BIOCRYST PHARMACEUTICALS INC.
STATISTICAL ANALYSIS PLAN
PHASE 3

VERSION: FINAL 1.0

DATE OF PLAN:

04-NOV-2019

BASED ON:

Protocol Version 5.0: 29 August 2019

CRF Version 5.0: 31 July 2019

STUDY DRUG:

BCX7353

PROTOCOL NUMBER:

BCX7353-301

IND No. 135,058

EudraCT No. 2017-003966-29

STUDY TITLE:

APeX-J: A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema

SPONSOR:

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

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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 Investigational 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

Title of Study:

APeX-J: A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema

Study Centers: Approximately 15 centers in Japan

Enrollment Period: Approximately 3 months	**Phase of development:** 3

Part 1 Primary Objective:

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

Part 1 Secondary Objectives:

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

Part 1 Primary Efficacy Endpoint:

- The rate of expert-confirmed angioedema events during dosing in the entire 24-week treatment period (Days 1 to 168).

Part 1 Secondary Efficacy Endpoints:

- Change from baseline in AE-QoL at Week 24 (total score)
- Number and proportion of days with angioedema symptoms through 24 weeks
- Rate of expert-confirmed angioedema events 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 angioedema events over 24 weeks
- Use of medications to treat angioedema events over 24 weeks
- The proportion of responders to study drug, separately defined as at least a 50%, 70%, or 90% relative reduction in the rate of expert-confirmed angioedema events during treatment compared with the baseline expert-confirmed angioedema event rate

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

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 Objective:

- To evaluate the long-term safety and tolerability of BCX7353 110 and 150 mg in subjects with HAE

Part 2 Secondary Objectives:

- To assess the effectiveness (ie, angioedema event frequency over time) of BCX7353 over a 24- to 52-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 24- to 52-week administration period time
- To evaluate subject satisfaction with BCX7353 over a 24- to 52-week administration period

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

Part 2 Secondary Endpoints:

- Number and rate of angioedema events

- Durability of response (angioedema event rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of medications to treat angioedema events
- 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 Objective:

- To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 52- to up to 104-week administration period in subjects with HAE

Part 3 Secondary Objectives:

- To assess the effectiveness (ie, angioedema event frequency over time) of BCX7353 over a 52- to up to 104-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 52- to up to 104-week administration period
- To evaluate subject satisfaction with BCX7353 over a 52- to up to 104-week administration period

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 angioedema events
- Durability of response (angioedema event rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of medications to treat angioedema events
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores

- Durability in WPAI scores

Methodology:

This is a randomized, placebo-controlled, double-blind, parallel-group, 2-part study. Part 1 is designed to test the hypothesis that the angioedema event rate during 24 weeks of prophylactic BCX7353 treatment at 2 dosage levels will be less than that observed during 24 weeks of placebo.

An angioedema event is defined as an attack, symptoms or swelling due to a subject's underlying HAE disease. 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. All subjects will receive BCX7352 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 angioedema events documented during a prospective run-in period of 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 QD administered orally for 24 weeks
- Group 2: BCX7353 150 mg QD administered orally for 24 weeks
- Group 3: Placebo QD administered orally for 24 weeks

Enrollment into treatment groups will be stratified by the baseline angioedema event rate (≥ 2 angioedema events per month vs. < 2 angioedema events per month).

Details of all angioedema events (attack, symptoms, or swelling due to HAE) and compliance with study drug will be recorded in an electronic diary (e-diary). Angioedema events will be treated in accordance with the subject's normal standard of care. Treatment medication for angioedema events will not be provided by the sponsor.

Within approximately 2 business days of the end of each angioedema event that occurs beginning at the screening visit through the Week 24 visit, subjects will be contacted by the investigator (or appropriately-trained designee) to discuss the clinical characteristics of the angioedema event, any questions the investigator has on the entered data, or to gain additional details of the event that are not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable.

The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each event recorded in the e-diary as a confirmed angioedema event. All expert-confirmed angioedema events must include symptoms of swelling; prodromal symptoms in the absence of swelling are not considered angioedema events, regardless of treatment.

The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling. Under no circumstances should the run-in angioedema event requirement for eligibility be disclosed to study subjects.

The study will include adolescent and adult subjects (≥ 12 years of age).

Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, electrocardiograms (ECGs), 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 interacting with sites during Part 1.

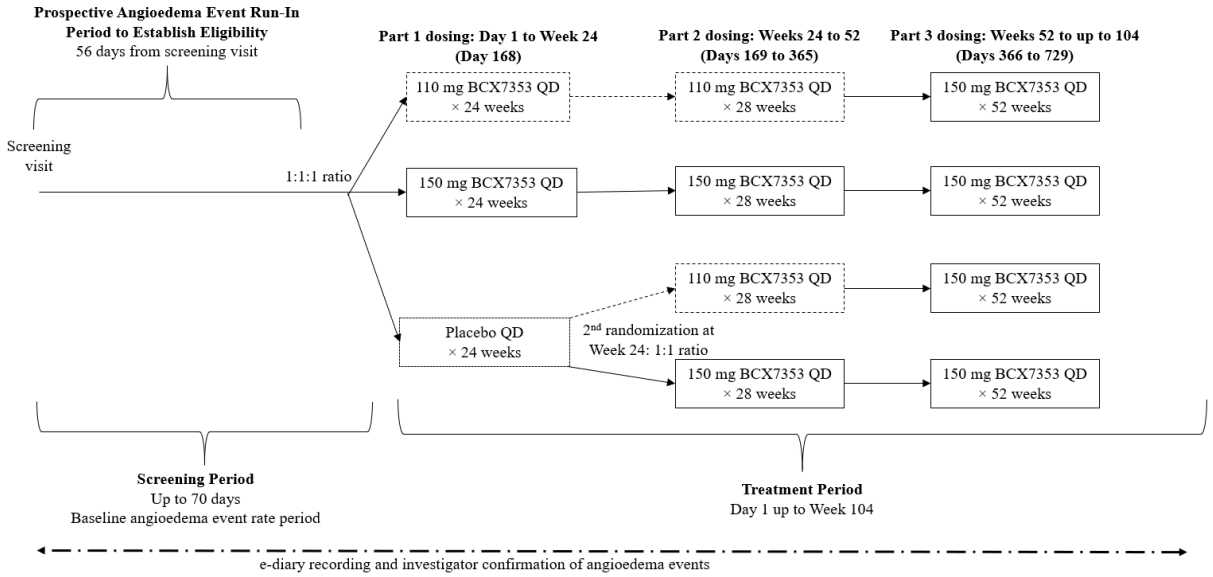
Part 2 (evaluation of safety of blinded BCX7353)

