study following consent obtained from the subject.

[q] Bedside 12-lead ECGs will be conducted in triplicate (ie, 3 separate readings) at 1- to 5-minute intervals predose on Day 1 and Week 24, with values for this visit calculated from an average of the 3 readings. All other ECGs during the study will be single assessments. Prior to obtaining an ECG, subjects should rest quietly in a supine position for at least 10 minutes. ECGs should be obtained prior to any blood sampling. An ECG should be repeated for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec.

[r] The EQ-5D-5L will be administered once at baseline and 1 to 2 × at the Week 4, 8, 12, 18, and 24 visits. The subject will fill out the first EQ-5D-5L at baseline and on-study to describe their current health state today as instructed per the instrument. The subject will also fill out a second EQ-5D-5L based on

a recollection of their health state during an average attack that they experienced since the last study visit. If the subject has not had an attack since their last study visit, the subject is not required to fill out the second, attack-related EQ-5D-5L.

[s] Where possible, quality of life and health outcome questionnaires should be collected as the first assessments at a visit.

[t] Sites will randomize eligible subjects in the IXRS at the Day 1 visit for Part 1 and at the Week 24 visit for Part 2 study drug. At Baseline, it is preferred that randomization occur preferably after all Baseline assessments have been completed. Sites using a centralized pharmacy may randomize the subject the day prior to the baseline and Week 24 visits.

[u] The Investigator (or designee) will set up the e-diary at the Screening visit and as needed during the study; any issues (including mediocre or poor compliance) warranting e-diary re-education should occur on an as-needed basis.

[v] At any time the e-diary is in a subject's possession, up to the Week 48 visit, they will enter HAE attacks and relevant details and dosing information (as applicable) at least once per day.

[w] Study drug should be taken at approximately the same time each day, with whichever meal is typically the largest of the day. Subjects are not required to take their doses at clinic visits. Subjects will take study drug in Part 1 beginning on Day 1 and will complete Part 1 dosing on Study Day 168 (day before Week 24 visit). Subjects will take Part 2 active study drug no sooner than the conclusion of the Week 24 visit on Study Day 169, after all other study procedures have been completed.

[x] The Investigator (or designee) will review the e-diary record of all HAE attacks that occur from Screening through Week 48 and either confirm or reject the attack as an HAE attack. At least 2 attacks that occur during the run-in period must meet the requirements outlined in Footnote 'n' in order to qualify the subject to randomize in the study. For all attacks that occur, subjects will be contacted within approximately 2 business days of the end of the attack to discuss the clinical characteristics of the attack, any questions the Investigator has on the entered data or to gain additional attack details not included in the e-diary that the Investigator deems important to clinically evaluate the event, as applicable. This information, in conjunction with the e-diary record, will be used by the Investigator to verify or reject the event recorded in the diary as an HAE attack. The e-diary data review, subject contact summary, and Investigator verification of the attack will be documented in the source records; the Investigator attack verification (confirmed or rejected) will also be recorded.

[y] PK and PD blood samples will be drawn on all subjects with no particular relationship to the timing of study drug dosing. The Investigator (or designee) must ensure that the time of the last dose prior to PK and PD draw is recorded in the subject's e-diary (this may also be captured in the CRF).

Table 3. Schedule of Assessments: Part 2 of Study BCX7353-302

Assessment	Part 2 Double-Blind, Active Study Drug Administration[a]						
	Week 26[b] Day 183 ±2 days	Week 28 Day 197 ±2 days	Week 32 Day 225 ±2 days	Week 36 Day 253 ±2 days	Week 40	Week 44	Week 48 Day 337 + 7 days
In-clinic evaluations	X	X	X	X			X
Telephone contact[c]					X	X	
Subject weight		X	X	X			X[q]
Physical examination[d]		X	X	X			X
Urine pregnancy test[p]		X	X	X			X
Vital signs[e]		X	X	X			X
Safety laboratory evaluations[f]	X[b]	X	X	X			X
Troponin I and Troponin T		X	X	X			X
NGAL		X	X	X			X
CK-MB		X	X	X			X
Urinalysis[f]	X[b]	X	X	X			X
12-lead ECG[g]		X	X	X			X
EQ-5D-5L[h,i]		X	X	X			X
AE-QoL, TSQM, WPAI[i]		X	X	X			X
Concomitant medications	←	—	—	—	—	—	→
AEs	←	—	—	—	—	—	→
e-diary instruction/review[j]		X	X	X	X	X	X
e-diary daily completion[k]	←	—	—	—	—	—	→
Study drug dosing[l]	←	—	—	—	—	—	→
Investigator confirmation of attacks[m]	←	—	—	—	—	—	→
Study drug accountability/ dispensing		X	X	X			X
Plasma for PK analysis[o]		X	X	X			X
Plasma for kallikrein inhibition[o]		X	X	X			X

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EQ-5D-5L = EuroQoL 5-dimensional, 5-level questionnaire; CK-MB = creatine kinase MB isoenzyme; CRF = case report form; ECG = electrocardiogram; e-diary = electronic diary; GGT = gamma glutamyl transferase; HAE = hereditary angioedema ; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic; PK = pharmacokinetic; QoL = quality of life; QTcF = QT interval corrected using Fridericia's method; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI = Work Productivity and Activity Index.

[a] Period 2 study drug is to be initiated upon administration of study drug dispensed at the Week 24 visit.

[b] The Week 26 visit will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, ALP); urine and additional tubes of blood may be required to accommodate possible reflex testing for abnormal GGT, AST or ALT. If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

[c] The Investigator (or designee) must call and talk to the subject during Week 40 and 44; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of attack details (if applicable), or any usability issues with the e-diary. The phone call may be omitted if the subject records an attack as the Investigator must call and confirm or reject the attack (see Footnote 'm').

[d] Abbreviated physical examinations targeted to signs and symptoms will be performed at post-baseline visits.

[e] To include blood pressure and pulse rate. Prior to obtaining vital signs, subjects should rest in a supine position for at least 5 minutes.

[f] The protocol lists parameters to be assessed.

[g] ECGs may be single assessments. Prior to obtaining an ECG, subjects should rest quietly in a supine position for at least 10 minutes. ECGs should be obtained prior to any blood sampling. An ECG should be repeated for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec.

[h] The EQ-5D-5L will be administered once at baseline and 1 to 2 × at Weeks 28, 32, 36, and 48. The subject will fill out the first EQ-5D-5L at baseline and on-study to describe their current health state today as instructed per the instrument. The subject will also fill out a second EQ-5D-5L based on a recollection of their health state during an average attack that they experienced since the last study visit. If the subject has not had an attack since their last study visit, the subject is not required to fill out the second, attack-related EQ-5D-5L.

[i] Where possible, QoL and health outcome questionnaires should be collected as the first assessments at a visit.

[j] Any issues (including mediocre or poor compliance) warranting e-diary re-education should occur on an as-needed basis.

[k] At any time the e-diary is in a subject's possession up to the Week 48 visit, they will enter HAE attacks and relevant details and dosing information (as applicable) at least once per day.

[l] Study drug should be taken at approximately the same time each day, with whichever meal is typically the largest of the day. Subjects are not required to take their doses at clinic visits.

[m] The Investigator (or designee) will review the e-diary record of all HAE attacks that occur from Screening through Week 48 and either confirm or reject the attack as an HAE attack. For all attacks that occur, subjects will be contacted within approximately 2 business days of the end of the attack to discuss the clinical characteristics of the attack, any questions the Investigator has on the entered data or to gain additional attack details not included in the e-diary that the Investigator deems important to clinically evaluate the event, as applicable. This information, in conjunction with the e-diary record, will be used by the Investigator to verify or reject the event recorded in the diary as an HAE attack. The e-diary data review, subject contact summary, and Investigator verification of the attack will be documented in the source records; the Investigator attack verification (confirmed or rejected) will also be recorded.

[n] Early termination visit only (if occurring during dosing phase)

[o] PK and PD blood samples will be drawn on all subjects with no particular relationship to the timing of study drug dosing. The Investigator (or designee) must ensure that the time of the last dose prior to PK and PD draw is recorded in the subject's e-diary (this may also be captured in the CRF).

[p] In addition to urine pregnancy tests at study visits, women of childbearing potential who enroll at sites in Europe will be dispensed urinary pregnancy tests to be completed at home at Weeks 40 and 44. Sites will confirm negative test results by telephone and record in source documents.

[q] Adolescent subjects will also have height measured at Week 48.

Table 4. Schedule of Assessments: Part 3 of Study BCX7353-302

Assessment	**Part 3 Open-Label, Active Study Drug Administration[a]**				**Follow-up/ Early Termination Visit**
	Week 60 Day 421 ± 6 days	Week 72 Day 505 ± 6 days	Week 84 Day 589 ± 6 days	Week 96 Day 673 + 7 days	Week 99 + 1 week
In-clinic evaluations	X	X	X	X	X
Telephone contact[b]					
Subject weight	X	X	X	X	X
Physical examination[c]	X	X	X	X	X
Urine pregnancy test	X	X[d]	X[d]	X	X
Vital signs[e]	X	X	X	X	X
Safety laboratory evaluations[f]	X	X	X	X	X
Troponin I and Troponin T	X	X	X	X	X
NGAL	X	X	X	X	X
CK-MB	X	X	X	X	X
Urinalysis[f]	X	X	X	X	X
12-lead ECG[g]	X	X	X	X	X
EQ-5D-5L[h,i]	X	X	X	X	
AE-QoL, TSQM, WPAI[i]	X	X	X	X	
Concomitant medications	←	—	—	—	→
AEs	←	—	—	—	→
Diary instruction/review[j]	X	X	X	X	X
Diary daily completion[k]	→	—	—		
Study drug dosing[l]	→	—	—		
Study drug accountability/ dispensing	X	X	X	X	X[m]
Plasma for PK analysis[n]					X[m]
Plasma for kallikrein inhibition[n]					X[m]

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life; CK-MB = creatine kinase MB isoenzyme; CRF = case report form; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-dimensional, 5-level questionnaire; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic; PK = pharmacokinetic; QoL = quality of life; QTcF = QT interval corrected using Fridericia's method; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI = Work Productivity and Activity Index.

[a] Period 3 study drug is to be initiated on Day 337, the day of the Week 48 visit.

[b] The Investigator (or designee) must call and talk to the subject during Weeks 52, 56, 64, 68, 76, 80, 88, and 92; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the investigator (or designee) will assess the subject's overall wellbeing, and proper recording of attack details (if applicable).

[c] Abbreviated physical examinations targeted to signs and symptoms will be performed at post-baseline visits.
[d] At the Week 60, 72, and 84 visits, sites in Europe will dispense urinary pregnancy tests to subjects who are women of childbearing potential. These will be performed by the subject at home at Weeks 64, 68, 76, 80, 88, and 92.
[e] To include blood pressure and pulse rate. Prior to obtaining vital signs, subjects should rest in a supine position for at least 5 minutes.
[f] The protocol lists parameters to be assessed.
[g] ECGs may be single assessments. Prior to obtaining an ECG, subjects should rest quietly in a supine position for at least 10 minutes. An ECG should be repeated for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec.
[h] Two EQ-5D-5L assessments will be administered at Weeks 60, 72, 84, and 96. The subject will fill out the first EQ-5D-5L to describe their current health state today as instructed per the instrument. The subject will also fill out a second EQ-5D-5L based on a recollection of their health state during an average attack that they experienced since the last study visit. If the subject has not had an attack since their last study visit, the subject is not required to fill out the second, attack-related EQ-5D-5L.
[i] Where possible, QoL and health outcome questionnaires should be collected as the first assessments at a visit.
[j] Any issues (including mediocre or poor compliance) warranting diary re-education should occur on an as-needed basis.
[k] Any time the diary is in the subject's possession after Week 48 the subject will enter HAE attacks and relevant details at least once per day. No dosing information will be collected in in subject diaries in Part 3.
[l] Study drug should be taken at approximately the same time each day, with whichever meal is typically the largest of the day. Subjects are not required to take their doses at clinic visits.
[m] Early termination visit only (if occurring during dosing phase).
[n] PK and PD blood samples will be drawn on all subjects with no particular relationship to the timing of study drug dosing. The Investigator (or designee) must ensure that the time of the last dose prior to PK and PD draw is recorded in the subject’s diary (this may also be captured in the CRF).

5. PLANNED ANALYSES

5.1. Interim Analyses

A blinded interim analysis for the purpose of sample size re-estimation after 50% of subjects (48 subjects) complete 24 weeks (See Section 4.3.2) may be conducted. A primary analysis is planned at the end of Part 1 when all subjects have completed Part 1 of the study.

An additional interim cut of the data may be required for purposes of regulatory filings when a total of 100 subjects have completed 48 weeks of dosing at 150 mg in either the current study or Study BCX7353-204, an open-label study of safety of 2 active doses, 110 and 150 mg. At the time of this data cut, an analysis of integrated safety data from Studies BCX7353-204 and BCX7353-302 may be performed. The integrated analysis will be the subject of a separate SAP. Additionally, summaries of attack rates over time by month and AE-QoL by visit, including all available data post Week 24, may be produced for the current study at the time of the integrated analysis.

5.2. Primary Efficacy Analysis at the End of Part 1

The primary efficacy analysis is planned after all subjects have completed Part 1 of the study (Part 1 analysis). Unblinding of the database will occur after database freeze for the Part 1 analysis. This analysis will include all data through the end of Part 1 (24-week assessment).

This is a double-blind study throughout both Parts 1 and 2. As such, study drug assignment for each subject will be blinded to the Investigator, site staff, study subjects, and clinical research organization (CRO) staff involved with study operations. Part 3 is open-label and will unblind the subject, Investigator, and site staff to Part 2 treatment assignment (but not Part 1 treatment) at the time that the subject transitions to Part 3 as Part 3 involves a continuation of the treatment received in Part 2.

During Part 1, Sponsor employees will also be blinded to the treatment allocation of individual subjects, with the exception of Sponsor staff responsible for managing clinical supplies.

The Sponsor and all other personnel who are blinded to study treatment will remain blinded to Part 1 treatment until after the database has been locked for the primary analysis at the end of Part 1.

5.3. Final Analysis

Final analysis for the study will occur when the last subject completes the study, the data are cleaned, and the database is locked for analysis.

5.4. Other Analyses to Support Safety Review and Regulatory Submissions

Ongoing safety analyses for the purpose of Data Monitoring Committee (DMC) review will be conducted. Sponsor and CRO staff who work on the reporting of the study will remain blinded during Part 1. See Section 5.2 for discussion of blinding during Part 2. A CRO statistician and

CRO programmers separate from the group working on the primary analyses will be unblinded for purpose of DMC analyses.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Tables and listings will be prepared in accordance with the current ICH guidelines (ICH 1995). The information and explanatory notes in the "footer" or bottom of each table and listing will include the following information:

- Date of data extraction
- Date of output generation
- Statistical Analysis System (SAS®) program name, including the path where the program is stored
- Any other output specific details that require further elaboration

Version 9.4 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings. All SAS programs prepared to analyze the data will be properly annotated to permit uninvolved outside statistical experts to replicate all the analyses specified in this SAP.

Listings for the Part 1 interim analysis will include Part 1 treatment only. These listings will generally be sorted by subject ID, and visit, if applicable. Listings for the entire study period will include will generally be sorted by subject ID, treatment, and visit, if applicable.

Adjusted visit (as described in Table 8) will be included on listings that cover the entire study period as applicable. Listings will also include visit date, days relative to first dose of Part 1 treatment, and days relative first dose of Part 2 treatment, if applicable.

One exception to the sort order is that laboratory listings will be sorted by laboratory parameter first and then by the other variables.

For the Part 1 interim analysis, displays will be summarized by Part 1 treatment. A column that combines both active treatments will also be included (see Table 5).

Table 5: Treatment Descriptors for Part 1 Only Displays

Sort order	Part 1 Treatment Descriptor	Notes
1	110 mg	110 mg
2	150 mg	150 mg
3	All active	Combined 110 mg and 150 mg groups
4	Placebo	Placebo

Column order will be in order of ascending dose, combined active doses, and placebo. A total column will be included as applicable. Generally, total columns are included on demographic and baseline characteristics tables as well as on certain safety tables, such as AE tables.

Demographic and baseline characteristic displays will be repeated for Part 2 to characterize the subset of subjects who continue in Part 2. Total columns will be included. For these displays the treatment descriptors will be as shown in Table 6. The descriptors shown in Table 6 also apply to any displays specific to Part 3.

Table 6: Treatment Descriptors for Displays using only Part 2 or Part 3

Sort order	Treatment Descriptor	Notes
1	110 mg	110 mg
2	150 mg	150 mg
3	110 mg after placebo	For subjects who were originally randomized to placebo and were randomized to 110 mg for Parts 2 with continuation of treatment in Part 3.
4	150 mg after placebo	For subjects who were originally randomized to placebo and were randomized to 150 mg for Parts 2 with continuation of treatment in Part 3.

For tables that cover the entire study period, 110 and 150 mg data from subjects assigned to placebo in Part 1 will be separated from 110 and 150 mg data from subjects assigned to active treatment in Part 1. For some tables, there will also be columns that combine data from each active treatment whether received in Part 2 and 3 only or during the entire study. Treatment descriptors are provided in Table 7.

Table 7: Treatment Descriptors for Displays for Entire Study

Sort order	Treatment Descriptor	Notes
1	110 mg	110 mg (originally randomized)
2	110 mg after placebo	Active treatment data from subjects who were originally randomized to placebo and were randomized to 110 mg for Parts 2 and 3
3	All 110 mg	Combines 110 mg data from subjects originally assigned to placebo with 110 mg data from subjects originally assigned to 110 mg
4	150 mg	150 mg (originally randomized)
5	150 mg after placebo	Active treatment data from subjects who were originally randomized to placebo and were randomized to 150 mg for Parts 2 and 3
6	All 150 mg	Combines 150 mg data from subjects originally assigned to placebo with 150 mg data from subjects originally assigned to 150 mg
7	All active	Combines all data collected for 110 and 150 mg treatment regardless of original randomization of subject
8	Placebo	Placebo (includes data from Part 1 only)

Note: Not all columns will be required for any given table.

For tables produced by visit that combine active treatment data for those originally assigned to active treatment with those originally assigned to placebo there will be an adjusted visit that corresponds to the time since active dosing (either Day 1 for those originally assigned to active dose or Week 24 visit for those originally assigned to placebo; see Table 8). This will allow for combining data from active treatments in Part 1 (either 110 or 150 mg) with active treatment in Parts 2 and 3 that follows placebo (either 110 or 150 mg). The adjusted visit for those assigned to 110 or 150 mg in Part 1 will equal the original visit (ie, Day 1).

Table 8: Adjusted Visit for Active Treatment for Subjects Originally Assigned to Placebo

Original Visit	Adjusted Visit
Week 24	Day 1
Week 26	Week 2
Week 28	Week 4
Week 32	Week 8
Week 36	Week 12
Week 48	Week 24
Week 60	Week 36
Week 72	Week 48
Week 84	Week 60
Week 96	Week 72

Note: There is no visit in Part 2 that corresponds with the Week 18 visit in Part 1. Likewise, there are no Part 3 adjusted visits corresponding with original visits of Weeks 26, 28, and 32

For tables with count data, such as TEAE tables, additional displays based on the number of TEAEs per person-years of exposure may also be provided to adjust for the differing periods of exposure to active treatment for those originally randomized to placebo with those originally randomized to active treatment.