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 or 150 mg QD dose of BCX7353 in a blinded manner beginning at the Week 24 visit (see figure below for visual depiction of treatments in all study parts). 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, 48, and 52, with telephone contact at Weeks 40 and 44. Subjects will continue to document all angioedema events (attack, symptoms, or swelling due to HAE) that occur while on study drug, as well as compliance with the study drug, in their e-diary and will have regular visits to assess safety and tolerability. Investigator confirmation of angioedema events will continue to be required for Part 2. Interim safety analyses will be conducted while Parts 2 and 3 are ongoing to support regulatory filings.



Abbreviations: e-diary = electronic diary; QD = once daily.

Part 3 (up to 52-week evaluation of the safety of open-label BCX7353)

Part 3 of the study will start with the administration of the study drug dispensed at the Week 52 visit. Based on the safety profile and efficacy of the 150 mg dose in Part 1 of the similarly-designed Study BCX7353-302 (Study 302), all subjects in the current study receiving 110 mg QD will be transitioned to open-label 150 mg QD at the Week 52 visit.

Study visits during Part 3 will occur during Week 60 and approximately every 12 weeks thereafter, for a total study duration of up to 104 weeks, until another mechanism is available to provide drug to the subject (eg, market access), or until the Sponsor discontinues development of the product for the prevention of angioedema events, whichever comes first. Telephone contacts will occur at Weeks 56, 64, 68, 76, 80, 88, 92, and 100. A final study follow-up visit (Week 107) will be scheduled approximately 3 weeks following the last administration of study drug. Subjects will continue to document all angioedema events (attack, symptoms or swelling due to HAE) that occur while on study drug in their e-diary in Part 3. However, subjects will not be required to document compliance with the study drug. In addition, investigator confirmation of angioedema events will not be required in Part 3. All angioedema events 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 will be outlined in the Statistical Analysis Plan.

Number of Subjects (planned):

Approximately 24 subjects with Type 1 or 2 HAE are planned to be enrolled (n = approximately 8 per group in Part 1 [110 mg BCX7353, 150 mg BCX7353, and placebo]).

Main criteria for inclusion:

1. Males and non-pregnant, non-lactating females ≥ 12 years of age.
2. Able to provide written, informed consent. Subjects aged 12 to 17 years must be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent.
3. A clinical diagnosis of HAE Type 1 or Type 2, defined as having a C1 esterase inhibitor (C1-INH) functional level < 50% and a complement 4 (C4) level below the lower limit of the normal (LLN) reference range, as assessed during the screening period.

   In the absence of a low C4 value drawn during the inter-critical period (ie, subject is not having an angioedema event), 1 of the following is acceptable to confirm the diagnosis of HAE: 1) a SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or 2 assessed during the screening period; 2) a confirmed family history of C1-INH deficiency; 3) a C4 redrawn and retested during an angioedema event in the screening period with the results below the LLN reference range.

   For a C1-INH that is between 50% and the LLN (74%), a SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or 2 HAE is acceptable to confirm the diagnosis of HAE.

   SERPING-1 gene analysis results indicating a "possibly pathogenic" mutation will be considered on a case-by-case basis by the medical monitor and may require additional testing for eligibility.
4. Access to and ability to use an acute treatment for angioedema events approved by the Japan Ministry of Health, Labor, and Welfare (plasma-derived C1-INH or icatibant).
5. Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study; that is, subjects must be medically appropriate to be managed without prophylactic treatments for HAE.
6. The subject must have at least 2 angioedema events as assessed by an independent expert that meet all requirements below during the run-in period of 56 days beginning at the screening visit:
   - The angioedema events are unique, which is defined as an angioedema event that does not begin within 48 hours of the end of a previous angioedema event.
   - The angioedema events must have either been treated, required medical attention, or be documented to cause functional impairment based on subject entry in the e-diary. Functional impairment is defined as the subject not being able to perform daily activities without restriction (ie, subject records that he/she is at least slightly restricted in daily activities during the angioedema event).
   - The angioedema events must include symptoms of swelling. The expert will consider that 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 angioedema events are otherwise confirmed by an independent expert to be angioedema events.

   Under no circumstances should the run-in angioedema event requirement for eligibility be disclosed to study subjects.
7. Female subjects must agree to the contraception requirements and must meet the inclusion criteria regarding contraception, as outlined in Section 8.2.1 of the protocol.
8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate adequate compliance with all study procedures required from the screening visit through randomization, including e-diary recording of angioedema events beginning at the screening visit.