Summary tables for medications and free-text fields for HAE medication history are coded according to the World Health Organization (WHO) Drug Dictionary from March 2017. AE preferred terms (PT) and body/organ systems are coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 19.1.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Tables, listings, and figures will be numbered using a decimal system to indicate the main levels of unique displays and sub-levels of replicate displays. The first level represents the appendix within which the tables, figures, and listings will appear. This will be 14 for tables and figures and 16.2.x for listings. The second level of the numbering represents the type of data; 1 for study population, 2 for efficacy, 3 for safety, 4 for health outcomes, 5 for pharmacokinetics (PK), and 6 for PD. The third level of numbering represents the type of endpoint within the data type, the fourth represents a count of displays for the endpoint, and the fifth level is used for repeated tables. For example, tables may be repeated using a different population or for a subset of subjects.

Secondary titles will be used to identify the analysis population used for the displays.

In general, the listings should be sorted and presented by treatment assignment, subject number, and visit, if applicable. For Part 1 listings that include visit, visit date and study day should be

included on listings. For listings produced for the entire study that include visit, displays should include visit, adjusted visit, visit date, study day, and adjusted study day.

6.3. Data Management

A data management plan will be developed and approved prior to commencement of data entry. Data will be captured using the Medidata electronic data capture system. Electronic validation steps (edit checks) will be utilized, and data cleaning will occur in conjunction with each site. Prior to transfer of data provided by vendors (eg, laboratory data), a data transfer agreement including specifications for the type of file, definitions of variables, and contact information for the sending and receiving parties will be developed and finalized. The standard operating procedures (SOPs) of PharPoint, the selected statistics and programming vendor for this study, will be used.

Data will be mapped to Study Data Tabulation Model (SDTM)-compliant datasets prior to creation of Analysis Data Model (ADaM)-compliant derived datasets for use in the creation of summary tables. All analyses will be generated using SAS version 9.4 or above and in accordance with PharPoint SOPs.

6.4. Data Presentation Conventions

Continuous variables (eg, age) are summarized using descriptive statistics (the number of subjects with available data, the mean, SD, median, and minimum and maximum). Categorical variables (eg, race) are summarized using counts and percentages. Percentages are calculated using the total number of subjects per treatment group unless otherwise specified.

The following conventions are applied to all data presentations and summaries:

- For continuous variables, all mean and median values are formatted to 1 more decimal place than the measured value. SD values are formatted to 2 more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time (24-hour clock) as HH:MM for presentation. Dates missing day are denoted as MMMYYYY and dates missing both day and month are denoted as YYYY in listings. Handling of partial dates for analysis is discussed in Section 6.8.
- Wherever possible, data will be decimal aligned.

The table of contents of statistical displays is provided in Section 17.1 as part of this SAP. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP, nor will they be considered as deviations from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not necessarily specified in the individual sections throughout the document.

6.5. Analysis Populations

6.5.1. Screen Failures

Subjects who give informed written consent but are not randomized to study treatment and are noted as screen failures in the electronic case report form (eCRF) are considered screen failures. Reasons for screen failure will be summarized using this population.

6.5.2. Safety Population

The safety population will include all subjects who receive at least 1 capsule of study treatment. This population will be used in the assessment and reporting of demographic information, BCX7353 drug concentrations, accountability, baseline disease characteristics, and safety data. Data will be analyzed according to the actual treatment received at first dose for all subjects or at first dose of Part 2 for subjects originally randomized to placebo.

6.5.3. Intent to Treat Population

The intent to treat (ITT) population will include all randomized subjects, regardless of whether study treatment was administered. This population is the primary population for the analysis of the efficacy and health outcomes data. Data will be analyzed according to randomized treatment.

6.5.4. Per-Protocol Population

The per protocol (PP) population will include subjects in the safety population who complete Part 1. In addition, a decision will be made prior to database lock on which (if any) subjects are to be excluded from the PP population based upon major protocol deviations. In the PP analysis, subjects will be assessed based on the actual treatment received. The PP population may be used as a secondary population for efficacy analyses.

6.5.5. Completers

The subset of subjects in the ITT population who complete Part 1 of the study will comprise the completers population. The completers population will be used for a sensitivity analysis of the primary efficacy analysis for Part 1 only. Data will be analyzed according to randomized treatment.

6.5.6. Pharmacodynamic Population

The PD population will include all subjects for whom at least 1 pre- and post-dose plasma kallikrein inhibition result can be estimated. Data will be analyzed according to the actual treatment received. This population will be used for the listings and summaries of PD data.

6.5.7. Pharmacokinetic/Pharmacodynamic Population

The PK/PD population will include all subjects for whom at least 1 pre- and post-dose plasma kallikrein inhibition result can be estimated with a corresponding plasma BCX7353 concentration (placebo samples not analyzed will be assumed to have a zero concentration). This population will be used for plots comparing plasma kallikrein inhibition and plasma BCX7353 concentrations.

6.6. Baseline Definition

In general, the baseline value is the last available assessment prior to the time of first dose of study drug unless otherwise specified. For tables that include adjusted visit information, the baseline for active treatment for subjects who originally were assigned to placebo will be the last available assessment prior to the time of first dose of active treatment in Part 2, unless otherwise specified. The date and time of first dose of treatment in Part 2 is recorded in the eCRF at the Week 24 assessment.

6.6.1. Baseline Attack Rate

Enrollment into treatment groups is stratified by the baseline HAE attack rate as determined by the IXRS system based on the number of attacks and duration of screening as input by the sites (≥ 2 attacks/month vs. < 2 attacks/month). For analysis purposes, the baseline attack rate will be calculated from the diary data and expressed as attacks per month where 1 month = 28 days as follows:

$$\frac{\text{Number of HAE attacks meeting baseline criteria from Screening to First Dose Date/time} \times 28}{\text{Date of First Dose} - \text{Screening Date} + 1}$$

Criteria that must be met for attacks to qualify for confirmation by the Investigator during the baseline period are provided in Section 4.1.

Baseline attack rate will be included in statistical models as appropriate.

6.6.2. Categorized Baseline Attack Rate

Categorized baseline attack rate refers to the categorization of the calculated baseline attack rate into strata (≥ 2 attacks/month vs < 2 attacks/month).

6.6.3. Baseline Age

Age at time of consent is collected on the demographics form. This will be the baseline age for analyses and for determination of whether the subject is classified as an adult (≥ 18 years) or an adolescent (12 to 17 years).

6.7. Derived and Transformed Data

6.7.1. Study Day

In this study, it is possible that the randomization date and date of first dose could differ. Study Day 1 is defined as the date of first dose.

If the date of measurement for a particular endpoint occurs on or after the first dose date, then study day will be calculated as:

$$(date\ of\ measurement\ -date\ of\ first\ dose)\ +1$$

If the date of measurement occurs prior to the first dose date then study day will be calculated as:

$$date\ of\ measurement\ -date\ of\ first\ dose$$

There is no Day 0.

6.7.2. Change from Baseline

Change from baseline is calculated as:

$$post\ baseline\ result - baseline\ result$$

Percent change from baseline is calculated as:

$$(change\ from\ baseline \div baseline\ result) \times 100$$

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.7.3. Visit Windows

For summary purposes in general, records will be assigned to the scheduled visit collected on the case report form (CRF). Unscheduled and early termination visits will be assigned to an analysis window according to the study day of the actual visit date using the visit windows displayed in Table 9. All information collected at an unscheduled visit will be identified as such in the listings.

Table 9: Visit Windows (Days)

Visit	Relative Target Day	Protocol-Specified Visit Window	Analysis Visit Window
Screening visit	-14 to -56	-70 to -14	-70 to -14
Baseline	1	1	1
Week 2	15	13 to 17	2 to 22
Week 4	29	27 to 31	23 to 43
Week 8	57	55 to 59	44 to 71
Week 12	85	83 to 87	72 to 106
Week 18	127	125 to 129	107 to 148
Week 24	169	169	149 to 176
Week 26	183	181 to 185	177 to 190
Week 28	197	195 to 199	191 to 211
Week 32	225	223 to 227	212 to 239
Week 36	253	251 to 255	240 to 295
Week 48	337	330 to 343	296 to 373
Week 60	421	415 to 427	374 to 463
Week 72	505	499 to 511	463 to 547
Week 84	589	583 to 595	548 to 631
Week 96	673	664 to 680	≥632

6.7.4. Multiple Assessments

Where multiple planned scheduled measurements are recorded for a given time point (eg, electrocardiograms [ECGs]), the mean of the measurements will be calculated and used in any derivation of summary statistics. All available data will be listed.

When multiple visits occur within the same window, the scheduled visit will be used in analysis if available. If no scheduled visit occurs within the window and an unscheduled visit(s) and/or early termination visit occur within the window, the analysis visit closest to the target day will be selected for use in analysis. If deemed appropriate by the Sponsor (eg, in the case of a retest), unscheduled visits may be chosen for analysis given documentation of the desired visit from the Sponsor. Results from unscheduled visits will be eligible for inclusion in analyses of worst post-baseline results. Listings will display all visits as recorded on the CRF, including the date and study day. All available data including any totals, domains, or subscales of scale assessments summarized will be listed.

6.7.5. Derived Efficacy Endpoints

6.7.5.1. Attack Rate

General Formula for Attack Rate

In general, the formula for computing an attack rate is the number of attacks meeting the attack criteria divided by the duration of treatment during the reporting period of interest.

$$\begin{aligned} &duration\ of\ treatment\ during\ the\ reporting\ period\ of\ interest \\ &= the\ last\ day\ in\ the\ reporting\ period \\ &- the\ first\ day\ in\ the\ reporting\ period + 1 \end{aligned}$$

$$\begin{aligned} &Attack\ Rate\ \left(\frac{attacks}{month}\right)\ During\ Reporting\ Period\ of\ Interest \\ &= \frac{\text{Number of Attacks} * 28}{\text{Duration of Treatment During Reporting Period in Days}} \end{aligned}$$

If the subject discontinues treatment early, any attacks that occur within 24 hours after last dose will be counted in the calculation of attack rate and the additional 24 hour period will be included in the duration of the reporting period.

Subject-Reported Attack Rate

Diary entries for attacks are considered subject-reported attacks. The count of subject-reported attacks can differ from the count of confirmed attacks. In Parts 1 and 2, the investigator reviews each attack and either confirms it as an attack or rejects it as an attack. For Part 3, there is no investigator review of attacks, but an adjusted subject-reported attack rate will be computed based on a list of programmable requirements.

Subject-reported attack rates will be computed for Parts 1, 2, and 3.

Adjusted Subject-Reported Attack Rate for Part 3

Because there is no investigator-confirmation of attacks during Part 3, an adjusted subject-reported attack rate will be computed.

Subject-reported attacks must meet the following criteria (applied in order) for inclusion in the adjusted subject-reported rate computation:

- Attack must include at least 1 symptom of swelling
- Subject response to diary question, "In retrospect, could there be an alternative explanation for your symptoms other than an HAE attack (ie, allergic reaction, viral cold, etc)?" must be "no"
- Attack must be unique (attack begins > 24 hours from end of the prior attack), otherwise the event will be combined with and treated as a continuation of the preceding attack
- If untreated, attack must have a duration > 24 hours.

Adjusted subject-reported attack rates will be computed for the following reporting periods and expressed in units of attacks/month where 1 month = 28 days:

- Part 3, by month
- Part 3, entire dosing period

For adjusted subject-reported attack rates by month, months will be defined in blocks of 28 days, beginning on the first day of dosing in Part 3. If the subject discontinues treatment early, any attacks that occur within 24 hours after last dose will be counted in the calculation of subject-reported adjusted attack rate and the additional 24 hour-period will be included in the duration of the reporting period.

Confirmed Attack Rate

Confirmed attack rates will be computed based on the number of confirmed attacks that occur during the reporting period of interest.

Confirmed attack rates will be computed for the following reporting periods and expressed in units of attacks/month where 1 month = 28 days:

- Parts 1 and 2, By month
- Parts 1 and 2, Entire dosing period
- Parts 1 and 2, Effective dosing period

Confirmed attack rates will be computed for Part 1 and at the end of Part 2. For confirmed attack rates by month, months will be defined in blocks of 28 days, beginning on Day 1, the day of first dose. The entire dosing period begins on Day 1 or adjusted Day 1 during Part 2 for subjects originally randomized to placebo. The effective dosing period similarly begins on Day 8 or adjusted Day 8. Part 1 continues until the time of Part 2 dose. Part 2 continues until the time of first dose for Part 3. Investigator confirmation is not done in Part 3 and so confirmed attack rate

will not be computed for Part 3. If the subject discontinues treatment early, the reporting period will continue through 24 hours post last dose and any attacks that occur within 24 hours after last dose will be counted in the calculation of attack rate. If there are confirmed attacks in the eCRF without corresponding diary information, as may happen if a subject verbally reports an attack to an investigator but does not enter it into the ediary, the attack will be counted.

For sensitivity analyses for missing data for the Part 1 primary analysis, confirmed attack rates for the entire dosing period for subjects who discontinue treatment early will be re-computed as a weighted average of the observed post-treatment discontinuation attack rate and an imputed attack rate for periods of missing data post-treatment discontinuation. Details are provided in Section 6.8.1.

Confirmed Attack Rate by Location

Confirmed abdominal-only, peripheral, and mixed attack rates will be computed using the location definitions provided in Section 6.7.5.9.

Adjusted Confirmed Attack Rate

An adjusted confirmed attack rate will be computed for use in the determination of the 50% responder endpoint comparing post-baseline attack rates to baseline attack rates. For the adjusted confirmed attack rate, the 2 additional requirements for confirmation of attack rates used during screening will be applied to post-baseline confirmed attacks to determine the number of confirmed attacks meeting the additional requirements. The additional requirements are:

- The attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
- The attacks must have either been treated, required medical attention or be documented to cause functional impairment based on subject entry in the diary. Functional impairment is defined as the subject being unable to perform their daily activities without restriction (ie, subject records that they are at least slightly restricted in their daily activities during their HAE attack).

6.7.5.2. Number and Percentage of Subjects Who Are Attack Free over Entire Dosing Period and Effective Dosing Period

The following attack-free endpoints will be derived for the entire dosing period and for the effective dosing period for Parts 1 and 2:

- The number and percentage of subjects with no confirmed attacks during the period of interest. Subjects with no confirmed attacks who discontinue before the end of the planned treatment period are not considered attack-free.

The attack-free rate for active treatment for subjects originally randomized to placebo will be based on the 24-Week period during Part 2.

6.7.5.3. Number and Proportion of Days with Angioedema Symptoms

The number of days with angioedema symptoms is the sum of the days during the reporting period for which at least 1 symptom is reported during an investigator-confirmed HAE attack.

This endpoint will be determined for Parts 1 and 2 as investigator-confirmation will not be calculated for Part 3. As with the calculation of attack rate, if the subject discontinues treatment during the reporting period, any symptoms during confirmed attacks that occur within 24 hours after last dose will be counted in the calculation of days with angioedema symptoms and the additional 24-hour-period will be included in the duration of the reporting period.

The percentage of days with angioedema symptoms is derived as the number of days with angioedema symptoms divided by the duration of the treatment period of interest.

6.7.5.4. Responder Endpoint

A subject is defined as being a responder to study treatment if the rate of adjusted confirmed attacks during study treatment represents at least a 50% relative reduction compared with the baseline attack rate as defined in Section 6.6.1.

The relative reduction is calculated for Part 1 as:

$$Relative\ reduction = \frac{\text{Baseline attack rate} - \text{Adjusted Confirmed attack rate on treatment}}{\text{Baseline attack rate}} \times 100\%$$

where the adjusted confirmed attack rate while on study treatment is computed as shown in Section 6.7.5.1.

A subject is classified as a responder if the relative reduction in monthly attack rate for Part 1 is ≥ 50%. Otherwise, the subject is classified as a non-responder.

Responder analysis will be conducted for Part 1 only.

6.7.5.5. Attack Duration

The duration of each confirmed on-treatment attack will be calculated in hours, based on the start and stop date and time of the confirmed attack (time the attack finished). Investigators have the option to count more than 1 subject-reported attack as a single confirmed attack. For a confirmed attack that includes more than 1 subject-reported attack, the duration is calculated from the start of the first subject-reported attack to the end of the last subject-reported attack that has been combined into 1 attack. A similar adjustment for duration will be made for adjusted subject-reported attacks that are combinations of two or more subject-reported attacks in Part 3. The duration of the attack from start of the attack to time that the worst was over will also be calculated and summarized.

6.7.5.6. Attack Onset Relative to Prior Dose of Study Drug

For each confirmed on-treatment attack, the time to attack onset from the time of the prior dose of study drug reported in the subject CRF page will be calculated. If there is no dosing time reported for the dose taken prior to the attack, the attack onset time relative to prior dose will be missing. The attack onset time relative to prior dose of study drug is information is used in the listing of attack data only.

6.7.5.7. Medications to Treat HAE Attacks

The following medications reported as taken as acute treatment in the subject diary or androgens listed as acute treatment in the concomitant medications log will be classified in the analyses as targeted medications to treat subject-reported HAE attacks: Androgens, Berinert, Cinrzye, Kalbitor, Firazyr, Ruconest, fresh frozen plasma. Other medications listed in the diary for treatment of HAE attacks will be considered non-targeted medications to treat subject-reported HAE attacks.

6.7.5.8. Attack Symptoms

Symptoms reported for confirmed on-treatment attacks will be included in summaries of attack characteristics. In addition, listings of diary data will show symptoms for all attacks, whether subject-reported or investigator-confirmed.

6.7.5.9. Attack Location

The location of each subject-reported and confirmed on-treatment attack will be determined based on the symptoms indicated in the e-diary as shown in Table 10.

Table 10: Determination of Attack Location Using Symptoms Collected in the e-Diary

Abdominal-Only Attack	**Mixed Attack**	**Peripheral Attack (Inclusive of Skin and Airway Swelling)**
Symptoms checked must only come from this box: Internal swelling or symptoms of internal swelling in the abdomen: • Nausea • Abdominal discomfort • Cramps (colicky pain) • Vomiting • Abdominal pain • Diarrhea [a]	Must have at least 1 symptom from left and right box (from abdominal and peripheral attack characterization)	Symptoms checked must only come from this box: Visible swelling: • Face/head • Neck (outer swelling) • Legs, buttocks/genitals • Eyes • Arms • Feet • Stomach (outside) • Mouth/tongue/lips • Hands • Chest/back • Joints Internal swelling or symptoms of internal swelling in the airways: • Lump in throat/tightness • Change in voice • Difficulty swallowing • Difficulty breathing • Pink rings (erythema marginatum) [a]

Note: headache and fatigue symptoms may be checked but play no role in characterization of a subject-reported or confirmed attack

[a] Diarrhea, erythema marginatum, headache, and/or fatigue cannot be selected alone or in combination without another symptom(s) of swelling or internal swelling to be considered a confirmed attack.

6.7.5.10. Attack Triggers

All attack triggers for each subject-reported attack will be included in listings of attack data.

6.7.5.11. AE-QoL

The AE-QoL (Weller, Groffik et al. 2012) consists of 4 domains and a total score. 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.