Main criteria for exclusion:

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject by participating in the study.
2. Dementia, altered mental status, or any psychiatric condition or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
3. Anticipated use of short-term prophylaxis of angioedema events for a preplanned procedure during the screening or study periods.
4. Concurrent diagnosis of any other type of recurrent angioedema.
5. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a corrected QT interval using Fridericia's method (QTcF) > 470 msec for women, a QTcF > 450 msec for men, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
6. Any clinically significant history of angina, myocardial infarction, syncope, cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
7. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
8. History of or current implanted defibrillator or pacemaker.
9. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the investigator, is clinically significant and relevant for this study. A calculated creatinine clearance of ≤ 30 mL/min or aspartate aminotransferase or alanine aminotransferase value ≥ 3 × the upper limit of the normal reference range value obtained during screening is exclusionary.
10. Prior enrollment in a BCX7353 study.
11. Suspected C1-INH resistance in the opinion of the investigator or sponsor.
12. History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcohol intake > 3 drinks/day).
13. Positive serology for human immunodeficiency virus or current infection with hepatitis B virus or hepatitis C virus.
14. Pregnant or planning to become pregnant during the study.
15. Currently breastfeeding. Women who want to enter the study must agree to suspend breastfeeding at the screening visit. Women must wait at least 3 weeks after the last dose of BCX7353 to commence breastfeeding.
16. Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
17. History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
18. Use of androgens or tranexamic acid for prophylaxis of angioedema events within the 28 days prior to the screening visit or initiation during the study.
19. Use of C1-INH for prophylaxis of angioedema events within the 14 days prior to the screening visit or initiation during the study. Use of a C1-INH therapy for treatment of angioedema events is not excluded at any time, nor is C1-INH for preprocedural prophylaxis for an unplanned/unforeseen procedure.
20. Use of concomitant medications that are metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
21. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study.
22. Use of a medication that is transported by P-glycoprotein and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
23. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
24. Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study.

25. Current participation in any other investigational drug study or received another investigational drug within 30 days of the screening visit.
26. An immediate family relationship to either sponsor employees, the investigator, or employees of the study site named on the delegation log.
27. Held in an institution by a government or judicial order.

Investigational product, dosage, and mode of administration:

BCX7353 capsules, to be administered orally.

Parts 1 and 2

BCX7353 capsules contain 55 and 75 mg of the active ingredient (free base equivalents). Subjects will take the following orally once daily 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 of study drug in both Parts 1 and 2.

Subjects randomized to Treatment Group 3 in Part 1 will be automatically 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 150 mg of the active ingredient (free base equivalent). 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.

Subjects randomized to Treatment Groups 1 and 2 will receive a total of up to 104 weeks of active BCX7353 treatment. Subjects randomized to Treatment Group 3 will receive a total of up to 80 weeks of active BCX7353 treatment.

Reference therapy, dosage, 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.

Duration of treatment:

Subjects will take capsules of BCX7353 or placebo orally for 24 weeks in Part 1 and capsules of BCX7353 orally for up to 80 weeks (28 weeks in Part 2 and up to 52 weeks in Part 3), for a total duration of study drug treatment of up to 104 weeks.

Criteria for evaluation:

Efficacy:

Number of angioedema events and related details (timing, duration of symptoms, anatomical location, treatment used, emergency room visits, hospitalizations), number of days with HAE symptoms, number of subjects who are angioedema event-free, assessment of angioedema event severity, and discontinuations due to lack of efficacy.

Safety:

AEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis, creatine kinase-MB, troponin I and T, neutrophil gelatinase-associated lipocalin), vital signs, ECGs, and physical examinations. An independent Data Monitoring Committee (DMC) will periodically review safety data in accordance with a DMC Charter. Relationships between safety assessment findings and human leukocyte antigen typing results may be examined on a meta-study basis.

Health Outcomes:

AE-QoL, EQ-5D-5L, TSQM, and WPAI questionnaire scores.

Pharmacodynamics:

Kallikrein inhibition. Additional exploratory assays to elucidate PD properties of BCX7353 may also be conducted on plasma samples drawn for PD analyses.

Pharmacokinetics:

Blood samples for BCX7353 concentrations will be drawn. Population pharmacokinetic parameters of BCX7353 will be evaluated on a meta-study basis.

Statistical methods:

The primary study hypothesis is that the rate of angioedema events during 24 weeks of prophylactic BCX7353 will be less than the corresponding rate on placebo. The primary efficacy endpoint in Study BCX7353-301 (Study 301) is the monthly expert-confirmed angioedema event rate in the entire treatment period (Day 1 [post-dose] to Day 168) in the intent-to-treat (ITT) population, which includes all randomized subjects. The primary analysis will be conducted on the Study 301 population. It should be noted that the sample size considered feasible for enrollment in Japan has limited statistical power.

A supplemental analysis will combine data from Part 1 of this study with data from Study 302, Part 1. The primary efficacy endpoint in Study 302 is the monthly investigator-confirmed angioedema event rate in the entire treatment period (Day 1 [post-dose] to Day 168) in the ITT population.

The angioedema event rate and the treatment comparisons between each BCX7353 dose and placebo in the rate of investigator- or expert-confirmed HAE angioedema events during the entire dosing period will be analyzed using a negative binomial regression model. The number of investigator or expert-confirmed angioedema events will be included as the dependent variable, the treatment will be included as a fixed effect, the stratification variable (baseline angioedema event 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 angioedema event for each treatment group, the treatment differences expressed as the angioedema event rate ratio (BCX7353 over placebo rate ratio), and their associated 95% confidence intervals will be provided from the negative binomial regression model. Monthly will be defined as 4 weeks.