Dimensions	Item
Functioning	1. Impairment of work
	2. Impairment of physical activity
	3. Impairment of spare time activities
Fatigue/mood	4. Impairment of social relations
	6. Difficulties of falling asleep
	7. Waking up during the night
	8. Feeling tired during the day
	9. Difficulties in concentrating
	10. Feeling downhearted
Fears/shame	12. Feeling burdened at having swellings
	13. Fear of new suddenly appearing swellings
	14. Fear of increased frequency of swellings
	15. Ashamed to visit public places
	16. Embarrassed by the appearance of swellings
	17. Fear of long term negative drug effects
Nutrition	5. General limitations in foods and eating
	11. Limitations in the selection of food and beverages
Total score	Items 1 to 17

The AE-QoL domain scores and the AE-QoL total score are calculated using the following formula:

$$(\Sigma\ items) \div (\max \Sigma\ items) \times 100$$

where

Σ items = Sum of reported item scores per CRF

Max Σ items = Sum of the maximum possible score for each domain

The calculated AE-QoL ranges from 0 (best) to 100 (worst).

Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0 to 100 scale), the calculated scores are not highly influenced by missing items. An AE-QoL domain score should not be calculated if more than 1 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. Note that subjects who do not work were instructed to leave question 1 blank. As long as that is the only question in the functioning domain that is missing, the functioning domain can still be calculated.

6.7.6. Derived Health Outcomes Endpoints

6.7.6.1. EQ-5D-5L

The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EuroQoL Visual Analogue Scale (EQ VAS). The descriptive system is comprised of five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as shown in Table 11. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number to express the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number to describe the respondent's health state. For example, 11122 would represent the health state for someone who has no problems with mobility, self-care, or usual activities, but who has slight pain or discomfort and slight anxiety or depression.

Note that this study uses the questionnaire in its validated form for subjects to report their health status "*today"*. If the subject has had an HAE attack since their last visit, starting at Week 4, they complete it a second time to reflect on their health status during a *"usual attack*". On summary tables, the "*today"* and *"usual attack*" questionnaire results should appear in different rows.

Table 11: EQ-5D-5L Dimensions (UK English Sample Version)

Dimensions	Item
Mobility	I have no problems in walking about
	I have moderate problems in walking about
	I am unable to walk about
	I have severe problems in walking about
	I am unable to walk about
Self-care	I have no problems washing or dressing myself
	I have slight problems washing or dressing myself
	I have moderate problems washing or dressing myself
	I have severe problems washing or dressing myself
	I am unable to wash or dress myself
Usual activities *(eg, work, study, housework, family or leisure activities)*	I have no problems doing my usual activities
	I have slight problems doing my usual activities
	I have moderate problems doing my usual activities
	I have severe problems doing my usual activities
	I am unable to do my usual activities
Pain/discomfort	I have no pain or discomfort
	I have slight pain or discomfort
	I have moderate pain or discomfort
	I have severe pain or discomfort
	I have extreme pain or discomfort
Anxiety/depression	I am not anxious or depressed
	I am slightly anxious or depressed
	I am moderately anxious or depressed
	I am severely anxious or depressed
	I am extremely anxious or depressed

Abbreviations: EQ-5D-5L = EuroQoL 5-dimensional, 5-level questionnaire; UK = United Kingdom.

The EQ VAS records the respondent's self-rated health on a 20-cm vertical visual analogue scale (VAS). The VAS is numbered from 0 to 100 with 0 meaning 'the worst health you can imagine' and 100 meaning 'the best health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ-5D-5L asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

For each subject and visit, the 5-digit health state will be converted into a single summary index, the EQ-5D Index, using the EQ-5D-5L Index calculator with US value set (van Hout, Janssen et al. 2012).

A manual for EQ-5D is available (van Reenen and Janssen 2015).

6.7.6.2. Treatment Satisfaction Questionnaire for Medication

The TSQM consists of 14 items of which 13 items are made up of 3 specific scales (effectiveness, side effects, and convenience) and a global satisfaction scale (global satisfaction). In addition, 1 item (Item 4) questions whether as a result of taking this medication, the subject experienced any side effects at all, which can be answered by yes or no. Scale scores are calculated for each scale and are transformed into scores ranging from 0 to 100, with higher scores indicating higher satisfaction.

The 14 questions are detailed in Table 12.

Table 12: List of Questions for TSQM

Item #	TSQM Item
1 [a]	How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
2 [a]	How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
3 [a]	How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
4 [b]	As a result of taking this medication, do you currently experience any side effects at all?
5	How bothersome are the side effects of the medication you take to treat your condition?
6	To what extent do the side effects interfere with your physical health and ability to function (ie, strength, energy levels, etc.)?
7	To what extent do the side effects interfere with your mental function (ie, ability to think clearning, stay awake, etc.)?
8	To what degree have medication side effects affected your overall satisfaction with the medication?
9	How easy or difficult is it to use the medication in its current form?
10	How easy or difficult is it to plan when you will use the medication each time?
11	How convenient or inconvenient is it to take the medication as instructed?
12	Overall, how confident are you that taking this medication is a good thing for you?
13	How certain are you that the good things about your medication outweigh the bad things?
14 [a]	Taking all things into account, how satisfied or dissatisfied are you with this medication?

Abbreviations: TSQM = Treatment Satisfaction Questionnaire for Medication.
[a] These items are scaled on a 7-point bipolar scale from “extremely dissatisfied” to “extremely satisfied”.
[b] Item #4 is a dichotomous response option with a conditional skip to Item #9.
Source: (Atkinson, Sinha et al. 2004)

The scale scores, also with higher numbers indicating higher satisfaction, are calculated as:

Effectiveness

$$([(Item\ 1 + Item\ 2 + Item\ 3) - 3] \div 18) \times 100$$

If 1 item is missing:

$$([Sum\ of\ Available\ Items) - 2] \div 12) \times 100$$

Side Effects

If Item 4 answer is "No" then score = 100.

Else:

$$([Sum\ of\ Item\ 5\ to\ Item\ 8) - 4] \div 16) \times 100$$

If 1 item is missing:

$$([(Sum\ of\ Available\ Items) - 3] \div 12) \times 100$$

Convenience

$$([Sum\ of\ Item\ 9\ to\ Item\ 11) - 3] \div 18) \times 100$$

If 1 item is missing:

$$([(Sum\ of\ Available\ Items) - 2] \div 12] \times 100)$$

Global Satisfaction

$$([Sum\ of\ Item\ 12\ to\ Item\ 14) - 3] \div 14) \times 100$$

If Item 12 or Item 13 is missing:

$$([(If\ Sum\ (the\ 2\ Completed\ Items) - 2] \div 10) \times 100$$

If Item 14 is missing:

$$([Sum\ of\ Available\ Items) - 2] \div 8) \times 100$$

If more than 1 item is missing from any subscale, then the subscale will not be calculated.

6.7.6.3. Work Productivity and Activity Impairment Questionnaire

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes). There are 4 impairment scores. The scoring is as follows (Reilly Associates 2002):

1. Absenteeism: Percent work time missed due to health:

$$100 \times [Q2 \div (Q2 + \text{Q4})]$$

2. Presenteeism: Percent impairment while working due to health:

$$100 \times [Q5 \div 10]$$

3. Work productivity loss: Percent overall work impairment due to problem:

$$100 \times \{Q2 \div (Q2 + Q4) + [(1 - Q2 \div (Q2 + Q4) \times (Q5 \div Q10)]\}$$

4. Activity impairment: Percent activity impairment due to health:

$$100 \times (Q6 \div 10)$$

where,
Q2 = hours missed due to health problems
Q3= hours missed due to other reasons
Q4 = hours actually worked
Q5 = degree health affected productivity while working (circle a number from 0 to 10, where 10 is worst impairment)
Q6 = degree health affected regular activities (circle a number from 0 to 10, where 10 is worst impairment)

Q1 asks whether the individual works for pay (yes/no). If the answer to that question is 'No' then the subject is instructed to skip to Q6.

6.8. Handling of Missing Data

6.8.1. Imputation of Missing Efficacy Endpoints Post Study Treatment Discontinuation

The attack rate used in the Part 1 primary analysis will be based on the observed data until the time of treatment discontinuation, if applicable. For the primary analysis at the end of Part 1, missing data sensitivity analyses will be conducted for handling of data for subjects who discontinue study treatment prior to the end of Part 1 in three ways:

1. Using observed post-treatment discontinuation data where available without imputation for missing data. For this analysis, the attack rate will be computed through the last date of observed data up to the Part 2 treatment start date/time, including data collected after treatment discontinuation.
2. Observed post-treatment discontinuation data will be used in combination with an imputed attack rate for the time period, post-treatment discontinuation, where data were not observed. An imputed rate for the entire 24-week period will be a weighted average of the observed rate up to the last day of diary collection (including days post treatment discontinuation) and the imputed rate for the time after treatment discontinuation during which data were not observed, with weighting based on the fraction of days with observed vs. unobserved data. For this rate, actual diary data collected after discontinuation of study treatment will be included in the observed rate where it is available by extending the time period in the denominator of the attack rate calculation to the last day that diary data were collected, even if past study treatment discontinuation. The only exception to this is if the subject started other prophylactic treatment after discontinuation of study treatment. In that case, actual diary data will be used up until the time of start of other prophylactic treatment.

   For subjects for whom no diary data is missing post study treatment discontinuation, no imputation is necessary. An observed confirmed attack rate will be computed to include data post study treatment discontinuation as applicable, as long as the subject did not start other prophylactic therapy.

   For subjects with missing data post study treatment discontinuation, missing data will be imputed as follows:

$$f = Fraction\ of\ Non\text{-}missing\ Data$$

$$= \frac{\text{Date of Last Day of Diary Collection Prior to Any Other Prophylactic Treatment} - \text{Date of First Dose} + 1}{169}$$

$$r_{observed} = Observed\ \ Monthly\ Attack\ Rate\ Regardless\ of\ Study\ Treatment\ Discontinuation$$

$$= \frac{\text{Number of Attacks} * 28}{\text{Date of Last Day of Diary Collection Prior to Any Other Prophylactic Treatment} - \text{Date of First Dose} + 1}$$

$$r_{imputed} = Imputed\ Monthly\ Attack\ Rate\ for\ the\ Unobserved\ Period$$

$$= \begin{cases} if\ missing\ at\ random, impute\ from\ complete\ cases\ in\ same\ treatment\ group \\ if\ not\ missing\ at\ random, median\ value\ of\ highest\ (worst)\ quartile\ rate\ in\ same\ treatment\ group\ or\ subject\ observed\ rate, if\ worse \end{cases}$$

$$r_{analyzed} = f * r_{observerd} + (1 - f) * r_{imputed}$$

As shown above, if a subject discontinues study treatment or withdraws from the study, the imputation of $r_{imputed}$ will differ depending on whether the data are considered missing at random or not missing at random based on the reason for study treatment discontinuation or study withdrawal as shown in Table 13. Data missing at random will be imputed using multiple imputation with 10 separate founds of imputations, randomly selecting from observed confirmed attack rates of other subjects in the treatment group who completed the treatment for Part 1. Data not missing at random will be imputed using the median attack rate of subjects in the worst quartile of performance (ie, highest attack rate quartile) with regard to the primary endpoint for the given treatment group or the subject's observed rate over the time period of available data, if worse.

Table 13: Reason for Study Treatment Discontinuation and Whether Data are Considered Missing at Random or Not

Missing Data Considered Missing at Random	Missing Data Considered Not Missing at Random
Subsequent determination that inclusion/exclusion criteria were not met	Laboratory abnormality or adverse event
Intercurrent illness or emergence of new illness/medical condition/pregnancy	Discontinuation due to QT prolongation
Subject noncompliance with study drug or procedures	Discontinuation due to rash
Subject withdrew consent	Perceived lack of efficacy
Other [a]	Other [a]
Sponsor discontinuation [a]	Sponsor discontinuation [a]
Investigator judgment [a]	Investigator judgment [a]

[a] A review of discontinuations for Sponsor discontinuation, Investigator judgment, or other reason will be completed prior to unblinding of Part 1 data for determination of missing at random or not missing at random.

1. A tipping point analysis will be conducted using the observed data post treatment-discontinuation combined with imputed data for missing time periods. However, for tipping point analysis, $r_{imputed}$ will be multiplied by a factor, δ, for the active treatment group in the determination of the analyzed rate, as shown below. For the placebo group, there will be no such multiplicative factor. The tipping point is the value of δ that leads to a reversal of a significant p-value. It shows how much larger than expected the attack rate would need to be for the time period of missing data for the active group in order to "tip" the significance level to non-significant. For tipping point analysis, the analyzed rate for the active treatment group is:

$$r_{analyzed} = f * r_{observerd} + (1 - f) * \delta * r_{imputed}$$

For the placebo group, the analyzed rate would remain as:

$$r_{analyzed} = f * r_{observerd} + (1 - f) * r_{imputed}$$

6.8.2. Other Sensitivity Analyses for Missing Data

The PP population analyses will serve as a sensitivity analysis for missing data by displaying the results of analysis for subjects who generally followed the protocol. Analysis of the primary efficacy endpoint based on the completers population will also serve as a sensitivity analysis for missing data by showing the attack rate in subjects who completed Part 1 of the study.

6.8.3. Missing Start and Stop Dates for Prior and Concomitant Medication

For analysis of medications, a complete date should be established to identify medication as occurring during treatment or not. For the purposes of handling partially reported start and stop dates for medication the following algorithm will be applied:

- Missing start day, but month and year present:

  If trial medication had been taken in the same month and year as the occurrence of the medication, then the start day of the medication will be assigned to the day of first dose of trial medication.

  Otherwise the start day will be set to the first day of the month.

- Missing start day and month, but year present:

  If trial medication had been taken in the same year as the occurrence of the medication, then the start date of the medication will be assigned to the date of first application of trial medication.

  Otherwise the start day and month will be set to 01 January.

- Missing end day, but month and year present:

  The day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to the date of trial termination.

However, if trial termination year is greater than the year of the event/medication, then the day and month will be set to 31 December.

- For paper diaries where the date of an acute concomitant medication is missing, the date will be imputed as the date of the attack.

In subject data listings, start and stop date of medication will be displayed as reported on the eCRF.

6.8.4. Missing Start Date, Stop Date, Severity, or Relationship for Adverse Event

The same conventions to address incomplete dates for prior and concomitant medications will also be used for AEs. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study treatment.

6.8.5. Missing Time of First Dose or Time of Last Dose

In case of missing time for first dose, it will be assumed that baseline measures that were to be taken prior to first dose according to the protocol were in fact taken prior to dosing.

In case the time of the last dose is not reported, time of dose will be assigned as the median dosing time from all prior doses for the subject, as subjects are to dose once per day at approximately the same time each day.

6.8.6. Incomplete Date and Time for a Subject-Reported Attack

For HAE attacks reported with a missing stop date and or time, the following algorithm will be applied:

- Missing start time but start date present:
  The start time will be set to 12:00PM.
- Missing start date and time:
  The start date will be set to the date for which the question was answered “Yes”. The start time will be set to 12:00PM
- Missing stop time, but stop date present:
  The stop time will be set to 11:59PM
- Missing stop date and time:
  The stop date will be set to the attack start date, the stop time will be set to 11:59PM

7. STUDY POPULATION

7.1. Subject Disposition

A summary table will be generated to provide the number and percentage (based on subjects randomized) of subjects in each of the analysis populations.

Subject status at the end of Part 1 will be listed and summarized as a Part 1 only display based on the ITT population, showing the number and percentage of subjects with early discontinuation of study treatment and early withdrawal from the study along with reasons for each item. Subjects

will be considered to have completed Part 1 if they have a Week 24 visit. A similar summary table and listing will be provided at the end of the study and will show discontinuations over the entire study period. The listings will include whether subjects discontinued from the study drug, whether they withdrew from the study and the reasons for the discontinuation of study drug, along with the date of first and last dose and the date of completion or discontinuation from the study drug and date of study withdrawal. Duration on study treatment and on the study will also be provided.

A CONSORT diagram will be created based on the summary tables for the CSR, starting with the number of subjects screened.

A summary of enrollment by country and investigator site will be provided.

7.2. Screen Failures

The number of screen failures and percent of screened subjects who are screen failures will be summarized along with reasons for screen failure. A summary and listing of demographic information for screen failures will be provided.

Confirmation of clinical diagnosis of HAE will be summarized based on the protocol inclusion criterion: C1 esterase inhibitor (C1-INH) functional levels, C4 levels, SERPING-1 gene mutation, and family history.

Additionally, SERPING result listings will show whether tested subjects were positive or negative for the SERPING-1 gene mutation and hence whether they failed screening due to a negative SERPING result.

7.3. Protocol Deviations and Listing of Subject Inclusion and Exclusion Criteria

Subjects who were randomized but did not satisfy all inclusion and exclusion criteria will be listed. A listing of subjects for whom the treatment blind was broken during the study will also be provided, if appropriate.

Protocol deviations will be included in listings and summaries for the CSR. A separate document will detail decision-making guidelines for determining whether a protocol deviation is major or minor and, for major protocol deviations, whether they would result in exclusion from the PP population. It will also detail a list of categories of protocol deviations. Protocol deviations will be reviewed in data review meetings prior to Part 1 unblinding to classify protocol deviations into categories, determine whether they are major or minor and to determine whether they will result in exclusion from the PP population.

Analyses based on the PP population will only be produced for Part 1 analysis.

A summary of all protocol deviations by type of deviation will be provided for Part 1.

A review of protocol deviations for Parts 2 and 3 will be conducted prior to database lock for the final CSR after the last subject has completed the last study visit. Protocol deviations for Parts 2 and 3 will be summarized by Part 2/3 treatment (Table 6) and category of deviation and will be listed but will not result in exclusion from the PP population.

7.4. Demographic and Baseline Characteristics

Demographic summary tables will be provided separately for Part 1 and the end of study (Table 6). The ITT and PP populations will be the primary populations for analyses of demographics. Demographics, including age, gender, race, ethnicity, childbearing potential, weight, height, and body mass index (BMI) will be listed and summarized. Age (in years) will be reported as the age at consent or assent, as collected in the eCRF.

BMI (kg/m^2) will be calculated using the standard formula:

$$\text{BMI } (kg/m^2) = \text{Weight } (kg)/[\text{Height } (m)]^2$$

Confirmation of clinical diagnosis of HAE will be summarized based on the protocol inclusion criterion: C1-INH functional levels, C4 levels, SERPING-1 gene mutation, and family history. All SERPING results will be listed.

7.5. HAE Medical and Medication History

HAE and HAE medication history will be summarized for the following where possible:

- HAE history
- Past on-demand treatments of HAE
- Current on-demand treatments of HAE
- Past prophylactic treatments of HAE

Past on-demand treatments will include those medications that were taken as needed and discontinued prior to the initiation of study treatment as recorded on the HAE Medication History Page. Past prophylactic treatments will include those medications that were taken as prophylaxis and discontinued prior to the initiation of study treatment as recorded on the HAE Medication History Page. Current on-demand medications will include those that are noted at screening as currently used for on-demand treatment as recorded on the HAE Medication History Page. Summaries will include a grouping of any C1-INH medication as well as displays of individual medications. The C1-INH grouping will include plasma-derived C1-INH replacement (brand names = Cinryze, Berinert, HAEgarda), recombinant C1-INH replacement (brand name = Ruconest), icatibant (Brand name = Firazyr), Ecallentide (brand name = Kalbitor), fresh frozen plasma, and lanadelumab (brand name = Takhzyro). The summary of androgens will include androgens (unspecified), oxandrolone, danazol (brand name = Danocrine), and stanozolol.