Descriptive summaries, figures, and listings will be produced for efficacy endpoints of interest. Safety data analyses will be conducted using data from the current study alone.

The safety analyses will be analyzed separately for Part 1 alone; a later data analysis will evaluate long-term safety data for the current study. Safety endpoints that will be summarized include, at a minimum, the number and proportion of subjects

1) with a TEAE;

2) who discontinue BCX7353 due to a TEAE

3) who experience a TESAE;

4) who experience a Grade 3 or 4 TEAE; and

5) who experience a treatment-emergent Grade 3 or 4 laboratory abnormality. In addition, the proportion of subjects with treatment-emergent, treatment-related AEs consistent with a drug rash will also be summarized.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

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
C3	complement 3
C4	complement 4
CFB	change from baseline
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
EC_{50}	half-maximal effective concentration
ECG	Electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EOSI	event of special interest
EQ-5D-5L	EuroQoL 5-dimensional, 5-level questionnaire
EQ VAS	EuroQoL Visual Analogue Scale
FDA	Food and Drug Administration
GI	gastrointestinal
HAE	hereditary angioedema
HLGT	high-level group term
ICH	International Council for Harmonization
ID	identification
ITT	intent-to-treat
IXRS	interactive (web or voice) response system

%KKI	percent kallikrein inhibition
KM	Kaplan-Meier
LLN	lower limit of normal
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
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
SD	standard deviation
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
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
ULN	upper limit of normal
US	United States
VAS	Visual Analog Scale
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
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 BCX7353-301 (Study 301).

Protocol Revision Chronology:		
Protocol	19 July 2018	Version 1
	26 September 2018	Version 2
	11 October 2018	Version 3 (matches the Pharmaceutical and Medical Devices Agency-accepted v1.1 dated 1 October 2018)
	15 October 2018	Version 4
	29 August 2019	Version 5

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 301. 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 interim and final analysis will be made, the SAP will be finalized, approved by the Sponsor, and placed on file before the database is locked for the interim analysis.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Part 1 Primary Objective

- To determine the efficacy of BCX7353 110 and 150 mg administered once daily (QD) for 24 weeks compared to placebo in the prevention of angioedema events 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 QD administered for 24 weeks
- To assess the effects of BCX7353 on HAE disease activity and angioedema 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 and 150 mg in subjects with HAE

3.1.4. Part 2 Secondary Objectives

- To assess the effectiveness (ie, angioedema event frequency over time) of BCX7353 over a 24- to 52-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 24- to 52-week administration period
- To evaluate subject satisfaction with BCX7353 over a 24- to 52-week administration period

3.1.5. Part 3 Primary Objectives

- To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 52- to up to 104-week administration period in subjects with HAE

3.1.6. Part 3 Secondary Objectives

- To assess the effectiveness (ie, angioedema event frequency over time) of BCX7353 over a 52- to up to 104-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 52- to up to 104-week administration period
- To evaluate subject satisfaction with BCX7353 over a 52- to up to 104-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 expert-confirmed angioedema events during dosing in the entire 24-week treatment period (Days 1 to 168)

3.2.2. Part 1 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- Change from baseline in AE-QoL at Week 24 (total score)
- Number and proportion of days with angioedema symptoms through 24 weeks
- Rate of expert-confirmed angioedema events 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 angioedema events over 24 weeks
- Use of medications to treat angioedema events over 24 weeks
- The proportion of responders to study drug, separately defined as at least a 50%, 70%, or 90% relative reduction in the rate of expert-confirmed angioedema events

during treatment, compared with the baseline expert-confirmed angioedema event 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 (EQ-5D-5L) questionnaire scores
- Treatment Satisfaction Questionnaire for Medication (TSQM) scores
- Work Productivity and Activity Index (WPAI) questionnaire 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 angioedema events
- Durability of response (angioedema event rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of medications to treat angioedema events
- 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

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 angioedema events
- Durability of response (angioedema event rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of medications to treat angioedema events
- 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, 2-part study. Part 1 is designed to test the hypothesis that the primary efficacy endpoint of the angioedema event rate during 24 weeks of prophylactic BCX7353 treatment at 2 dosage levels will be less than that observed during 24 weeks of placebo. This 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. An angioedema event is defined as an attack, symptoms, or swelling due to a subject's underlying HAE disease.

In addition, all efficacy outcomes along with the pharmacokinetic (PK)/PD displays in Part 1, where appropriate, will be statistically analyzed by combining data from this study with data

from Phase 3 Study BCX7353-302 (Study 302) to ensure adequate statistical power. Safety data will not be combined.

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 qualifying angioedema events documented during a prospective run-in period of 8 weeks from the date of the screening visit.

Approximately 24 treatment-eligible subjects ≥ 12 years of age 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 = 8): BCX7353 110 mg QD administered orally for 24 weeks

Group 2 (N = 8): BCX7353 150 mg QD administered orally for 24 weeks

Group 3 (N = 8): placebo administered orally QD for 24 weeks

Enrollment into treatment groups will be stratified by the baseline angioedema event rate (≥ 2 angioedema events per month from the date of screening vs. < 2 angioedema events per month from the date of screening).

Qualifying angioedema events that are counted in the baseline angioedema event rate for stratification and those that are used to qualify a subject during the run-in period must be characterized as follows:

- The angioedema events must be unique, which is defined as an angioedema event that does not begin within 48 hours of the end of a previous angioedema event.
- The angioedema events must have either been treated, required medical attention, or have been 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 an angioedema event).
- The angioedema events must include symptoms of swelling. The expert will consider that 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 angioedema events are otherwise confirmed by an independent expert to be angioedema events.

A study schematic can be found in Figure 1.

Throughout the entire study, details of all angioedema events (attacks, symptoms, or swelling due to HAE) and compliance with study drug will be recorded in an e-diary. Angioedema events will be treated in accordance with the subject's normal standard of care. Within approximately 2 business days of the end of each angioedema event that occurs from the screening visit through the follow-up visit after Part 2, subjects will be contacted by the investigator (or appropriately trained designee) to discuss the clinical characteristics of the angioedema event, any questions on

the entered data, or to gain additional details on the event that are not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable. The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each angioedema event recorded in the e-diary as a confirmed angioedema event. All expert-confirmed angioedema events must include symptoms of swelling; prodromal symptoms in the absence of swelling are not considered angioedema events, regardless of treatment. The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling. Under no circumstances should the run-in angioedema event requirement for eligibility be disclosed to study subjects.

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.

Part 2 (evaluation of safety of blinded BCX7353)

Part 2 of the study will start upon 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 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, 48, and 52, with telephone contact at Weeks 40 and 44. Subjects will continue to document all angioedema events that occur while on study drug, as well as compliance with the study drug, in their e-diary and will have regular visits to assess safety and tolerability; investigator confirmation of angioedema events will continue to be required for Part 2. Interim safety analyses will be conducted while Parts 2 and 3 are ongoing to support regulatory filings.

Part 3 (up to a 52-week evaluation of the safety of open-label BCX7353 150 mg QD)

Part 3 of the study will start with the administration of the study drug dispensed at the Week 52 visit. Based on the safety profile and efficacy of the 150 mg dose in Part 1 of the similarly-designed Study 302, all subjects in the current study receiving 110 mg QD will be transitioned to open label 150 mg QD at the Week 52 visit.

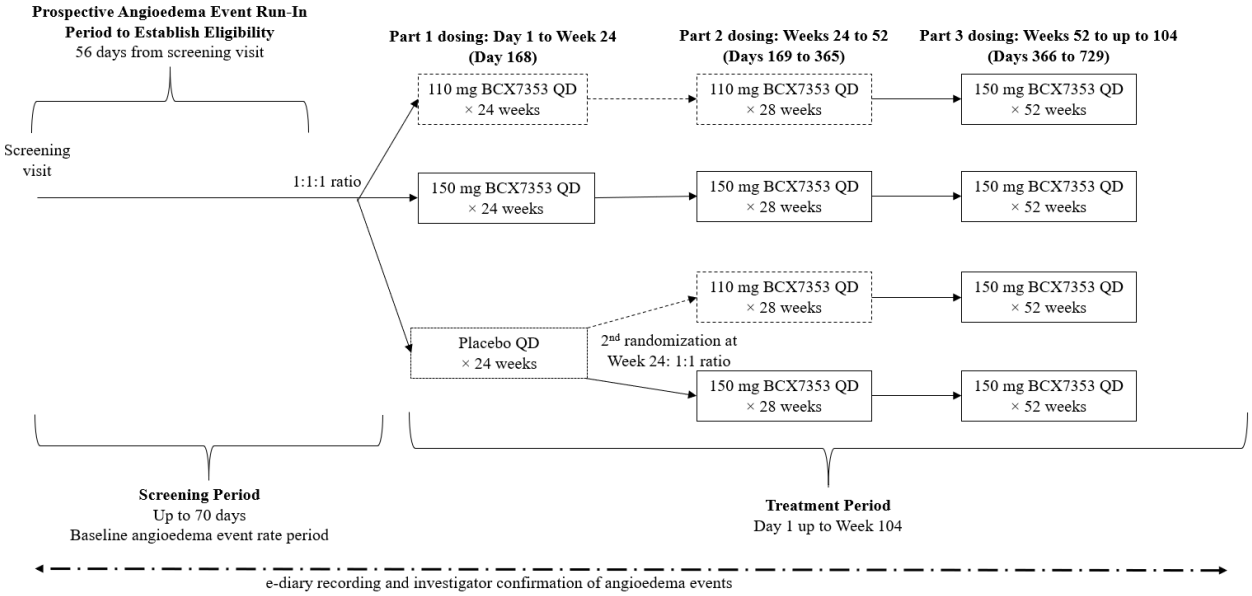
Study visits in Part 3 will occur during Week 60 and approximately every 12 weeks thereafter, for a study duration of up to 104 weeks, until another mechanism is available to provide drug to the subject (eg, market access), or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Telephone contact will occur at Weeks 56, 64, 68, 76, 80, 88, 92, and 100.

Subjects will continue to document all angioedema events that occur in their diary throughout Part 3 and will have regular visits to assess safety and tolerability. However, subjects will not be required to document compliance with the study drug. In addition, investigator and expert confirmation of angioedema events will not be required in Part 3. All angioedema events

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.

A final study follow-up visit will be scheduled approximately 3 weeks following the last administration of study drug (up to Week 104).

Figure 1: Study Schema



Abbreviations: e-diary = electronic diary; 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.

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 for Part 3.

Placebo QD is supplied as 2 capsules of matching placebo per dose (Part 1 only).

4.3. Sample Size Considerations

Power calculations for the primary efficacy endpoint for the current study alone and those for the combined analyses with Study 302 are provided in Table 2 and described in Sections 4.3.1 and 4.3.2, respectively.

4.3.1. Sample Size for Analysis of Study 301 Alone

Assuming a weekly angioedema event rate for placebo subjects of 0.9 and a common standard deviation (SD) of 0.50 angioedema events per week for BCX7353 and placebo and with 8 subjects per treatment group in the current study alone, the power to detect a ≥ 67% angioedema event rate reduction (a treatment difference of 0.6 angioedema events per week) for each comparison of angioedema event rates between active and placebo treatment would be 61%.