7.6. Medical History and Medical Conditions Present at Entry

Past or current relevant medical history information will be summarized and listed.

7.7. Prior and Concomitant Non-HAE and HAE Medications

Medication use is collected for the period from 30 days prior to Screening to study completion, except for contraceptives which are collected from 60 days prior. Medications collected in the eCRF that were received and stopped prior to the date of first dose will be considered prior medications. Medications will be considered as concomitant if the start date of the medication is

on or after the date of first intake of study drug or if the start date is prior to the first date of study drug but the medication is ongoing during the treatment period in the study. Medications taken at any time during Part 1 of the study will be considered with Part 1 treatment. Similarly, medications taken at any time during Part 2 or 3 of the study will be considered with Part 2 treatment. For example, a medication which is started during Part 1 while a subject is assigned to a Part 1 treatment of placebo will appear in the Part 1 only summary under the placebo column. If that treatment is continued into Part 2 where the subjects is assigned to a treatment of 110 mg, the medication will also be summarized in the treatment column labeled "110 mg after placebo" in the summary of concomitant medications for the entire study period.

Medication verbatim text will be coded using the WHO Drug Dictionary, March 2017. A summary by Part 1 treatment of recently discontinued medications taken within 30 days of screening but discontinued prior to dosing will be provided.

Separate summaries of concomitant medications for Part 1 only and for the entire study period will be presented using the treatment descriptors in Table 5 and Table 7, respectively. The number and percentages of subjects taking each medication will be summarized by WHO preferred name. Multiple uses of the same medication (by preferred name) will be counted once only per subject per study treatment. No inferential statistics will be provided.

HAE-related medications will be similarly summarized for Part 1 only and for the entire study period.

An attack-level summary will also be provided showing the number of attacks for which the various HAE-related medications were taken based on the subject diary and the concomitant medication form (androgens) in the eCRF.

All medication data will be listed.

7.8. Baseline Physical Examination

Physical examination data will be listed.

7.9. Baseline Primary and Secondary Efficacy Evaluations

All attacks will be listed. The baseline attack rate and the categorized baseline attack rate will be summarized by Part 1 treatment using descriptive statistics for baseline attack rate and n [%] for the categorized baseline attack rate. The proportion of days with HAE symptoms will also be included in the summary.

Similarly, a summary of baseline of AE-QoL total and domain scores will be provided by Part 1 treatment.

8. EFFICACY

8.1. General Considerations

Data from all centers will be combined for analysis.

Hypothesis tests will be 2-sided. Hypotheses comparing each of the 2 active dose groups to placebo will be separately tested. Analyses of Part 2 data will be descriptive. No hypotheses will

be tested for Parts 2 and 3 nor will hypothesis testing be conducted to compare the 2 active dose groups.

8.2. Testing Statistical Assumptions Including Comparability at Baseline

A summary of subgroups will be provided by Part 1 treatment. In addition, the duration of baseline period, baseline attack rate, categorized baseline attack rate (≥ 2 attacks/month vs. < 2 attacks/month), and baseline AE-QoL will be summarized by Part 1 treatment.

8.3. Statement of the Null and Alternate Hypotheses

Hypothesis testing will be conducted for Part 1 only. The primary null and alternative hypotheses, for each active dose separately, are:

- H_o: $R_A = R_P$; active treatment does not have a differential effect on the rate of investigator-confirmed HAE attacks
- H_A: $R_A \neq R_P$; active treatment does have a differential effect on the rate of investigator-confirmed HAE attacks

where R_A is the monthly attack rate for active treatment and R_P is the monthly attack rate for placebo treatment.

Secondary hypotheses are (in order of hierarchical testing):

1. AE-QoL
   - H_o: $\beta = 0$; active treatment does not have a differential effect on the change from baseline AE-QoL at Week 24
   - H_A: $\beta \neq 0$; active treatment does have a differential effect on the change from baseline AE-QoL at Week 24

   where β is the parameter representing treatment effect for the dose of interest in a mixed-effects model with repeated measures (MMRM).
2. Proportion of days with angioedema symptoms
   - Ho: $\beta = 0$; active treatment does not have a differential effect on the proportion of days with angioedema symptoms over the entire treatment period
   - HA: $\beta \neq 0$; active treatment does have a differential effect on the proportion of days with angioedema symptoms over the entire treatment period

   where β is the parameter representing treatment effect for the dose of interest in an analysis of covariance (ANCOVA) model.
3. Rate of investigator-confirmed HAE attacks during the effective treatment period (beginning on Day 8 through 24 weeks)
   - H_o: $R_A = R_P$; active treatment does not have a differential effect on the rate of investigator-confirmed HAE attacks during the effective treatment period
   - H_A: $R_A \neq R_P$; active treatment does have a differential effect on the rate of investigator-confirmed HAE attacks during the effective treatment period

where R_A is the monthly attack rate for active treatment and R_P is the monthly attack rate for placebo treatment during the effective treatment period.

8.4. Subgroup Analyses

Subgroup analyses for the primary endpoint of investigator-confirmed attack rate during the entire 24-week dosing period and the secondary endpoint of Week 24 change from baseline AE-QoL (total score) will be provided by:

1. Region (North America vs. Europe)
2. Sex
3. Race (white vs. other)
4. Baseline attack rate (≥ 2 attacks/month vs. < 2 attacks/month)
5. Age group (< 18, 18 to 65, > 65 years)

Forest plots showing the original results and the results by subgroups will be provided.

A summary of TEAEs by age group will also be provided.

8.5. Multiple Comparisons and Multiplicity

There are 4 endpoints being tested. For each endpoint, there are 2 potential doses to be tested against placebo. The Type I error rate will be controlled at the study level by using a combination of hierarchical testing and the Hochberg procedure. The 4 endpoints will be tested in a hierarchical fashion, and the 2 doses will be tested using the Hochberg step-up procedure at each level of the hierarchy to which both doses progress through the hierarchy.

The first endpoint to be tested is the primary endpoint, the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period of Part 1. Using the Hochberg step-up procedure, each of the 2 doses will be tested at the $\alpha = 0.05$ level, comparing active treatment to placebo. If the maximum of the 2 p-values is < 0.05, the null hypotheses of no difference between the rate of attacks for subjects on active and placebo treatment will be rejected for both doses and testing will proceed to the next endpoint in the hierarchy with $\alpha = 0.05$. If the maximum of the 2 p-values is > 0.05 but the minimum of the 2 p-values is < 0.025, the null hypothesis for the dose with $p < 0.025$ will be rejected and testing for that dose only will proceed to the next endpoint in the hierarchy with $\alpha = 0.025$. Otherwise, the null hypotheses for both doses will not be rejected, testing will stop, and the next endpoint in the hierarchy cannot be tested.

The first, second, third, and fourth endpoints in the hierarchy are:

1. The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to Day 168)
2. Change from baseline in AE-QoL at Week 24 (total score)
3. Number and proportion of days with angioedema symptoms through 24 weeks
4. Rate of investigator-confirmed HAE attacks during dosing in the effective treatment period (beginning on Day 8 through 24 weeks)

The process described above will be continued for each endpoint in the hierarchy until either all 4 endpoints have been tested or testing has stopped due to non-rejection of the null hypotheses for both doses for endpoints earlier in the hierarchy. At each level of the hierarchy, the Hochberg step-up procedure is used to control Type I error rates if 2 doses are to be tested. Otherwise, if only 1 dose is being tested, the single test is conducted with $\alpha = 0.025$.

8.6. Analysis of the Primary Efficacy Endpoint

8.6.1. Primary Efficacy Analysis

The primary efficacy endpoint for Part 1 of the study is the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period during Part 1 (Day 1 to first dose of Part 2). The first dose in Part 2 is expected on Day 169. The primary efficacy analysis will be produced using the ITT population. The estimand will be based on data from subjects who are on study treatment and this analysis will not include data post treatment discontinuation.

The number of investigator-confirmed HAE attacks for Part 1 will be analyzed by treatment group using appropriate descriptive statistics for the confirmed attack rate (expressed as attacks/month) based on the 24-week dosing period or until study treatment discontinuation, if applicable. An additional summary of confirmed attack rate by month, including change from baseline attack rate and percentage change from baseline attack rate by month, will be produced. The primary efficacy analysis will be conducted using Part 1 data and the primary efficacy endpoints will be summarized and listed by Part 1 treatment group.

The attack rate and the treatment comparisons between each BCX7353 dose and placebo in the rate of investigator-confirmed HAE attacks during the Part 1 dosing period will be analyzed using a Poisson regression model. The number of investigator-confirmed attacks will be included as the dependent variable, the treatment will be included as a fixed effect, the stratification variable (baseline attack rate) will be included as a covariate and the logarithm of duration on treatment will be included as an offset variable. The estimated rate of attack for each treatment group, the treatment differences expressed as the attack rate ratio (BCX7353 over placebo rate ratio) and their associated 95% confidence intervals (CIs) will be provided from the Poisson regression model. The percentage reduction from placebo will be calculated for each dose as:

$$Rate\ reduction = 1 - attack\ rate\ ratio = 1 - \frac{R_A}{R_P}$$

Where R_P is the estimated attack rate for Placebo treatment and R_A is the estimated attack rate for Active treatment.

Example SAS pseudo-code for the Poisson regression analysis is as follows:

```
proc genmod data = datasetname;
  class trt01p catblatk/param=glm;
  model icattacks = trt01p catblatk /dist=poisson link=log offset=logdurtrt;
run;
```

All statistical tests will be 2-sided. Multiplicity adjustments for Part 1 analyses for the 2 dose groups are discussed in Section 8.5 along with handling of testing of multiple endpoints.

The Poisson model assumes that the mean and variance are equal. When the variance in the data is larger than the mean, the model is said to be over-dispersed. Over-dispersion is more likely to be a problem if a significant number of subjects have no attacks during the 24-week treatment period. As a sensitivity analysis to examine the appropriateness of the Poisson model, a negative binomial model will be used in place of the Poisson regression model. When the negative binomial dispersion parameter is equal to zero, the negative binomial and Poisson models are equivalent. If the results of the model obtained using the negative binomial distribution are similar to that of the model that assumes the Poisson distribution and a statistical test of the dispersion parameter does not show that it is significantly greater than zero, the Poisson model will remain as the primary model for analysis.

Plots of mean confirmed attack rate by month and scatter plots of baseline attack rate vs. 24-week attack rate will be produced with a different color for each treatment. Plots of mean attack rate per month will be updated to include the Part 2 data at the end of the study. Adjusted subject-reported attack rate data per month will be plotted separately for Part 3, as Part 3 does not include investigator confirmation of attacks.

8.6.2. Sensitivity Analyses of the Primary Efficacy Results

Primary efficacy analysis will be based on the ITT population with a sensitivity analyses for efficacy based on the PP and Completers populations. A second analysis using the ITT population with subject-reported rather than investigator-confirmed attacks will also be conducted.

In addition, there will be 3 sensitivity analyses to examine the effect of missing data.

1. A missing data sensitivity analysis will be conducted in which observed data post study drug discontinuation are included in attack rate determination. The estimand for this analysis is referred to as the de facto estimand. Details on the determination of the attack rate are provided in Section 6.8.1.

2. A missing data sensitivity analysis will be conducted in which observed data post study drug discontinuation are used in combination with imputed data for subjects who discontinue study treatment prior to the end of Part 1 and do not continue to provide attack information. The method of imputation will depend upon whether the data are considered missing at random or not missing at random. Details on the imputation methodology are provided in Section 6.8.1.

3. A tipping point analysis will be conducted in which observed data post study drug discontinuation are combined with imputed data for subjects who discontinue study treatment prior to the end of Part 1 and do not continue to provide attack information. However, for this analysis the imputed attack rates will be multiplied by a factor, δ, for subjects on active treatment. No such factor will be used for subjects on placebo treatment. The tipping point will be estimated as the value of δ that tips the analysis to non-significant. It shows how much greater than expected the attack rate on active treatment would need to be for the missing data to alter the result of the analysis. Details are provided in Section 6.8.1.

A forest plot will be provided to visually compare the results obtained using first 2 methods of sensitivity analyses to the primary efficacy result.

8.7. Analysis of the Secondary Efficacy Endpoints

8.7.1. Angioedema Quality of Life (Total and Domain Scores)

Change from baseline in AE-QoL questionnaire at Week 24 (total score) is a secondary endpoint for Part 1. Durability in AE-QoL questionnaire scores is a secondary endpoint for Parts 2 and 3.

The actual and change from baseline domain and total scores will be summarized by visit and treatment. For Part 1, changes from baseline in AE-QoL will be assessed with a MMRM model with fixed effects for treatment, baseline attack rate, baseline AE-QoL, visit, and a visit by treatment interaction and a random effect for subject. An unstructured covariance structure will be used. The estimated treatment difference comparing each active treatment to placebo at each post-baseline visit (Weeks 4, 6, 12, 18, and 24) will be displayed together with the 95% CI and the associated p-value. Least squares means (LSM) for each visit will also be presented with the standard error and the number of subjects contributing to the LSM. Total and domain scores will be listed for each subject and visit. The responses to the individual AE-QoL questions will also be listed.

Figures of mean actual and change from baseline AE-QoL total and domain scores will be produced with 1 line per treatment group. In addition, a cumulative distribution plot of AE-QoL Total Score at Week 24 will be provided.

Final analyses at the end of study will also include data from visits at Weeks 28, 32, 36, 48, 60, 72, 84, 96, and follow-up. Summaries will be updated to include the additional information. An additional descriptive summary of change from Week 24 will be provided for Part 2 and 3 visits for subjects originally randomized to placebo treatment.

A summary and analysis of the number and percent of subjects with at least a 6-point decrease (Minimum Clinically Important Difference [MCID]) in total AE-QoL score will be performed by visit for Part 1. The summary will be repeated at the end of the study. The analysis for Part 1 will be based on a logistic model with response of achievement of the MCID (yes/no), baseline attack rate and baseline AE-QoL total score as covariates and a fixed effect for treatment.

8.7.2. Number and Proportion of Days with Angioedema Symptoms

The number of proportion of days with angioedema symptoms through 24 weeks is a secondary endpoint for Part 1. The number and proportion of days with angioedema symptoms is also a secondary endpoint for Parts 2 and 3. Definitions of the endpoints are provided in Section 6.7.5.3.

For Part 1, the number and proportion of days with angioedema symptoms through Week 24 will be determined. Both the number and proportion of days will be summarized. The proportion of days with angioedema symptoms through Week 24 will be analyzed using an ANCOVA model with baseline attack rate as a covariate and treatment included as a fixed effect. The estimated treatment difference comparing each active treatment to placebo will be displayed together with the 95% CI and the associated p-value. LSMs will be presented with the standard error and the

number of subjects contributing to the LSM. The number and proportion of days with angioedema symptoms will be listed for each subject. A similar analysis will be conducted based on the effective dosing period, beginning on Day 8 and continuing through Week 24.

Final analyses at the end of the study will include a summary of the number and proportion of days with angioedema symptoms through Week 48 for those subjects originally randomized to active treatment and a summary through adjusted Week 24 for active treatment for subjects originally randomized to placebo. Only subjects who received at least 1 dose of study treatment in Part 2 of the study will be included in this summary. The subject listing will be updated to include the number and proportion of days with angioedema symptoms through Week 48. The number and proportion of days with angioedema symptoms during Part 3 of the study will be reported separately from Part 2.

8.7.3. Rate of Investigator-Confirmed HAE Attacks during Dosing in the Effective Treatment Period

The rate of investigator-confirmed HAE attacks during dosing in the effective treatment period is a secondary endpoint for Part 1.

Summaries and analysis of the investigator-confirmed attack rate using the ITT population for the effective treatment period (Day 8 through Week 24, inclusive) will be conducted using Poisson regression, similar to what is done for the primary efficacy endpoint analysis.

Summary displays will be updated at the end of Part 2 to include data collected during Part 2 of the study. For subjects originally randomized to placebo, data on active treatment will be summarized using the adjusted visits.

8.7.4. Use of HAE Attack Medications

The use of HAE attack medications over 24 weeks is an exploratory efficacy endpoint for Part 1 and a secondary endpoint for Parts 2 and 3. Use of HAE medications based on diary data will be summarized separately from concomitant medications. In addition, summaries and analyses of the rate of investigator-confirmed HAE attacks requiring treatment will be provided for Part 1 and for the study period from Day 1 to the end of Part 2. The analysis will be performed similarly to the analysis of rate of confirmed HAE attacks. For a list of medications that qualify as targeted and non-targeted HAE attack medications, see Section 6.7.5.7**.** Separate summaries of HAE attack medication use for Part 3 will be produced based on adjusted subject-reported attacks.

A Kaplan-Meier plot of time to first use of a targeted HAE rescue medication to treat an investigator-confirmed attack and corresponding summary table will be produced for Part 1.

8.7.5. Discontinuations due to Lack of Efficacy

Discontinuation due to lack of efficacy is a secondary endpoint for Parts 2 and 3.

A summary of the number of subjects who discontinue due to lack of efficacy will be provided with subject disposition. The summary will include the number and percent of subjects who discontinue due to lack of efficacy during Part 1, 2 and 3 as well as overall.

8.8. Analysis of Additional Exploratory Efficacy Endpoints

8.8.1. Number and Proportion of Subjects with No Attacks

The number and proportion of subjects with no attacks over 24 weeks is an exploratory endpoint for Part 1. This information will be descriptively summarized. The summary will be repeated at the end of Part 2 as a summary of the number and proportion of subjects with no attacks over the entire dosing period of 48 weeks for those originally randomized to active treatment. A summary of 24-Week data at the end of Part 2 will be conducted including subjects originally randomized to placebo. The summary will show the number and proportion of subjects with no attacks during the first 24 weeks of active treatment, whether received in Part 1 or Part 2 and separately for those who started active treatment in Part 2. Subjects who discontinue treatment prior to the end of the reporting period of interest will not be considered attack-free. A separate summary of the number and proportion of subjects with no adjusted subject-reported attacks in Part 3 will be provided.

For Part 1, a chi-squared test will be used to test whether there is a difference in the proportion of subjects with no attacks comparing each active dose to placebo. For the chi-squared analysis, if the expected number of subjects in any individual cell is < 5, Fisher's exact test will be used instead the chi-squared test.

A Kaplan-Meier plot and corresponding summary of time to first attack will be produced for Part 1 for both the entire dosing period and the effective dosing period (Day 8 to Week 24).

8.8.2. Proportion of Responders to Study Drug.

Subjects will be classified as responders or non-responders for Part 1 as discussed in Section 6.7.5.4. A responder is defined as a subject who has at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks meeting the stricter screening criteria during treatment compared with the baseline attack rate. A summary of the number and proportion of responders by study treatment will be produced. Logistic regression with responder status as the outcome variable and treatment and baseline attack rate as independent variables in the model will be used to compare each active treatment to placebo treatment. Point estimates of the odds ratios for response comparing 110 mg to placebo and 150 mg to placebo will be calculated along with corresponding 95% CIs. If the proportion of responders is near zero for the placebo treatment (or for either active treatment), logistic regression may not be an appropriate methodology for analysis and Fisher's exact test will be used in place of logistic regression.