The primary analysis will be conducted on the Study 301 population.

4.3.2. Sample Size for Combined Analysis of Studies 301 and 302

The sample size considered feasible for enrollment in Japan has limited statistical power. Therefore, all efficacy data for Part 1, where appropriate, will also be analyzed by combining data from this study with data from Study 302, to ensure adequate statistical power (Table 2). For the combined analysis with Study 302, the sample size is expected to be 48 subjects per treatment group.

Assuming a weekly angioedema event rate for placebo subject of 0.9 and a common SD of 0.50 angioedema events per week for BCX7353 and placebo, a sample size of 120 subjects (40 per treatment group: 8 from Study 301 and 32 from Study 302) will provide > 99% power to detect a ≥ 67% angioedema event rate reduction (a treatment difference of 0.6 angioedema events per week) between each BCX7353 active dose and placebo, based on a 2-sided test at significance level of 0.05. To control for familywise type I error, the Hochberg step-up procedure will be used to adjust for the comparison of the active doses to placebo. Note that sample size calculations were based on the originally planned sample size for Study 302. Actual sample size was slightly larger, indicating that actual power for combined analyses may be slightly increased.

The assumptions underlying the sample size calculations for this study and the combined analysis of results from this study and Study 302 are based on the results of Study BCX7353-203 (Study 203). In Study 203, the mean weekly angioedema event rate during the effective dosing period (Days 8 to 29) for placebo subjects in the full analysis set population was 0.939. The reduction in angioedema event rate during the effective dosing period for subjects receiving 125 mg BCX7353 was 73.8%. The model-derived SD of the weekly angioedema event rate was 0.487. Sample size calculations have been conducted using the weekly angioedema event rate to be consistent with Study 203, although the monthly angioedema event rate will be reported for this study. The power calculations using the monthly angioedema event rate would be the same. See Table 2 for details.

Table 2: Power Calculations to Support Sample Size

Study	Sample Size Per Treatment Group	Event Rate for Placebo Subjects (events/ week)	Event Rate for Active Treatment (events/week)	Common SD for Event Rate	Type I Error Rate (α)	Power for Pairwise Comparison with Placebo
Study 301 alone	8	0.9	0.3	0.5	0.05	61%
Combined Studies 301 and 302	40	0.9	0.3	0.5	0.05	>99%

Abbreviations: SD = standard deviation.

4.4. Randomization

Subjects will be randomized via the interactive response system (IXRS).

4.4.1. Part 1 Randomization

Approximately 24 subjects will be randomized in a 1:1:1 (active: active: placebo) ratio to 1 of the following treatments in Part 1:

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

Randomization will proceed in accordance with a computer-generated randomization schedule prepared by an unblinded statistician.

Sites will randomize eligible subjects in the IXRS, preferably after all baseline assessments to reconfirm eligibility have been completed. If required by site procedures (ie, dispensing of randomized study drug must occur through a pharmacy), the subject may be randomized on the business day prior to the planned baseline visit.

The sponsor may require review of screening data prior to randomizing a subject (eg, concomitant medications); any requirements will be provided to the site separately.

Enrollment into treatment groups will be stratified by the qualifying angioedema event rate at baseline (≥ 2 angioedema events per month vs. < 2 angioedema events per month) entered into the IXRS at the time of randomization. The baseline angioedema event rate must be provided during randomization and is calculated by:

> (the number of angioedema events meeting the criteria of an angioedema event below from the screening visit through the time of randomization *28) divided by the number of days during the timeframe from the screening visit through randomization, rounded up to 2 decimal places

Angioedema events to be utilized in calculation of the baseline angioedema event rate must meet the following criteria:

- The angioedema events must be unique, which is defined as an angioedema event that does not begin within 48 hours of the end of a previous angioedema event.
- The angioedema events must have either been treated, required medical attention, or be documented to cause functional impairment based on subject entry in the e-diary. Functional impairment is defined as the subject being unable to perform his or her daily activities without restriction (ie, subject records that he or she is at least slightly restricted in daily activities during the angioedema event).
- The angioedema events must include symptoms of swelling. The expert will consider that 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 angioedema events must be confirmed by an independent expert to be angioedema events, based upon the e-diary record and investigator-collected information.