8.8.3. Attack Characteristics

Characteristics of attacks including location of attack, duration of attacks from start to finish and from start to the time the worst symptoms of the attack were over, time since last dose, triggers, swelling, other symptoms, whether the attack was treated, severity as assessed by the subject and by the investigator, ability to do daily activities, appearance affected, professional care sought, and location of professional care will be summarized and listed.

A summary of duration of attack for abdominal, peripheral and mixed attacks will also be provided.

8.9. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

A listing of subjects excluded from the PP population will be provided along with reason for exclusion.

9. HEALTH OUTCOMES

9.1. EQ-5D-5L

EQ-5D-5L is a health outcomes endpoint for Part 1 and a secondary endpoint for Parts 2 and 3. The 5-digit numbers representing the health state of each subject will be listed along with the VAS score and computed index value (Section 6.7.6.1). The VAS score and computed EQ-5D-5L index value will be summarized descriptively for Part 1 and for the entire study period.

Note that this study uses the questionnaire in its validated form for subjects to report their health status "*today"*. If the subject has had an HAE attack since the last visit, starting at Week 4, the subject completes the questionnaire a second time to reflect back on health status during a *"usual attack*". On summary tables, the "*today"* and *"usual attack*" questionnaire results will appear in different rows and analyses should be separated.

For Part 1, MMRM will be used to compare each active dose to placebo for each time point. For this analysis, either the change from baseline VAS score or EQ-5D-5L index value using the "*today*" questionnaire will be included as the dependent variable in the model with fixed effects for treatment, baseline attack value, baseline VAS or EQ-5D-5L index score as appropriate, visit, visit by treatment interaction, and a random effect for subject included as independent variables. An unstructured covariance structure will be used.

Analyses at the end of the study will be descriptive and will cover the entire study period.

For Part 1 and entire study period analyses, categorical summaries by treatment group and visit will be provided for responses to each individual question. In addition, summaries of VAS and index scores during a "*usual attack*" will be provided.

Plots of VAS and EQ-5D-5L index mean scores over time and change from baseline mean scores will be provided for Part 1 analysis and for the analysis at end of the study using the health status "*today*". For Parts 2 and 3, plots of mean scores over time by treatment will be shown separately for active treatment for the subjects originally randomized to placebo.

9.2. Treatment Satisfaction Questionnaire for Medication

TSQM is a health outcomes endpoint for Part 1 and a secondary endpoint for Parts 2 and 3. TSQM is measured at baseline.

TSQM scores for Effectiveness, Side Effects, Convenience, and Global Satisfaction will be calculated for each visit as discussed in Section 6.7.6.2. The TSQM scores will be summarized by score, treatment, and visit with separate summaries for Part 1 and for the entire study period. For Part 1, MMRM will be used to compare each active dose to placebo for each time point. For this analysis, the TSQM change from baseline score of interest will be included as the dependent variable in the model with fixed effects for treatment, baseline attack value, baseline TSQM

score, visit, visit by treatment interaction and a random effect for subject included as independent variables. An unstructured covariance structure will be used.

Separate figures of Effectiveness, Side Effects, Convenience, and Global Satisfaction mean scores over time with 1 line per treatment group will be provided. There will be 1 set of figures for Part 1 and another for the entire study period. For the analysis at the end of the study, the figure will have separate lines for active treatment for subjects originally randomized to placebo, showing mean scores over time by treatment.

In addition, categorical summaries by treatment group and visit will be provided for responses to each individual question.

9.3. Work Productivity and Activity Impairment

WPAI is a health outcomes endpoint for Part 1 and a secondary endpoint for Parts 2 and 3. Absenteeism, presenteeism, work productivity loss, and activity impairment will be calculated as described in Section 6.7.6.3. WPAI scores will be summarized descriptively by treatment group and visit for Part 1 and for the entire study period. For Part 1, MMRM will be used to compare each active dose to placebo for each time point. For this analysis, the change from baseline WPAI score of interest will be included as the dependent variable in the model with fixed effects for treatment, baseline attack value, baseline WPAI score, visit, visit by treatment interaction and a random effect for subject included as independent variables. An unstructured covariance structure will be used.

In addition, summaries statistics by treatment group and visit will be provided for responses to each individual question (Q2 to Q6) with a categorical summary provided for Q1.

Separate figures of each of the WPAI mean scores and change from baseline mean scores over time with 1 line per treatment group will be provided. There will be 1 set of figures for Part 1 and another for the entire study period. For the plots produced at the end of the study, the figure will have separate lines for active treatment for subjects originally randomized to placebo.

10. SAFETY AND TOLERABILITY

Analyses of safety and tolerability will be conducted at the end of Part 1 of the study and repeated for the entire study period.

10.1. Adverse Event Preferred Term and System Organ Class Summary Tables

The following are Part 1 secondary endpoints and Part 2 and 3 primary endpoints:

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE

AEs will be mapped to the MedDRA version 19.1 PT and system organ class (SOC). AEs are assessed by the Investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening) according to Division of Microbiology and Infectious Diseases (DMID) using the November 2007 criteria. If a subject experiences multiple events that map to a single PT, the greatest severity grade according to the DMID criteria and strongest investigator assessment of relation to study medication will be assigned to the PT for the appropriate summaries. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

TEAEs are defined as AEs that occurred on or after first dose of study treatment, whether in Part 1, 2 or 3, and will be assigned to the relevant treatment depending on when the TEAE began (Part 1 or Part 2 and 3 treatment). AEs occurring 30 days after the last dose for subjects who discontinue study treatment in Part 1 or up to 30 days after last dose in Part 2 or 3 will be considered as TEAEs and will be associated with Part 1, 2 or 3 respectively. Note that Investigators are not required to contact subjects after the last follow-up if it occurs prior to 30 days from last dose. All AEs that occurred prior to the initiation of study treatment or those recorded more than 30 days after the last dose of study treatment will be excluded from the tables but will be included in the listings.

Drug-related events are defined as those AEs that the Investigator believes were possibly, probably, or definitely related to the study drug.

10.1.1. Summaries of Adverse Event Incidence Rates for All Subjects and Incidence Rates for Serious Adverse Events, Discontinuations due to Adverse Events, and Deaths

A brief summary of TEAEs will show, by treatment group, the number and percentage of subjects who 1) had any TEAE, 2) had any drug-related event, 3) permanently discontinued from study drug due to an TEAE, 4) had any serious adverse event (SAE), 5) had any Grade 3 or higher TEAE, 6) had any Grade 3 or higher drug-related TEAE, 7) had any TEAE leading to interruption of study drug, 8) had a drug-related SAE, or 9) had a fatal SAE.

TEAEs will be summarized by treatment group. For each SOC and PT, the number and percentage of subjects reporting an event will be calculated. In summary tables, SOCs and events within a SOC will be presented by decreasing frequency count based on the total number of events. Multiple events (by subject or SOC as appropriate) will be counted only once per subject per dose in each summary. For summaries that use severity grade, the most severe event will be selected.

The following summary tables (number and percentage of subjects) of TEAEs (by SOC and PT) will be provided by treatment group:

- Overall summary of TEAEs
- Summary of TEAEs
- Summary of drug-related TEAEs
- Summary of TEAEs by severity
- Summary of treatment-emergent Grade 3 or Grade 4 AEs
- Summary of drug-related, treatment-emergent Grade 3 or Grade 4 AEs

- Summary of TESAEs
- Summary of TEAEs leading to permanent discontinuation of study treatment
- Summary of TEAEs leading to interruption of study treatment
- Summary of drug-related TESAEs

In addition, a summary of frequent TEAEs will be provided by PT (not by SOC and PT), in decreasing order of frequency. Frequent TEAEs will be defined as events that occur in at least 5% of the total number of subjects in the clinical trial.

A summary of TEAEs by age group will also be provided

Data listings will be provided for all AE data. In addition to listing all AEs, distinct data listings will also be provided for the following:

- Grade 3 or Grade 4 AEs
- AEs leading to permanent study discontinuation
- SAEs (fatal and non-fatal)

A forest plot of most-frequent treatment-emergent AEs sorted by relative risk will be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). The format of the plot to be used is the example plot of most-frequent on-therapy AEs sorted by risk difference. However, the relative risk (aka risk ratio) will be displayed rather than the risk difference. The 95% confidence interval for the relative risk will be derived using the assumption of normality of the log of the relative risk.

10.1.2. Investigator-Identified Rash Events of Special Interest and Gastrointestinal Abdominal-Related Adverse Events

The following is a primary endpoint for Parts 2 and 3:

- The proportion of subjects with a treatment-emergent, treatment-related AE consistent with a drug rash

All rashes, regardless of assessed causality or severity are reported as events of special interest by investigators in a protocol defined manner. However, the endpoint of interest is the proportion of subjects with a treatment-emergent, treatment-related AE consistent with drug rash.

Gastrointestinal (GI) abdominal-related TEAEs are also of interest, although these are not TEAEs of special interest for investigator reporting purposes. There are no appropriate standardized MedDRA queries in MedDRA to evaluate abdominal-related AEs that are appropriate to assess potential adverse events associated with BCX7353 use. To create a list of PTs that are pertinent, the events to be analyzed have been prospectively defined as all PTs within the MedDRA 19.1 hierarchy under the High-Level Group Terms (HLGTs) of 1) GI signs and symptoms; and 2) GI motility and defecation conditions. See Section 17 for a detailed list of PTs, High Level Terms, and HLGTs. This selection is broad enough so that GI events are appropriately identified and analyzed but excludes terms that, although in the GI SOC, are not representative of the events of concern such as oral or esophageal events.

For the investigator-identified rashes and the GI abdominal-related events, separate listings will be provided. In addition, for both investigator-identified rashes and GI abdominal-related events there will be a summary that shows, by treatment group, the number and percentage of subjects with:

- A TEAE
- A drug-related TEAE
- Permanent discontinuation from study drug due to the TEAE
- An AE that was considered an TESAE
- Any Grade 3 or higher TEAE
- Any Grade 3 or higher drug-related TEAE
- Any TEAE leading to interruption of study drug
- An TEAE that was considered a drug-related TESAE
- A TEAE that required use of concomitant medication

For treatment-emergent investigator-identified rashes and GI abdominal-related AEs, time to development of the TEAE will be estimated using the Kaplan-Meier method. The results will be displayed in summary tables as well as in a Kaplan-Meier plot. Subjects who do not experience the event of interest will be censored at the date of the last dose. Summary displays for the investigator-identified rashes and GI abdominal-related TEAEs will include a count of the number of TEAEs as well as the number of subjects who experience each TEAE.

A Kaplan-Meier plot and summary of duration of event will be provided for the investigator-identified rashes and GI abdominal-related TEAEs. The summary display will provide the median duration of event by treatment group, with the event as the unit of interest rather than the subject.

A separate analysis will be conducted in which the number and proportion of subjects with either a GI abdominal-related TEAE or an unconfirmed abdominal-only attack is presented. The number of events will also be included in the summary.

10.1.3. Missing and Partial Adverse Event Onset Dates

See Section 6.8.4.

10.1.4. Summaries of Adverse Event Incidence Rates per 100 Person-Years of Exposure to Study Treatment

For this study, the duration of exposure to study treatment will vary depending on whether the subject is initially assigned to placebo. Because of this, certain TEAE tables will be repeated using the number of TEAEs per 100 person-years of exposure instead of using a count, where 1 year = 365.25 days of exposure. These tables will not be created for the Part 1 primary efficacy analysis since the same amount of exposure is expected per treatment group for Part 1 analysis.

To determine the rate of TEAEs per person-year of exposure, the duration of treatment exposure will be computed for each subject and treatment. The rate of TEAEs per person-year will then

be calculated as the count of TEAEs divided by the duration of treatment exposure. This value will then be multiplied by 100 to compute the rate per 100 person-years of exposure. For subjects initially randomized to placebo, there will be exposure time for placebo treatment and a separate exposure time for treatment with either 110 or 150 mg. The total exposure for the treatment group of interest will sum the individual subject exposure time for each treatment group.

The following summary tables of rate of TEAEs per 100 person-years of exposure will be provided by treatment group (by SOC and PT):

- Summary of TEAE rate per 100 person-year of exposure
- Summary of drug-related, TEAE rate per 100 person-year of exposure
- Summary of TESAEs per 100 person-year of exposure

A listing of exposure to study treatment in 100 person-years will be provided by subject and treatment.

10.2. Exposure to Study Treatment and Treatment Compliance

The number of subjects exposed to study treatment and the number of subjects who discontinue treatment early will be presented on the disposition table. A summary of exposure to study treatment will be also be presented and will include a summary of 100 person-years of exposure to study treatment as described in Section 10.1.4. Listings of exposure to study treatment and of drug accountability will be provided by subject and treatment. Kaplan-Meier plots of duration of study treatment will be provided. Treatment compliance will be computed based on drug accountability by determining the number of capsules taken relative to the number of capsules that should have been administered.

For compliance (%) for the study period of interest based on the drug accountability page of the eCRF:

$$Number\ of\ Capsules\ Taken = Number\ of\ Capsules\ Dispensed - Number\ of\ Capsules\ Returned$$

$$Expected\ Number\ of\ Capsules\ Taken = 2 \times (Date\ of\ the\ Last\ Dose - Date\ of\ the\ First\ Dose + 1)$$

Treatment compliance based on dispensing information will be calculated for each study treatment that the subject received as follows:

$$\text{Treatment Compliance (Dispensing)} = \frac{Number\ of\ Capsules\ Taken}{Expected\ Number\ of\ Capsules\ Taken} \times 100$$

Treatment compliance will be listed and summarized for Part 1 and overall for the entire study period at the time of the end of study analysis. For subjects initially assigned to placebo, treatment compliance will be computed for placebo treatment and separately for the active treatment received in Parts 2 and 3.

A categorical summary of treatment compliance will be produced with the following categories shown in Table 14.

Table 14: Definition of Compliance Categories

Compliance	Range of Compliance (%)
Poor compliance	< 80%
Acceptable compliance	80% to < 90%
Good compliance	90% to 110%
Over-dosing	> 110%

A plot of change from baseline attack rate by % compliance will be produced for Part 1, with treatment groups overlaid.

10.3. Concomitant and Other Medications

Association of concomitant medications with treatment and coding of concomitant medications is described in Section 7.7. Concomitant medications will be summarized by treatment and WHO preferred name for Part 1 and for the entire study period. Multiple medication use (by preferred name) will be counted once only per subject. Concomitant medications started more than 30 days post last dose will not be included in summary displays but will be listed.

Concomitant medications that were used for HAE-related indications will also be summarized. separately for Part 1 and for the entire study period.

All medication data will be listed.

10.3.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

See Section 6.8.3.

10.4. Laboratory Data

The following endpoint is a Part 1 safety endpoint and a primary endpoint for Parts 2 and 3:

- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality

A listing of clinical laboratory evaluations is provided in the Protocol, Section 11.2.6.

Clinical laboratory assessments and corresponding changes from baseline will be summarized for each laboratory panel by treatment group and visit. Laboratory abnormalities will be graded according to the DMID Adult Toxicity Table (publish date: November 2007; see Protocol Appendix 16.1). Any graded abnormality that occurs following the initiation of study drug and represents at least 1-grade increase from the baseline assessment is defined as treatment emergent.

Urinalysis results will be summarized by treatment and visit and listed by subject and treatment.

The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized. Treatment-emergent Grade 3 or 4 laboratory abnormalities will be summarized separately. Laboratory toxicity shifts from baseline to worst postbaseline assessments will be summarized.

The number and percentage of subjects who have post-baseline elevations in liver transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or bilirubin abnormalities in relation to fold above the upper limit of normal will be summarized according to the FDA's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (DHHS 2009).

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments (where "and" indicates elevations occurring at the same visit). Within each treatment group and laboratory parameter grouping, a subject may be counted once per elevation criteria using the worst-case result. That is, a subject with a worst-case ALT elevation >3 × the upper limit of normal (ULN) for a given treatment group would be counted once in the ALT > 1.5 × ULN category and once in the ALT > 3 × ULN category, regardless of how many ALT elevations the subject had that met the > 3 × ULN and > 1.5 × ULN elevation criteria.

- ALT and/or AST > 3 × ULN and total bilirubin > 1.5 or 2 × ULN
- AST > 1.5, 3, 5, 10, and 20 × ULN
- ALT > 1.5, 3, 5, 10, and 20 × ULN
- Total bilirubin > 1, 1.5, or 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN

Profiles of liver enzymes and bilirubin over time will be graphically displayed for subjects with any Grade 3 or 4 abnormality in these analytes. In addition, a listing of all liver function test (ALT, AST, bilirubin, ALP, gamma-glutamyl transferase) results for subjects experiencing a treatment-emergent Grade 3 or 4 liver function test will be provided.

In addition, a Hy's law plot, a shift plot showing liver safety panel tests over time (baseline vs. on-study), and distribution plots of ALT, AST, ALP, bilirubin, cholesterol, and triglycerides over time will be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). The plots to be included are the scatter plot of maximum transaminase versus maximum bilirubin, the liver test safety panel over time and the distribution of ALT by time and treatment. The distribution plots for AST, ALP, bilirubin, cholesterol and triglycerides will use the same format as is used for ALT.

Separate Kaplan-Meier plots of time to event for a Grade 3 or higher ALT, AST, or bilirubin will be produced.

A listing of adverse events of nausea, vomiting, anorexia, abdominal pain, or fatigue occurring within 24 hours of an elevation of >3xULN for AST or ALT will be produced.

10.4.1. Prior Androgen Use and Liver Function Test Abnormalities

The summary display of abnormal hepatic laboratory values will be repeated by prior use of androgens (yes/no) at any time in the past based on medical history. Detailed listings of prior androgen use will be provided for subjects with any elevation in the indicated categories.

10.4.2. Complement Factors and HAE Diagnosis

Laboratory results related to HAE diagnosis, including complement factors C1-INHAg, C1-INHf, C3, and C4 will be included in summaries of laboratory data. Criteria used to confirm diagnosis of HAE Type 1 or 2 will be summarized and listed as described in Section 7.4.

10.4.3. Laboratory Assessments for Rash

For subjects with rash, peripheral blood mononuclear cells (PBMCs) will be collected for analysis of possible drug-specific immune responses and possible drug-responsive T-cells. The data from PBMC analysis, if collected, will be listed.

Other laboratory assessments taken at the time of a rash, including clinical chemistry, hematology with differential, C3 level, and urine eosinophils will be included in laboratory listings.

10.5. Pregnancy

A listing of pregnancy test results will be provided.

10.6. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) and body weight and corresponding changes from baseline will be summarized by treatment group and visit using descriptive statistics. These data will be listed by subject, treatment, and visit.

Distribution plots of systolic and diastolic blood pressure over time will be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). The graph format to be used is the same as the graph provided for the distribution of ALT by time and treatment.

10.7. 12-lead Electrocardiograms

Baseline (predose) and Week 24 ECGs will be obtained in triplicate (ie, 3 separate readings) at 1- to 5-minute intervals, with baseline values calculated from an average of the 3 readings. All other ECGs will be single assessments.

An ECG should be repeated for a change from baseline in corrected QT interval using Fridericia's method (QTcF) > 60 msec or a QTcF interval > 500 msec.

ECGs and corresponding changes from baseline will be summarized by treatment group and visit using descriptive statistics.

ECG findings will be summarized.

The change from baseline in QTcF will be determined by routine ECGs. At each time point where ECGs are analyzed, an individual subject's change from baseline will be calculated as:

$$\Delta ik = (QTcF\ for\ Subject\ i\ at\ Time\ Point\ k - Baseline\ QTcF)$$

QTcF measurements will be the average of triplicate ECGs at baseline and Week 24 and single values at all other time points.

A distribution plot of QTcF over time will be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). The graph format to be used is the same as the graph provided for the distribution of ALT by time and treatment.

For routine ECGs, the number and proportion of subjects with QTcF ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec; or changes of ≤ 30, > 30 to ≤ 60, or > 60 msec will be summarized. Unscheduled ECG results will be included in this summary table.

All ECG values and findings will be listed by subject, treatment, and visit.

10.8. Physical Examination

A full physical examination is conducted at Screening, Baseline, and at Week 24. Symptom-directed physicals are done at all other study visits except Week 2 and Week 26. Physical examination data will be listed by subject and treatment.

10.9. Study Termination Status

Study termination status will be presented on the subject disposition table.

11. PHARMACOKINETICS

Analyses of concentration data will be performed using the safety population. PK concentration data will be listed by subject, treatment, day, and time for Part 1 and this will be repeated for the entire study period for the analysis at the end of the study. Note that PK concentration data collected at each visit will not be summarized by visit as the timings of PK data collected was not pre-specified.

The following summary displays will be produced:

- Summary of number and percentage of collected samples > 4 × half-maximal effective concentration (EC_{50}), > 6 × EC_{50}, and > 8 × EC_{50} at each visit and overall
- Summary of number and percentage of samples within a subject > 4 × EC_{50}, > 6 × EC_{50}, and > 8 × EC_{50}

The value of EC_{50} used will be 9 ng/mL.

12. PHARMACODYNAMICS

Analyses of PD data will be performed using the PD population. Plasma kallikrein inhibition data will be expressed as percent inhibition compared to subject baseline activity (%KKI). The formula for percent inhibition is:

$$\%KKI = -\frac{postbaseline\ value - baseline\ value}{baseline\ value}$$

where the values are the amidolytic activity (%) at each time point. Multiple assessments of amidolytic activity from samples at a single time point will be handled as described in Section 6.7.4.

%KKI data will be listed by subject, treatment, day, and time. This analysis will be conducted for Part 1 and then repeated for the entire study period for the analysis at the end of the study.

The following summary displays will be produced:

- Summary of number and percentage of collected samples with > 50% and > 80% inhibition at each visit and overall
- Summary of number and percentage of samples within a subject with > 50% and > 80% inhibition

13. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

A scatter plot of %KKI (y-axis) by PK concentration/4 (x-axis) will be produced at the time of the Part 1 analysis and for the entire study period at the time of the analysis at the end of the study, using the PK/PD population. Note the division by 4 of the concentration corrects for the dilution of the plasma required for the PD assay.

14. PHARMACOGENETICS

Pharmacogenetic samples will be collected on all subjects who are willing to participate in pharmacogenetic testing. If a decision is made to analyze the samples and conduct a statistical analysis of the results, the statistical analysis will be the subject of a separate SAP.

Results of human leukocyte antigen typing will be evaluated in a separate cross-study analysis.

15. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Changes from protocol-specified analyses include:

- For Part 1 analyses, the protocol says efficacy displays will be generally be performed over the entire dosing period beginning on Day 1 and effective dosing period beginning on Day 8. In the SAP, a reduced number of displays have been selected for analysis over the effective dosing period.
- In the protocol, the PP population was originally defined as a subset of the ITT population. It has been redefined in the SAP as a subset of the safety population.
- Due to an error in the IXRS equation, the baseline attack rate for screening for purposes of stratification was slightly larger than it should have been because the denominator did not include the “+1”; ie, the number of days in screening was underestimated by 1 day. For analysis purposes, the baseline attack rate is recalculated using the intended equation for baseline attack rate as shown in Section 6.6.1.
- Clarified that Part 1 ends at the time of first dose for Part 2.
- Increased the sample size per group from 32 to 40 to account for potential dropout. Initial sample size estimates did not allow for any subject dropout.

- Due to rapid enrollment and the timing of planned sample size re-estimation when 50% of subjects reach Week 24, the planned sample size re-estimation was not conducted.

16. REFERENCES

Atkinson, M. J., A. Sinha, S. L. Hass, S. S. Colman, R. N. Kumar, M. Brod and C. R. Rowland (2004). "Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication, using a national panel study of chronic disease." Health Quality Life Outcomes **2**.

DHHS (2009). "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation."

ICH (1995). "ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3."

Reilly Associates (2002). "WPAI Scoring ".

van Hout, B., M. F. Janssen, Y. S. Feng, T. Kohlmann, J. Busschbach, D. Golicki, A. Lloyd, L. Scalone, P. Kind and A. S. Pickard (2012). "Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets." Value Health **15**(5): 708-715.

van Reenen, M. and B. Janssen (2015). "EQ-5D-5L User Guide Version 2.1."

Weller, K., A. Groffik, M. Magerl, N. Tohme, P. Martus, K. Krause, M. Metz, P. Staubach and M. Maurer (2012). "Development and construct validation of the angioedema quality of life questionnaire." Allergy **67**: 1289-1298.

17. APPENDIX

17.1. Table of Contents for Data Display Specifications

Tables

Output #	Population	Output Title
14.1.1.1	ITT	Summary of Subject Disposition by Country and Site, Part 1
14.1.1.1.ES	ITT	Summary of Subject Disposition by Country and Site, Entire Study
14.1.2.1	ITT	Summary of Analysis Populations
14.1.2.2	ITT	Summary of Subgroups
14.1.2.3.1	ITT	Summary of Inclusion/Exclusion Criteria Deviations
14.1.2.3.2	Screen Failures	Summary of Inclusion/Exclusion Criteria Deviations
14.1.2.4	ITT	Summary of Protocol Deviations, Part 1
14.1.2.4.ES	ITT	Summary of Protocol Deviations that Occurred During Part 2
14.1.2.5	ITT	Summary of Confirmation of Diagnosis of HAE Type I or II
14.1.3.1.1	ITT	Summary of Demographic Characteristics
14.1.3.1.1.ES	ITT	Summary of Demographic Characteristics - Subjects Who Transitioned to Part 2
14.1.3.1.2	PP	Summary of Demographic Characteristics
14.1.3.1.3	Screen Failures	Summary of Demographic Characteristics
14.1.3.2	ITT	Summary of Subject-Reported HAE Baseline Characteristics – HAE Medical History
14.1.3.3	ITT	Summary of Past Prophylactic Treatments of HAE
14.1.3.4	ITT	Summary of Current On-Demand Treatments of HAE
14.1.3.5	ITT	Summary of Subject-Reported HAE Baseline Characteristics – Primary Acute Attack Treatment Information
14.1.3.6	ITT	Summary of Pre-Treatment Investigator-Confirmed Attack Rates and Angioedema Symptoms
14.1.4.1	ITT	Summary of Medications Taken within 30 Days of Screening and Discontinued Prior to Dosing
14.1.4.2	ITT	Summary of Concomitant Medications, Part 1
14.1.4.2.ES	ITT	Summary of Concomitant Medications – Entire Study
14.1.4.3	ITT	Summary of Concomitant Medications for HAE, Part 1
14.1.4.3.ES	ITT	Summary of Concomitant Medications for HAE, Entire Study
14.1.4.3.P3	ITT	Summary of Concomitant Medications for HAE, Part 3
14.1.4.4	ITT	Summary of Concomitant Medications for HAE – Attack Level, Part 1
14.1.4.4.ES	ITT	Summary of Concomitant Medications for HAE – Attack Level, Entire Study
14.1.4.4.P3	ITT	Summary of Concomitant Medications for HAE – Attack Level, Part 3
14.1.5.1	Safety	Summary of Treatment Exposure and Treatment Compliance, Part 1
14.1.5.1.ES	Safety	Summary of Treatment Exposure and Treatment Compliance, Entire Study
14.2.1.1	ITT	Summary of Hierarchical Testing for Efficacy Endpoints
14.2.1.2.1	ITT	Overall Attack Summary During Part 1
14.2.1.2.1.ES	ITT	Overall Attack Summary During Entire Study
14.2.1.2.2	PP	Overall Attack Summary During Part 1

Output #	Population	Output Title
14.2.1.3.1	ITT	Overall Attack Summary During the Effective Dosing Period, Part 1
14.2.1.3.1.ES	ITT	Overall Attack Summary During the Effective Dosing Period, Entire Study
14.2.1.3.2	PP	Overall Attack Summary During the Effective Dosing Period, Part 1
14.2.1.4.1	ITT	Summary of Rate of Investigator-Confirmed Attacks During Part 1
14.2.1.4.1.ES	ITT	Summary of Rate of Investigator-Confirmed Attacks During Entire Study
14.2.1.4.2	PP	Summary of Rate of Investigator-Confirmed Attacks During Part 1
14.2.1.4.2.ES	PP	Summary of Rate of Investigator-Confirmed Attacks During Entire Study
14.2.1.4.3	Completers	Summary of Rate of Investigator-Confirmed Attacks During Part 1
14.2.1.4.4	ITT	Summary of Rate of Investigator-Confirmed Attacks During Part 1, Including Observed Data Post Treatment Discontinuation
14.2.1.4.5	ITT	Summary of Rate of Investigator-Confirmed Attacks During Part 1, Including Observed Data Post Treatment Discontinuation and Missing Data Post Treatment Discontinuation are Imputed
14.2.1.5	ITT	Summary of Rate of Investigator-Confirmed Attacks During Part 1, Tipping Point Analysis Results
14.2.1.6	ITT	Summary of Rate of Investigator-Confirmed Attacks During Part 1 by Subgroups
14.2.1.11.1	ITT	Summary of Rate of Investigator-Confirmed Attacks During Effective Dosing Period, Part 1
14.2.1.11.1.ES	ITT	Summary of Rate of Investigator-Confirmed Attacks During Effective Dosing Period, Entire Study
14.2.1.11.2	PP	Summary of Rate of Investigator-Confirmed Attacks During Effective Dosing Period, Part 1
14.2.1.11.2.ES	PP	Summary of Rate of Investigator-Confirmed Attacks During Effective Dosing Period, Entire Study
14.2.1.14	ITT	Summary of Rate of Investigator-Confirmed Attacks Requiring Treatment During Part 1
14.2.1.14.ES	ITT	Summary of Rate of Investigator-Confirmed Attacks Requiring Treatment During Entire Study
14.2.1.15	ITT	Summary of Rate of Investigator-Confirmed Abdominal-Only Attacks During Part 1
14.2.1.15.ES	ITT	Summary of Rate of Investigator-Confirmed Abdominal-Only Attacks During Entire Study
14.2.1.16	ITT	Summary of Rate of Investigator-Confirmed Peripheral-Only Attacks During Part 1
14.2.1.16.ES	ITT	Summary of Rate of Investigator-Confirmed Peripheral-Only Attacks During Entire Study
14.2.1.17	ITT	Summary of Rate of Investigator-Confirmed Mixed Location Attacks During Part 1
14.2.1.17.ES	ITT	Summary of Rate of Investigator-Confirmed Mixed Location Attacks During Entire Study
14.2.1.18	ITT	Summary of Rate of Subject-Reported Attacks During Part 1
14.2.1.18.ES	ITT	Summary of Rate of Subject-Reported Attacks During Entire Study
14.2.1.18.P3	ITT	Summary of Rate of Subject-Reported Attacks During Part 3
14.2.1.19.P3	ITT	Summary of Rate of Subject-Reported Attacks Requiring Treatment During Part 3
14.2.2.1	ITT	Summary of Rate of Investigator-Confirmed Attacks By Month During Part 1
14.2.2.1.ES	ITT	Summary of Rate of Investigator-Confirmed Attacks By Month During Entire Study
14.2.2.1.P3	ITT	Summary of Rate of Investigator-Confirmed Attacks By Month During Part 3
14.2.3.1.1	ITT	Summary of AE-QoL Scores, Part 1
14.2.3.1.1.ES	ITT	Summary of AE-QoL Scores, Entire Study
14.2.3.1.2	PP	Summary of AE-QoL Scores, Part 1
14.2.3.1.2.ES	PP	Summary of AE-QoL Scores, Entire Study
14.2.3.2	ITT	Summary of AE-QoL Scores, Part 1 by Subgroups
14.2.3.7	ITT	Number and Percent of Subjects Achieving the MCID (Decrease in Total AE-QoL Score), Part 1

Output #	Population	Output Title
14.2.3.7.ES	ITT	Number and Percent of Subjects Achieving the MCID (Decrease in Total AE-QoL Score), Entire Study
14.2.4.1	ITT	Summary of Number and Proportion of Subjects Who are Investigator-Confirmed Attack-Free, Part 1
14.2.4.1.ES	ITT	Summary of Number and Proportion of Subjects Who are Investigator-Confirmed Attack-Free, Entire Study
14.2.4.2	ITT	Summary of Number and Proportion of Subjects Who are Subject-Reported Attack-Free, Part 3
14.2.4.3	ITT	Summary of Number and Proportion of Subjects Who are Investigator-Confirmed Attack-Free in the Effective Dosing Period, Part 1
14.2.4.3.ES	ITT	Summary of Number and Proportion of Subjects Who are Investigator-Confirmed Attack-Free in the Effective Dosing Period, Entire Study
14.2.5.1.1	ITT	Summary of Number and Proportion of Days with Angioedema Symptoms from Investigator-Confirmed Attacks, Part 1
14.2.5.1.1.ES	ITT	Summary of Number and Proportion of Days with Angioedema Symptoms from Investigator-Confirmed Attacks, Entire Study
14.2.5.1.1.P3	ITT	Summary of Number and Proportion of Days with Angioedema Symptoms from Subject-Reported Attacks, Part 3
14.2.5.1.2	PP	Summary of Number and Proportion of Days with Angioedema Symptoms from Investigator-Confirmed Attacks, Part 1
14.2.5.1.2.ES	PP	Summary of Number and Proportion of Days with Angioedema Symptoms from Investigator-Confirmed Attacks, Entire Study
14.2.5.1.2.P3	PP	Summary of Number and Proportion of Days with Angioedema Symptoms from Subject-Reported Attacks, Part 3
14.2.6.1.1	ITT	Summary of Relative Reduction from Baseline in Adjusted Investigator-Confirmed Attack Rate, Part 1
14.2.6.1.2	PP	Summary of Relative Reduction from Baseline in Adjusted Investigator-Confirmed Attack Rate, Part 1
14.2.7.1	ITT	Attack-Level Duration of Investigator-Confirmed Attacks (hours) from Start of Attack to the Time the Attack Finished, Part 1
14.2.7.1.ES	ITT	Attack-Level Duration of Investigator-Confirmed Attacks (hours) from Start of Attack to the Time the Attack Finished, Entire Study
14.2.7.2	ITT	Attack-Level Duration of Investigator-Confirmed Attacks (hours) from Start of Attack Until Worst Was Over, Part 1
14.2.7.2.ES	ITT	Attack-Level Duration of Investigator-Confirmed Attacks (hours) from Start of Attack Until Worst Was Over, Entire Study
14.2.8.1	ITT	Summary of Time to First Investigator-Confirmed Attack (KM Estimates), Part 1
14.2.9.1	ITT	Time to First Use of Targeted HAE Rescue Medication to Treat an Investigator-Confirmed Attack (KM Estimates), Part 1
14.2.10.1	ITT	Summary of Attack Characteristics for Investigator-Confirmed Attacks, Part 1
14.2.10.1.ES	ITT	Summary of Attack Characteristics for Investigator-Confirmed Attacks, Entire Study
14.2.11.1	ITT	Summary of Attack Locations for Investigator-Confirmed Attacks, Part 1
14.2.11.1.ES	ITT	Summary of Attack Locations for Investigator-Confirmed Attacks, Entire study
14.3.1.1	Safety	Overall Summary of Treatment-Emergent Adverse Events, Part 1
14.3.1.1.ES	Safety	Overall Summary of Treatment-Emergent Adverse Events, Entire Study
14.3.1.2	Safety	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.2.ES	Safety	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Entire Study

Output #	Population	Output Title
14.3.1.3	Safety	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.3.ES	Safety	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.4	Safety	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.4.ES	Safety	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.5	Safety	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.5.ES	Safety	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.6	Safety	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.6.ES	Safety	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.7	Safety	Drug-Related Treatment-Emergent Grade 3 or 4 Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.7.ES	Safety	Drug-Related Treatment-Emergent Grade 3 or 4 Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.8	Safety	Treatment-Emergent Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.8.ES	Safety	Treatment-Emergent Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.9	Safety	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.9.ES	Safety	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.10	Safety	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity, Part 1
14.3.1.10.ES	Safety	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity, Entire Study
14.3.1.11	Safety	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Age Group, Part 1
14.3.1.11.ES	Safety	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Age Group, Entire Study
14.3.1.12	Safety	Summary of Frequent Adverse Events, Part 1
14.3.1.12.ES	Safety	Summary of Frequent Adverse Events, Entire Study
14.3.1.14	Safety	Summary of Drug-related Frequent Adverse Events, Part 1
14.3.1.14.ES	Safety	Summary of Drug-related Frequent Adverse Events, Entire Study
14.3.1.15	Safety	Overall Summary of Treatment-Emergent Investigator-identified Rash, Part 1
14.3.1.15.ES	Safety	Overall Summary of Treatment-Emergent Investigator-identified Rash, Entire Study
14.3.1.16	Safety	Treatment-Emergent Investigator-identified Rash by System Organ Class and Preferred Term, Part 1
14.3.1.16.ES	Safety	Treatment-Emergent Investigator-identified Rash by System Organ Class and Preferred Term, Entire Study
14.3.1.17	Safety	Drug-Related Treatment-Emergent Investigator-identified Rash by System Organ Class and Preferred Term, Part 1