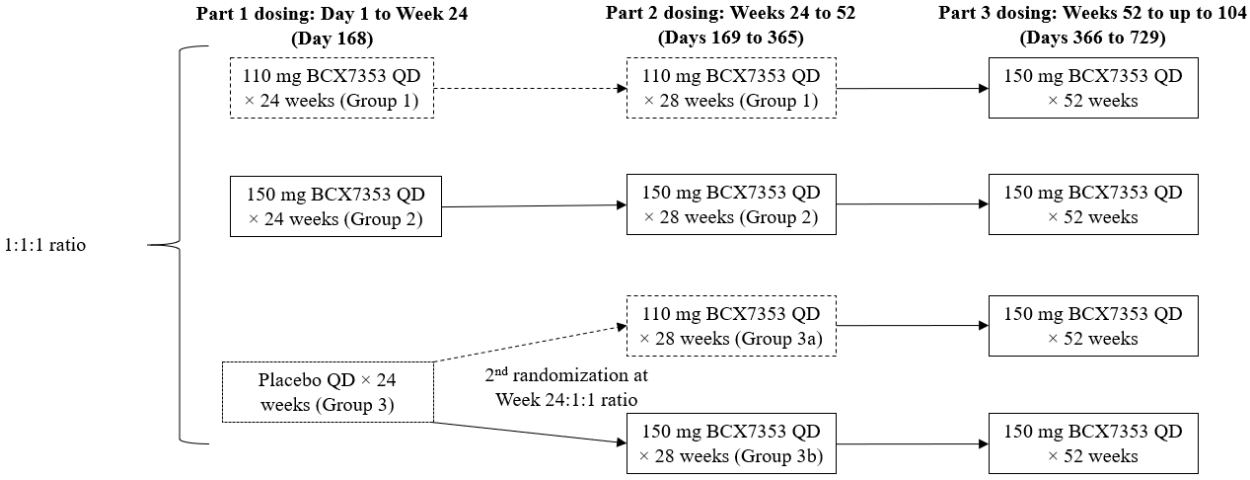
4.4.2. Part 2 Randomization

Subjects who received active BCX7353 in Part 1 of the study (treatment Groups 1 and 2) will continue to receive the same dosing regimen in Part 2. Subjects who received placebo (treatment Group 3) during Part 1 will be randomized in a 1:1 ratio to receive a 110 or 150 mg QD dose of BCX7353 during Part 2.

Subjects who received placebo during Part 1 will be automatically randomized for Part 2 in the IXRS, which will occur at the time of the Week 24 visit (see Figure 2). Sites will assign drug for Part 2 of the study in the IXRS beginning at the Week 24 visit. Sites using a centralized pharmacy may assign drug to a subject the day prior to the Part 2 visits.

Note: Sites will assign 150 mg kits in Part 3 of the study in the IXRS beginning at Week 52. Sites using a centralized pharmacy may assign drug to a subject the day prior to a study visit.

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 3, Table 4, and Table 5, respectively.

Table 3: Schedule of Assessments: Part 1 of Study 301

Assessment	Screening Period		Baseline	Part 1 Double-Blind, Placebo-Controlled Study Drug Administration					
	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	Week 24 Day 169[d]
Informed consent[b]	X								
In-clinic evaluation	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								
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								
Angioedema events eligibility determination[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
C1-INH antigenic level	X								
C3			X						
HLA typing[o]			X						
Optional sample for possible exploratory pharmacogenomic 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

Assessment	Screening Period		Baseline	Part 1 Double-Blind, Placebo-Controlled Study Drug Administration					
	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	Week 24 Day 169[d]
EQ-5D-5L[r,s]			X		X	X	X	X	X
AE-QoL, TSQM, and WPAI[s]			X		X	X	X	X	X
Concomitant medications	◄	———	———	———	———	———	———	———	►
AEs	◄	———	———	———	———	———	———	———	►
Randomization[t]			X						X
e-diary instruction/review/ set-up[u]	X	X	X		X	X	X	X	X
e-diary completion[v]	◄	———	———	———	———	———	———	———	►
Study drug dosing[w]			◄	———	———	———	———	———	►
Investigator review of angioedema events[x]	◄	———	———	———	———	———	———	———	►
Study drug accountability/ dispensing			X		X	X	X	X	X
Plasma for PK and PD analysis[y]			X		X	X	X	X	X

Abbreviations: AE = adverse event; AE-QoL = angioedema quality of life questionnaire; ALP = alkaline phosphatase; ALT = alanine transferase; AST = aspartate aminotransferase; BMI = body mass index; C1-INH = C1 esterase inhibitor; C3 = complement 3; CK-MB = creatine kinase MB isoenzyme; ECG = electrocardiogram; eCRF = case report form; e-diary = electronic diary; EQ-5D-5L = EuroQoL 5-dimensional, 5-level questionnaire; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; 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; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamics; PK = pharmacokinetics; QTcF = QT interval corrected by Fridericia's formula; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI = Work Productivity and Activity Impairment Questionnaire.

[a] The baseline visit must be held within 10 weeks (70 days) of the screening visit, accommodating a run-in period of 56 days. The investigator must gain sponsor approval to enroll subjects who are not randomized within 10 weeks of the screening visit; this may require screening laboratory tests to be redrawn. Subjects will not be permitted to rescreen if they did not meet the angioedema event 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 will be required to accommodate possible reflex testing for abnormal GGT, AST, or ALT.

[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 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 angioedema event details

(if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an angioedema event as the investigator must call and confirm or reject the angioedema event (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] Protocol Table 5 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 other post-baseline visits except for Week 2.

[j] For all women of childbearing potential (including adolescents), a serum pregnancy test will be administered at screening. Urine 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.

[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 1 or 2 must be demonstrated during screening for this study as outlined in Inclusion Criterion 3 (Protocol Section 8.2.1).

[n] The subject will be determined as eligible for the study based upon screening evaluations and the prospective recording of angioedema events during the run-in period of 56 days. The subject must have at least 2 angioedema events during the run-in period as assessed by an independent expert which meet all of the following requirements:1) the angioedema events are unique, which is defined as an angioedema event that does not begin within 48 hours of the end of a previous angioedema event; 2) the angioedema events must have either been treated, required medical attention, or be documented to cause functional impairment based on subject entry in the e-diary; 3) the angioedema events must include symptoms of swelling. The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling and; 4) the angioedema events are otherwise confirmed by an independent expert to be angioedema events (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 pharmacogenomic 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 these visits 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 Weeks 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 angioedema event experienced since the last study visit. If the subject has not had an angioedema event since the last study visit, the subject is not required to fill out the second, angioedema event-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, preferably after all baseline assessments have been completed. Sites using a centralized pharmacy may randomize the subject the day prior to the baseline visit. The baseline event rate generated from the date of screening through the time of randomization must be calculated at this time (Protocol Section 9.3.2.1).

[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, they will enter angioedema events (attacks, symptoms or swelling due to HAE) 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] An independent expert will review the e-diary record in conjunction with investigator-collected details of all angioedema events that occur from screening through follow-up and either confirm or reject each event as an angioedema event. At least 2 angioedema events 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 angioedema events that are recorded, subjects will be contacted within approximately 2 business days of the end of the angioedema event to discuss the clinical characteristics of the angioedema event, any questions the investigator has on the entered data, or to gain additional details on each event not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable. The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each event recorded in the diary as a confirmed angioedema event. The investigator e-diary data review and subject contact summaries will be documented in the source records and made available to an independent expert for their verification (confirmation or rejection) of the event.

[y] Concentration and PD blood samples will be drawn on all subjects at the scheduled visits. For at least one of these timepoints, a PK and PD sample should be drawn approximately 3 to 6 hours after the last dose of study drug. The remaining timepoints can be drawn 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 eCRF).

Table 4: Schedule of Assessments: Part 2 of Study 301

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	Week 52 (Day 365) ± 2 days
In-clinic evaluation	X	X	X	X			X	X
Telephone contact[c]					X	X		
Subject weight		X	X	X			X	X
Physical examination[d]		X	X	X			X	X
Urine pregnancy test		X	X	X			X	X
Vital signs[e]		X	X	X			X	X
Safety laboratory evaluations[f]	X[b]	X	X	X			X	X
Troponin I & troponin T		X	X	X			X	X
NGAL		X	X	X			X	X
CK-MB		X	X	X			X	X
Urinalysis[f]	X[b]	X	X	X			X	X
12-lead ECG[g]		X	X	X			X	X
EQ-5D-5L[h,i]		X	X	X			X	X
AE-QoL, TSQM, and WPAI[i]		X	X	X			X	X
Concomitant medications	←	—	—	—	—	—	—	→
AEs	←	—	—	—	—	—	—	→
e-diary instruction/review[j]		X	X	X	X	X	X	X
e-diary daily completion[k]	←	—	—	—	—	—	—	→
Study drug dosing[l]	←	—	—	—	—	—	—	→
Investigator review of angioedema events[m]	←	—	—	—	—	—	—	→
Study drug accountability/ dispensing		X	X	X			X	X
Plasma for BCX7353 concentration and PD analysis[n]		X	X	X			X	X

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

[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 will be required to accommodate possible reflex testing for abnormal GGT, AST, or ALT (see Protocol Table 5). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the eCRF.

[c] The investigator (or designee) must call and talk to the subject during Weeks 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 angioedema event details (if applicable), or any usability issues with the e-diary. The phone call may be omitted if the subject records an angioedema event as the investigator must call and discuss details of the event (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] Protocol Table 5 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 1 to 2 × at Weeks 28, 32, 36, 48, and 52. 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 angioedema event experienced since the last study visit. If the subject has not had an angioedema event since the last study visit, the subject is not required to fill out the second, angioedema event-related EQ-5D-5L.

[i] Where possible, QoL and health outcome questionnaires should be collected as the first assessments at a visit. Additional information about long-term experience on study may be collected at Week 52.

[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, they will enter angioedema events (attacks, symptoms or swelling due to HAE) 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] An independent expert will review the e-diary record in conjunction with investigator-collected details of all angioedema events that occur from screening through follow-up during Parts 1 and 2 and either confirm or reject each event as an angioedema event. For all angioedema events that are recorded, subjects will be contacted within approximately 2 business days of the end of the angioedema event to discuss the clinical characteristics of the angioedema event, any questions the investigator has on the entered data, or to gain additional details on the event that are not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable. The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each event recorded in the e-diary as a confirmed angioedema event. The investigator e-diary data review and subject contact summaries will be documented in the source records and made available to an independent expert for their verification (confirmation or rejection) of the event.

[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 e-diary (this may also be captured in the eCRF).

Table 5: Schedule of Assessments: Part 3 of Study 301

Assessment	Part 3 Open-Label, Active Study Drug Administration[a]										Follow-up/ Early Termination Visit Week 107 + 1 Week
	Week 56	Week 60 Day 421 ± 6 days	Weeks 64 and 68	Week 72 Day 505 ± 6 days	Weeks 76 and 80	Week 84 Day 589 ± 6 days	Weeks 88 and 92	Week 96 Day 673 ± 6 days	Week 100	Week 104 (Day 729 ± 7 days)	
In-clinic evaluation		X		X		X		X		X	X
Telephone contact[b]	X		X		X		X		X		
Subject weight/height[c]		X		X		X		X		X	X
Physical examination[d]		X		X		X		X		X	X
Urine pregnancy test		X		X		X		X		X	X
Vital signs[e]		X		X		X		X		X	X
Safety laboratory evaluations[f]		X		X		X		X		X	X
Troponin I & troponin T		X		X		X		X		X	X
NGAL		X		X		X		X		X	X
CK-MB		X		X		X		X		X	X
Urinalysis[f]		X		X		X		X		X	X
12-lead ECG[g]		X		X		X		X		X	X
EQ-5D-5L[h,i]		X		X		X		X		X	
AE-QoL, TSQM, and WPAI[i]		X		X		X		X		X	
Concomitant medications		←	—	—	—	—	—	—	—	→	
AEs		←	—	—	—	—	—	—	—	→	
Diary instruction/review[j]		X	X	X	X	X	X	X	X	X	X
Diary daily completion[k]		←	—	—	—	—	—	—	—	→	
Study drug dosing[l]		←	—	—	—	—	—	—	→		
Study drug accountability/ dispensing		X		X		X		X		X	X[m]
Plasma for BCX7353 