Output #	Population	Output Title
14.3.1.17.ES	Safety	Drug-Related Treatment-Emergent Investigator-identified Rash by System Organ Class and Preferred Term, Entire Study
14.3.1.18	Safety	Treatment-Emergent Investigator-identified Rash Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.18.ES	Safety	Treatment-Emergent Investigator-identified Rash Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.19	Safety	Drug-Related Treatment-Emergent Investigator-identified Rash Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.19.ES	Safety	Drug-Related Treatment-Emergent Investigator-identified Rash Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.20	Safety	Treatment-Emergent Grade 3 or Grade 4 Investigator-identified Rash by System Organ Class and Preferred Term, Part 1
14.3.1.20.ES	Safety	Treatment-Emergent Grade 3 or Grade 4 Investigator-identified Rash by System Organ Class and Preferred Term, Entire Study
14.3.1.21	Safety	Drug-Related Treatment-Emergent Grade 3 or 4 Investigator-identified Rash by System Organ Class and Preferred Term, Part 1
14.3.1.21.ES	Safety	Drug-Related Treatment-Emergent Grade 3 or 4 Investigator-identified Rash by System Organ Class and Preferred Term, Entire Study
14.3.1.22	Safety	Treatment-Emergent Investigator-identified Rash Leading to the Interruption of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.22.ES	Safety	Treatment-Emergent Investigator-identified Rash Leading to the Interruption of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.23	Safety	Treatment-Emergent Investigator-identified Rash Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.23.ES	Safety	Treatment-Emergent Investigator-identified Rash Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.24	Safety	Treatment-Emergent Investigator-identified Rash Requiring the Use of Concomitant Medication by System Organ Class and Preferred Term, Part 1
14.3.1.24.ES	Safety	Treatment-Emergent Investigator-identified Rash Requiring the Use of Concomitant Medication by System Organ Class and Preferred Term, Entire Study
14.3.1.25	Safety	Summary of Time to Development of Investigator-identified Rash, Part 1
14.3.1.25.ES	Safety	Summary of Time to Development of Investigator-identified Rash, Entire Study
14.3.1.27	Safety	Duration of Investigator-identified Rash, Part 1
14.3.1.27.ES	Safety	Duration of Investigator-identified Rash, Entire Study
14.3.1.29	Safety	Overall Summary of Treatment-Emergent GI Abdominal-Related Adverse Events , Part 1
14.3.1.29.ES	Safety	Overall Summary of Treatment-Emergent GI Abdominal-Related Adverse Events, Entire Study
14.3.1.30	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.30.ES	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.31	Safety	Drug-Related Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.31.ES	Safety	Drug-Related Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.32	Safety	Treatment-Emergent GI Abdominal-Related Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.32.ES	Safety	Treatment-Emergent GI Abdominal-Related Serious Adverse Events by System Organ Class and Preferred Term, Entire Study

Output #	Population	Output Title
14.3.1.33	Safety	Drug-Related Treatment-Emergent GI Abdominal-Related Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.33.ES	Safety	Drug-Related Treatment-Emergent GI Abdominal-Related Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.34	Safety	Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.34.ES	Safety	Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.35	Safety	Drug-Related Treatment-Emergent Grade 3 or 4 GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.35.ES	Safety	Drug-Related Treatment-Emergent Grade 3 or 4 GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.36	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.36.ES	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.37	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.37.ES	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.38	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events Requiring the Use of Concomitant Medication by System Organ Class and Preferred Term, Part 1
14.3.1.38.ES	Safety	Treatment-Emergent GI Abdominal-Related Adverse Events Requiring the Use of Concomitant Medication by System Organ Class and Preferred Term, Entire Study
14.3.1.39	Safety	Summary of Time to Development of GI Abdominal-Related Adverse Events, Part 1
14.3.1.39.ES	Safety	Summary of Time to Development of GI Abdominal-Related Adverse Events, Entire Study
14.3.1.41	Safety	Duration of GI Abdominal-Related Adverse Events, Part 1
14.3.1.41.ES	Safety	Duration of GI Abdominal-Related Adverse Events, Entire Study
14.3.1.44	Safety	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms, Part 1
14.3.1.44.ES	Safety	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms, Entire Study
14.3.1.45.ES	Safety	Summary of Treatment-Emergent Adverse Event Rate Per 100 Person-Years of Exposure, Entire Study
14.3.1.46.ES	Safety	Summary of Drug-Related Treatment-Emergent Adverse Event Rate Per 100 Person-Years of Exposure, Entire Study
14.3.1.47.ES	Safety	Summary of Treatment-Emergent Serious Adverse Event Rate Per 100 Person-Years of Exposure, Entire Study
14.3.5.1	Safety	Summary of Observed and Change from Baseline Laboratory Data: Clinical Chemistry, Part 1
14.3.5.1.ES	Safety	Summary of Observed and Change from Baseline Laboratory Data: Clinical Chemistry, Entire Study
14.3.5.2	Safety	Summary of Observed and Change from Baseline Laboratory Data: Hematology and Coagulation, Part 1
14.3.5.2.ES	Safety	Summary of Observed and Change from Baseline Laboratory Data: Hematology and Coagulation, Entire Study
14.3.5.3	Safety	Summary of Observed and Change from Baseline Laboratory Data: Complement Factors, Part 1
14.3.5.3.ES	Safety	Summary of Observed and Change from Baseline Laboratory Data: Complement Factors, Entire Study

Output #	Population	Output Title
14.3.5.4	Safety	Summary of Observed and Change from Baseline Laboratory Data: Additional Tests, Part 1
14.3.5.4.ES	Safety	Summary of Observed and Change from Baseline Laboratory Data: Additional Tests, Entire Study
14.3.5.5	Safety	Summary of Observed and Change from Baseline Laboratory Data: Continuous Urinalysis Parameters, Part 1
14.3.5.5.ES	Safety	Summary of Observed and Change from Baseline Laboratory Data: Continuous Urinalysis Parameters, Entire Study
14.3.5.6	Safety	Summary of Observed Laboratory Data: Categorical Urinalysis Parameters, Part 1
14.3.5.6.ES	Safety	Summary of Observed Laboratory Data: Categorical Urinalysis Parameters, Entire Study
14.3.5.7	Safety	Shift from Baseline to Worst Postbaseline Assessment: Clinical Chemistry, Part 1
14.3.5.7.ES	Safety	Shift from Baseline to Worst Postbaseline Assessment: Clinical Chemistry, Entire Study
14.3.5.8	Safety	Shift from Baseline to Worst Postbaseline Assessment: Hematology and Coagulation, Part 1
14.3.5.8.ES	Safety	Shift from Baseline to Worst Postbaseline Assessment: Hematology and Coagulation, Entire Study
14.3.5.9	Safety	Shift from Baseline to Worst Postbaseline Assessment: Urinalysis, Part 1
14.3.5.9.ES	Safety	Shift from Baseline to Worst Postbaseline Assessment: Urinalysis, Entire Study
14.3.5.10	Safety	Shift from Baseline to Worst Postbaseline Assessment: Additional Tests, Part 1
14.3.5.10.ES	Safety	Shift from Baseline to Worst Postbaseline Assessment: Additional Tests, Entire Study
14.3.5.11	Safety	Summary of Treatment-Emergent Graded Laboratory Abnormalities, Part 1
14.3.5.11.ES	Safety	Summary of Treatment-Emergent Graded Laboratory Abnormalities, Entire Study
14.3.5.12	Safety	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities, Part 1
14.3.5.12.ES	Safety	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities, Entire Study
14.3.5.13	Safety	Summary of Treatment-Emergent Laboratory Toxicity Grade Increases from Baseline, Part 1
14.3.5.13.ES	Safety	Summary of Treatment-Emergent Laboratory Toxicity Grade Increases from Baseline, Entire Study
14.3.5.14	Safety	Summary of Fold x ULN for Liver Function Tests, Part 1
14.3.5.14.ES	Safety	Summary of Fold x ULN for Liver Function Tests, Entire Study
14.3.5.15	Safety	Summary of Fold Change from Baseline for Liver Function Tests, Part 1
14.3.5.15.ES	Safety	Summary of Fold Change from Baseline for Liver Function Tests, Entire Study
14.3.5.16	Safety	Summary of Elevations in Post-baseline Liver Function Tests, Part 1
14.3.5.16.ES	Safety	Summary of Elevations in Post-baseline Liver Function Tests, Entire Study
14.3.5.17	Safety - Subjects with Prior Androgen Use	Summary of Elevations in Post-baseline Liver Function Tests, Part 1
14.3.5.17.ES	Safety - Subjects with Prior Androgen Use	Summary of Elevations in Post-baseline Liver Function Tests, Entire Study
14.3.5.18	Safety - Subjects with No Prior Androgen Use	Summary of Elevations in Post-baseline Liver Function Tests, Part 1
14.3.5.18.ES	Safety - Subjects with No Prior Androgen Use	Summary of Elevations in Post-baseline Liver Function Tests, Entire Study
14.3.5.19	Safety	Summary of Treatment-Emergent Elevations in Post-baseline Liver Function Tests, Part 1
14.3.5.19.ES	Safety	Summary of Treatment-Emergent Elevations in Post-baseline Liver Function Tests, Entire Study

Output #	Population	Output Title
14.3.5.25	Safety	Time to First Occurrence of Grade 3 or 4 ALT, Part 1
14.3.5.27	Safety	Time to First Occurrence of Grade 3 or 4 AST, Part 1
14.3.5.29	Safety	Time to First Occurrence of Grade 3 or 4 Total Bilirubin, Part 1
14.3.5.31.ES	Safety	Summary of Rate of Elevations in Post-baseline Liver Function Tests Per 100 Person-Years of Exposure, Entire Study
14.3.6.1	Safety	Summary of Observed and Change from Baseline Vital Signs, Part 1
14.3.6.1.ES	Safety	Summary of Observed and Change from Baseline Vital Signs, Entire Study
14.3.7.1	Safety	Summary of Observed and Change from Baseline ECG Interval Values, Part 1
14.3.7.1.ES	Safety	Summary of Observed and Change from Baseline ECG Interval Values, Entire Study
14.3.7.2	Safety	Summary of ECG Findings, Part 1
14.3.7.2.ES	Safety	Summary of ECG Findings, Entire Study
14.3.7.3	Safety	Summary of QTcF Observed and Change from Baseline Categorical Findings, Part 1
14.3.7.3.ES	Safety	Summary of QTcF Observed and Change from Baseline Categorical Findings, Entire Study
14.4.1.1	ITT	Summary of WPAI Scores, Part 1
14.4.1.1.ES	ITT	Summary of WPAI Scores, Entire Study
14.4.1.4	ITT	Summary of Responses to WPAI Individual Questions, Part 1
14.4.1.4.ES	ITT	Summary of Responses to WPAI Individual Questions, Entire study
14.4.2.1	ITT	Summary of EQ-5D-5L VAS Scores, Part 1
14.4.2.1.ES	ITT	Summary of EQ-5D-5L VAS Scores, Entire Study
14.4.2.4	ITT	Summary of EQ-5D-5L VAS Scores from Usual Attack, Part 1
14.4.2.4.ES	ITT	Summary of EQ-5D-5L VAS Scores from Usual Attack, Entire Study
14.4.2.7	ITT	Summary of EQ-5D-5L Index Scores, Part 1
14.4.2.7.ES	ITT	Summary of EQ-5D-5L Index Scores, Entire Study
14.4.2.10	ITT	Summary of EQ-5D-5L Index Scores from Usual Attack, Part 1
14.4.2.10.ES	ITT	Summary of EQ-5D-5L Index Scores from Usual Attack, Entire Study
14.4.2.13	ITT	Summary of Responses to EQ-5D-5L Individual Questions, Part 1
14.4.2.13.ES	ITT	Summary of Responses to EQ-5D-5L Individual Questions, Entire study
14.4.3.1	ITT	Summary of TSQM Scores, Part 1
14.4.3.1.ES	ITT	Summary of TSQM Scores, Entire Study
14.4.3.4	ITT	Summary of Responses to TSQM Individual Questions, Part 1
14.4.3.4.ES	ITT	Summary of Responses to TSQM Individual Questions, Entire study
14.5.1.1	Safety	Summary of Plasma BCX7353 Concentration (ng/mL), Part 1
14.5.1.1.ES	Safety	Summary of Plasma BCX7353 Concentration (ng/mL), Entire Study
14.5.2.1	Safety	Plasma BCX7353 Concentration (ng/mL) Trough Samples above Kallikrein Inhibition EC50, Part 1
14.5.2.1.ES	Safety	Plasma BCX7353 Concentration (ng/mL) Trough Samples above Kallikrein Inhibition EC50, Entire Study
14.6.1.1	PD	Summary of Plasma Kallikrein Inhibition (%), Part 1
14.6.1.1.ES	PD	Summary of Plasma Kallikrein Inhibition (%), Entire Study
14.6.2.1	PD	Plasma Kallikrein Inhibition Trough Samples above 50% and 80%, Part 1

Output #	Population	Output Title
14.6.2.1.ES	PD	Plasma Kallikrein Inhibition Trough Samples above 50% and 80%, Entire Study

Listings

Output #	Population Title	Output Title
16.2.1.1	All Subjects	Informed Consent and Screen Failures
16.2.1.2	All Subjects	Subject Randomization, Site, and Country
16.2.1.3	Safety	Planned and Actual Treatment Assignments for Subjects with Incorrect Treatment, Part 1
16.2.1.3.ES	Safety	Planned and Actual Treatment Assignments for Subjects with Incorrect Treatment, Entire Study
16.2.1.4	ITT	Subject Disposition
16.2.1.5	All Subjects	Confirmation of Clinical Diagnosis of HAE
16.2.1.6	ITT	Analysis Populations
16.2.1.7	ITT	Subgroups Based on Baseline Characteristics
16.2.2.2	ITT	Protocol Deviations, Part 1
16.2.2.2.ES	ITT	Protocol Deviations Occurring During Part 2 of the Study
16.2.2.3	Safety	Subjects for Whom the Treatment Blind Was Broken, Part 1
16.2.2.3.ES	Safety	Subjects for Whom the Treatment Blind Was Broken, Entire Study
16.2.4.1	ITT	Inclusion/Exclusion Criteria Not Met
16.2.4.2.1	All Subjects	Demography
16.2.4.2.2	All Subjects	Demography - Contraception
16.2.4.3.1	ITT	Medical History
16.2.4.3.2	ITT	HAE Baseline Characteristics – HAE Medical History
16.2.4.3.3	Safety	HAE Medication History: Past and Current On-Demand HAE Treatment
16.2.4.3.4	Safety	HAE Medication History: Past Prophylactic HAE Treatment
16.2.4.4.1	Safety	Medications Discontinued Within 30 Days of Screening
16.2.4.4.2	Safety	Concomitant Medication Use, Part 1
16.2.4.4.2.ES	Safety	Concomitant Medication Use, Entire Study
16.2.4.4.3	Safety	Use of Concomitant Medications for HAE, Part 1
16.2.4.4.3.ES	Safety	Use of Concomitant Medications for HAE, Entire Study
16.2.4.5	ITT	Pre-Treatment Investigator-Confirmed Attack Rates and Angioedema Symptoms
16.2.5.1	Safety	Drug Accountability, Part 1
16.2.5.1.ES	Safety	Drug Accountability, Entire Study
16.2.5.2	Safety	Dosing Diary, Part 1
16.2.5.2.ES	Safety	Dosing Diary, Entire Study
16.2.5.3	Safety	Person-Years of Exposure, Part 1
16.2.5.3.ES	Safety	Person-Years of Exposure, Entire Study
16.2.6.1.1	ITT	HAE Attack Diary and Investigator Confirmation for All Attacks, Part 1
16.2.6.1.1.ES	ITT	HAE Attack Diary and Investigator Confirmation dor All Attacks, Entire Study

Output #	Population Title	Output Title
16.2.6.1.2	ITT	HAE Attack Diary and Investigator Confirmation (Investigator-Confirmed Attacks Only), Part 1
16.2.6.1.2.ES	ITT	HAE Attack Diary and Investigator Confirmation (Investigator-Confirmed Confirmed Attacks Only), Entire Study
16.2.6.1.3	ITT	HAE Attack Diary Detail - Subject-Reported Attacks, Part 1
16.2.6.1.3.ES	ITT	HAE Attack Diary Detail - Subject-Reported Attacks, Entire Study
16.2.6.1.4	ITT	HAE Attack Diary Detail - Investigator-Confirmed Attacks, Part 1
16.2.6.1.4.ES	ITT	HAE Attack Diary Detail - Investigator-Confirmed Attacks, Entire Study
16.2.6.1.5	ITT	HAE Attack Level Summary - Subject-Reported Attacks, Part 1
16.2.6.1.5.ES	ITT	HAE Attack Level Summary - Subject-Reported Attacks, Entire Study
16.2.6.1.6	ITT	HAE Attack Level Summary - Investigator-Confirmed Attacks, Part 1
16.2.6.1.6.ES	ITT	HAE Attack Level Summary - Investigator-Confirmed Attacks, Entire Study
16.2.6.1.7	ITT	Attack Rate, Part 1
16.2.6.1.7.ES	ITT	Attack Rate, Entire Study
16.2.6.1.8	ITT	Imputed Investigator-Confirmed Attack Rates for Subjects with Missing Data, Part 1
16.2.6.1.9	ITT	Subjects Who Are Investigator-Confirmed Attack-Free During Entire Dosing Period and Effective Dosing Period, Part 1
16.2.6.1.9.ES	ITT	Subjects Who Are Investigator-Confirmed Attack-Free During Entire Dosing Period and Effective Dosing Period, Entire Study
16.2.6.1.10	ITT	Days with Angioedema Symptoms from Investigator-Confirmed Attacks, Part 1
16.2.6.1.10.ES	ITT	Days with Angioedema Symptoms from Investigator-Confirmed Attacks, Entire Study
16.2.6.1.11.1	ITT	Subject-Level Efficacy Endpoint Profile, Part 1
16.2.6.1.11.2	ITT	Subject-Level Additional Derived Endpoint Profile , Part 1
16.2.6.2.1	ITT	AE-QoL: Individual Question Responses and Days Missed, Part 1
16.2.6.2.1.ES	ITT	AE-QoL: Individual Question Responses and Days Missed, Entire Study
16.2.6.2.2	ITT	AE-QoL: Domain Scores, Part 1
16.2.6.2.2.ES	ITT	AE-QoL: Domain Scores, Entire Study
16.2.6.3.1	ITT	TSQM Global Satisfaction Individual Responses, Part 1
16.2.6.3.1.ES	ITT	TSQM Global Satisfaction Individual Responses, Entire Study
16.2.6.3.2	ITT	TSQM Effect, Side Effect, Convenience and Global Satisfaction Scores, Part 1
16.2.6.3.2.ES	ITT	TSQM Effect, Side Effect, Convenience and Global Satisfaction Scores, Entire Study
16.2.6.4.1	ITT	EQ-5D-5L Individual Question Responses, Part 1
16.2.6.4.1.ES	ITT	EQ-5D-5L Individual Question Responses, Entire Study
16.2.6.4.2	ITT	EQ-5D-5L Descriptive, VAS, and Index Scores, Part 1
16.2.6.4.3	ITT	EQ-5D-5L for Usual Attack Individual Question Responses, Part 1
16.2.6.4.3.ES	ITT	EQ-5D-5L for Usual Attack Individual Question Responses, Entire Study
16.2.6.4.4	ITT	EQ-5D-5L for Usual Attack Descriptive, VAS, and Index Scores, Part 1
16.2.6.4.4.ES	ITT	EQ-5D-5L for Usual Attack Descriptive, VAS, and Index Scores, Entire Study
16.2.6.5.1	ITT	WPAI Individual Question Responses, Part 1
16.2.6.5.1.ES	ITT	WPAI Individual Question Responses, Entire Study
16.2.6.5.2	ITT	WPAI Absenteeism, Presenteeism, Word Productivity Loss, and Activity Impairment Scores, Part 1

Output #	Population Title	Output Title
16.2.6.5.2.ES	ITT	WPAI Absenteeism, Presenteeism, Word Productivity Loss, and Activity Impairment Scores, Entire Study
16.2.7.1	Safety	Adverse Events, Part 1
16.2.7.1.ES	Safety	Adverse Events, Entire Study
16.2.7.2	Safety	Serious Adverse Events, Part 1
16.2.7.2.ES	Safety	Serious Adverse Events, Entire Study
16.2.7.3	Safety	Grade 3 or 4 Adverse Events, Part 1
16.2.7.3.ES	Safety	Grade 3 or 4 Adverse Events, Entire Study
16.2.7.4	Safety	Adverse Events Leading to Permanent Discontinuation of Study Drug, Part 1
16.2.7.4.ES	Safety	Adverse Events Leading to Permanent Discontinuation of Study Drug, Entire Study
16.2.7.5.1	Safety	Fatal Serious Adverse Events, Part 1
16.2.7.5.2	Safety	Fatal Serious Adverse Events, Entire Study
16.2.7.6	Safety	Adverse Events Leading to Interruption of Study Drug, Part 1
16.2.7.6.ES	Safety	Adverse Events Leading to Interruption of Study Drug, Entire Study
16.2.7.7	Safety	Investigator-identified Rash, Part 1
16.2.7.7.ES	Safety	Investigator-identified Rash, Entire Study
16.2.7.8	Safety	GI Abdominal-Related Adverse Events, Part 1
16.2.7.8.ES	Safety	GI Abdominal-Related Adverse Events, Entire Study
16.2.7.9	Safety	Adverse Events For Subjects with Elevated LFTs, Part 1
16.2.7.9.ES	Safety	Adverse Events For Subjects with Elevated LFTs, Entire Study
16.2.7.10	ITT	Listing of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms, Part 1
16.2.7.10.ES	ITT	Listing of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms, Entire Study
16.2.8.1	Safety	Clinical Chemistry, Part 1
16.2.8.1.ES	Safety	Clinical Chemistry, Entire Study
16.2.8.2	Safety	Hematology, Part 1
16.2.8.2.ES	Safety	Hematology, Entire Study
16.2.8.3	Safety	Coagulation, Part 1
16.2.8.3.ES	Safety	Coagulation, Entire Study
16.2.8.4	Safety	Urinalysis, Part 1
16.2.8.4.ES	Safety	Urinalysis, Entire Study
16.2.8.5	Safety	Other Laboratory Tests, Part 1
16.2.8.5.ES	Safety	Other Laboratory Tests, Entire Study
16.2.8.6	Safety	Complement Factors C3, C4, and C1-INH, Part 1
16.2.8.6.ES	Safety	Complement Factors C3, C4, and C1-INH, Entire Study
16.2.8.7	ITT	SERPING Results
16.2.8.8	ITT	Pregnancy Tests, Part 1
16.2.8.8.ES	ITT	Pregnancy Tests, Entire Study
16.2.8.9	Safety	Laboratory Abnormalities, Part 1

Output #	Population Title	Output Title
16.2.8.9.ES	Safety	Laboratory Abnormalities, Entire Study
16.2.8.10	Safety	Grade 3 or Grade 4 Laboratory Abnormalities, Part 1
16.2.8.10.ES	Safety	Grade 3 or Grade 4 Laboratory Abnormalities, Entire Study
16.2.8.11	Safety	All Liver Function Test Results for Subject Experiencing a Treatment-Emergent Grade 3 or 4 Liver Function Test, Part 1
16.2.8.11.ES	Safety	All Liver Function Test Results for Subject Experiencing a Treatment-Emergent Grade 3 or 4 Liver Function Test, Entire Study
16.2.8.12	Safety - Subjects with Prior Androgen Use	All Liver Function Test Results for Subject Experiencing a Treatment-Emergent Grade 3 or 4 Liver Function Test, Part 1
16.2.8.12.ES	Safety - Subjects with Prior Androgen Use	All Liver Function Test Results for Subject Experiencing a Treatment-Emergent Grade 3 or 4 Liver Function Test, Entire Study
16.2.8.13	Safety	Vital Signs, Part 1
16.2.8.13.ES	Safety	Vital Signs, Part 1, Entire Study
16.2.8.14	Safety	12-Lead Electrocardiogram, Part 1
16.2.8.14.ES	Safety	12-Lead Electrocardiogram, Entire Study
16.2.8.15	Safety	QTcF Values > 450 msec or QTF Change from Baseline Values > 30 msec, Part 1
16.2.8.15.ES	Safety	QTcF Values > 450 msec or QTF Change from Baseline Values > 30 msec, Entire Study
16.2.8.16	Safety	Physical Exam, Part 1
16.2.8.16.ES	Safety	Physical Exam, Entire Study
16.2.8.17	Safety	Pharmacokinetic Sample Collection, Part 1
16.2.8.17.ES	Safety	Pharmacokinetic Sample Collection, Entire Study
16.2.8.18	PD	Plasma Kallikrein Inhibition (%), Part 1
16.2.8.18.ES	PD	Plasma Kallikrein Inhibition (%), Entire Study

Figures

Output #	Population Title	Output Title
14.1.1.2	All Subjects	CONSORT Diagram, Part 1
14.1.1.2.ES	All Subjects	CONSORT Diagram, Entire Study
14.1.5.2	Safety	Plot of Duration of Exposure to Study Drug, Part 1
14.1.5.2.ES	Safety	Plot of Duration of Exposure to Study Drug, Entire Study
14.2.1.7	ITT	Box Plot of Individual Investigator-Confirmed Attack Rate for Entire Dosing Period, Part 1
14.2.1.7.ES	ITT	Box Plot of Individual Investigator-Confirmed Attack Rate for Entire Dosing Period, Entire Study
14.2.1.8	ITT	Cumuative Distribution Plot of Individual Investigator-Confirmed Attack Rate for Entire Dosing Period, Part 1
14.2.1.8.ES	ITT	Cumulative Distribution Plot of Individual Investigator-Confirmed Attack Rate for Entire Dosing Period, Entire Study
14.2.1.9	ITT	Forest Plot of Results of Sensitivity Analyses of Investigator-Confirmed Attack Rate for Entire Dosing Period, Part 1
14.2.1.10	ITT	Forest Plot of Results of Subgroup Analyses of Investigator-Confirmed Attack Rate for Entire Dosing Period, Part 1

Output #	Population Title	Output Title
14.2.1.12	ITT	Box Plot of Individual Investigator-Confirmed Attack Rate for Effective Dosing Period, Part 1,
14.2.1.12.ES	ITT	Box Plot of Individual Investigator-Confirmed Attack Rate for Effective Dosing Period, Entire Study
14.2.1.13	ITT	Cumulative Distribution Plot of Individual Investigator-Confirmed Attack Rate for Effective Dosing Period, Part 1
14.2.1.13.ES	ITT	Cumulative Distribution Plot of Individual Investigator-Confirmed Attack Rate for Effective Dosing Period, Entire Study
14.2.2.2	ITT	Histogram Plot of Baseline Investigator-Confirmed Attack Rate, Part 1
14.2.2.3	ITT	Plot of Mean Investigator-Confirmed Attack Rate by Month, Part 1
14.2.2.3.ES	ITT	Plot of Mean Investigator-Confirmed Attack Rate by Month, Entire Study
14.2.2.3.P3	ITT	Plot of Mean Subject-Reported Attack Rate by Month, Part 3
14.2.2.4	ITT	Plot of On-Study Investigator-Confirmed Attack Rate vs Baseline Investigator-Confirmed Attack Rate, Part 1
14.2.2.4.ES	ITT	Plot of On-Study Investigator-Confirmed Attack Rate vs Baseline Investigator-Confirmed Attack Rate, Entire Study
14.2.2.5	ITT	Plot of Difference Between On-Study Investigator-Confirmed Attack Rate and Baseline Investigator-Confirmed Attack Rate vs Baseline Investigator-Confirmed Attack Rate, Part 1
14.2.2.6	ITT	Plot of Change from Baseline Attack Rate Versus Percent Compliance, Part 1
14.2.3.3	ITT	Plot of Mean AE-QoL Scores Over Time, Part 1
14.2.3.3.ES	ITT	Plot of Mean AE-QoL Scores Over Time, Entire Study
14.2.3.4	ITT	Plot of Mean Change from Baseline AE-QoL Scores Over Time, Part 1
14.2.3.4.ES	ITT	Plot of Mean Change from Baseline AE-QoL Scores Over Time, Entire Study
14.2.3.5	ITT	Cumulative Distribution of Total AE-QoL Change from Baseline at Week 24
14.2.3.6	ITT	Forest Plot of Results of Subgroup Analyses of Total AE-QOL Change from Baseline at Week 24, Part 1
14.2.8.2	ITT	Kaplan-Meier Plot of Time to First Investigator-Confirmed Attack, Part 1
14.2.9.2	ITT	Kaplan-Meier Plot of Time to First Use of Targeted HAE Rescue Medication to Treat an Investigator-Confirmed Attack, Part 1
14.3.1.13	ITT	Forest Plot of Treatment-Emergent Adverse Events Sorted by Relative Risk, Part 1
14.3.1.13.ES	ITT	Forest Plot of Treatment-Emergent Adverse Events Sorted by Relative Risk, Entire Study
14.3.1.26	Safety	Kaplan-Meier Plot of Time to Development of Investigator-identified Rash, Part 1
14.3.1.26.ES	Safety	Kaplan-Meier Plot of Time to Development of Investigator-identified Rash, Entire Study
14.3.1.28	Safety	Kaplan-Meier Plot of Duration of Investigator-identified Rash, Part 1
14.3.1.28.ES	Safety	Kaplan-Meier Plot of Duration of Investigator-identified Rash, Entire Study
14.3.1.40	Safety	Kaplan-Meier Plot of Time to First Occurrence of a GI Abdominal-related Adverse Event Part 1
14.3.1.40.ES	Safety	Kaplan-Meier Plot of Time to First Occurrence of a GI Abdominal-related Adverse Event Entire Study
14.3.1.42	Safety	Kaplan-Meier Plot of Duration of GI Abdominal-related Adverse Events Part 1
14.3.1.42.ES	Safety	Kaplan-Meier Plot of Duration of GI Abdominal-related Adverse Events Entire Study
14.3.1.43	Safety	Plot of Occurrence of Treatment-Emergent GI Abdominal-related Adverse Events, Part 1
14.3.1.43.ES	Safety	Plot of Occurrence of Treatment-Emergent GI Abdominal-related Adverse Events, Entire Study
14.3.5.20	Safety	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities, Part 1
14.3.5.21	Safety	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT, Part 1

Output #	Population Title	Output Title
14.3.5.21.ES	Safety	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT, Entire Study
14.3.5.22	Safety	Liver Test Safety Panel Over Time, Baseline vs. On-Study, Part 1
14.3.5.22.ES	Safety	Liver Test Safety Panel Over Time, Baseline vs. On-Study, Entire Study
14.3.5.23	Safety	Distribution of Liver Tests Over Time: ALT, AST, ALP, and Bilirubin, Part 1
14.3.5.23.ES	Safety	Distribution of Liver Tests Over Time: ALT, AST, ALP, and Bilirubin, Entire Study
14.3.5.24	Safety	Distribution of Cholesterol and Triglycerides Over Time, Part 1
14.3.5.24.ES	Safety	Distribution of Cholesterol and Triglycerides Over Time, Entire Study
14.3.5.26	Safety	Kaplan-Meier Plot of Time to First Occurrence of Grade 3 or 4 ALT Part 1
14.3.5.28	Safety	Kaplan-Meier Plot of Time to First Occurrence of Grade 3 or 4 AST Part 1
14.3.5.30	Safety	Kaplan-Meier Plot of Time to First Occurrence of Grade 3 or 4 Total Bilirubin, Part 1
14.3.6.2	Safety	Distribution of Diastolic and Systolic Blood Pressure Over Time, Part 1
14.3.6.2.ES	Safety	Distribution of Diastolic and Systolic Blood Pressure Over Time, Entire Study
14.3.7.4	Safety	Distribution of QTcF Over Time, Part 1
14.3.7.4.ES	Safety	Distribution of QTcF Over Time, Entire Study
14.4.1.2	ITT	Plot of Mean WPAI Scores Over Time, Part 1
14.4.1.2.ES	ITT	Plot of Mean WPAI Scores Over Time, Entire Study
14.4.1.3	ITT	Plot of Mean Change from Baseline WPAI Scores Over Time, Part 1
14.4.1.3.ES	ITT	Plot of Mean Change from Baseline WPAI Scores Over Time, Entire Study
14.4.2.2	ITT	Plot of Mean EQ-5D-5L VAS Scores Over Time, Part 1
14.4.2.2.ES	ITT	Plot of Mean EQ-5D-5L VAS Scores Over Time, Entire Study
14.4.2.3	ITT	Plot of Mean Change from Baseline EQ-5D-5L VAS Scores Over Time, Part 1
14.4.2.3.ES	ITT	Plot of Mean Change from Baseline EQ-5D-5L VAS Scores Over Time, Entire Study
14.4.2.5	ITT	Plot of Mean EQ-5D-5L VAS Scores from Usual Attack Over Time, Part 1
14.4.2.5.ES	ITT	Plot of Mean EQ-5D-5L VAS Scores from Usual Attack Over Time, Entire Study
14.4.2.6	ITT	Plot of Mean Change from Baseline EQ-5D-5L VAS Scores from Usual Attack Over Time, Part 1
14.4.2.6.ES	ITT	Plot of Mean Change from Baseline EQ-5D-5L VAS Scores Usual Attack Over Time, Entire Study
14.4.2.8	ITT	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Over Time, Part 1
14.4.2.8.ES	ITT	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Over Time, Entire Study
14.4.2.9	ITT	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Over Time, Part 1
14.4.2.9.ES	ITT	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Over Time, Entire Study
14.4.2.11	ITT	Plot of Mean EQ-5D-5L Index Scores from Usual Attack Over Time, Part 1
14.4.2.11.ES	ITT	Plot of Mean EQ-5D-5L Index Scores from Usual Attack Over Time, Entire Study
14.4.2.12	ITT	Plot of Mean Change from Baseline EQ-5D-5L Index Scores from Usual Attack Over Time, Part 1
14.4.2.12.ES	ITT	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Usual Attack Over Time, Entire Study
14.4.3.2	ITT	Plot of Mean TSQM Scores Over Time, Part 1
14.4.3.2.ES	ITT	Plot of Mean TSQM Scores Over Time, Entire Study
14.4.3.3	ITT	Plot of Mean Change from Baseline TSQM Scores Over Time, Part 1

Output #	Population Title	Output Title
14.4.3.3.ES	ITT	Plot of Mean Change from Baseline TSQM Scores Over Time, Entire Study
14.6.1.2	PK-PD	Scatterplot of Kallekrein Inhibition (%) and BCX7353 Plasma Concentration/4by Study Visit, Part 1
14.6.1.2.ES	PK-PD	Scatterplot of Kallekrein Inhibition (%) and BCX7353 Plasma Concentration/4by Study Visit, Entire Study

Data Display Specifications

Table, listing, and figure shells will be stored in a separate document.

List of Preferred Terms, High Level Terms, and High-Level Group Terms for Gastrointestinal Abdominal-Related Treatment-Emergent Adverse Events

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10000059	Abdominal discomfort	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000060	Abdominal distension	Flatulence, bloating and distension	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000077	Abdominal mass	Abdominal findings abnormal	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10049714	Abdominal migraine	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000081	Abdominal pain	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000084	Abdominal pain lower	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000087	Abdominal pain upper	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10052489	Abdominal rebound tenderness	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000090	Abdominal rigidity	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10060926	Abdominal symptom	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000097	Abdominal tenderness	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000133	Abnormal faeces	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10058938	Acetonaemic vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10000647	Acute abdomen	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10052813	Aerophagia	Flatulence, bloating and distension	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10077605	Anal incontinence	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10006326	Breath odour	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10051650	Chilaiditi's syndrome	Abdominal findings abnormal	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10062937	Cyclic vomiting syndrome	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10013810	Dumping syndrome	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10013946	Dyspepsia	Dyspeptic signs and symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10013950	Dysphagia	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10053155	Epigastric discomfort	Dyspeptic signs and symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10015137	Eructation	Dyspeptic signs and symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10050248	Faecal volume decreased	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10049939	Faecal volume increased	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10064670	Faecal vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10056988	Faecalith	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10056325	Faecaloma	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10016100	Faeces discoloured	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10016101	Faeces hard	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10016102	Faeces pale	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10074859	Faeces soft	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10074216	Fixed bowel loop	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10016766	Flatulence	Flatulence, bloating and distension	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10017999	Gastrointestinal pain	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10067715	Gastrointestinal sounds abnormal	Abdominal findings abnormal	Gastrointestinal signs and symptoms	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10075724	Gastrointestinal wall thickening	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10075726	Gastrointestinal wall thinning	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10021746	Infantile colic	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10063338	Infantile spitting up	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10075315	Infantile vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10073530	Intestinal calcification	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10065611	Intestinal congestion	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10067576	Malignant dysphagia	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10028140	Mucous stools	Faecal abnormalities NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10069369	Myochosis	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10028813	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10053634	Oesophageal discomfort	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10065567	Oesophageal food impaction	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10030180	Oesophageal pain	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10034647	Peristalsis visible	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10057030	Pneumatosis intestinalis	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10064711	Portal venous gas	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10066220	Post-tussive vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10067171	Regurgitation	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10038776	Retching	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10078474	Scaphoid abdomen	Abdominal findings abnormal	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10047700	Vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10047708	Vomiting projectile	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10078438	White nipple sign	Gastrointestinal signs and symptoms NEC	Gastrointestinal signs and symptoms	Gastrointestinal disorders
10063541	Bowel movement irregularity	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10007645	Cardiospasm	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10008399	Change of bowel habit	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10057078	Colonic pseudo-obstruction	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
			defaecation conditions	
10010774	Constipation	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10012110	Defaecation urgency	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10051153	Diabetic gastroparesis	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10012735	Diarrhoea	Diarrhoea (excl infective)	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10012741	Diarrhoea haemorrhagic	Diarrhoea (excl infective)	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10012743	Diarrhoea neonatal	Diarrhoea (excl infective)	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10060865	Duodenogastric reflux	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10051244	Dyschezia	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10013924	Dyskinesia oesophageal	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10017367	Frequent bowel movements	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10017753	Gastric atony	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10017779	Gastric dilatation	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10052406	Gastric hypermotility	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10062931	Gastric hypertonia	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10052405	Gastric hypomotility	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10052402	Gastrointestinal hypermotility	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10052105	Gastrointestinal hypomotility	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10061173	Gastrointestinal motility disorder	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10017885	Gastrooesophageal reflux disease	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10062879	Gastrooesophageal sphincter insufficiency	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10021333	Ileus paralytic	Non-mechanical ileus	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10021335	Ileus spastic	Non-mechanical ileus	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10021518	Impaired gastric emptying	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10059158	Infrequent bowel movements	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10022642	Intestinal dilatation	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10023003	Irritable bowel syndrome	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10027110	Megacolon	Non-mechanical ileus	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10072286	Narcotic bowel syndrome	Non-mechanical ileus	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10058934	Neonatal intestinal dilatation	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10076953	Obstructive defaecation	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10030136	Oesophageal achalasia	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10071554	Oesophageal atony	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10067752	Oesophageal hypomotility	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10072419	Oesophageal motility disorder	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10030184	Oesophageal spasm	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10060696	Presbyoesophagus	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10075246	Pseudoachalasia	Gastrointestinal dyskinetic disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10073166	Pyloric sphincter insufficiency	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10037628	Pylorospasm	Gastrointestinal spastic and hypermotility disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10066142	Sandifer's syndrome	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders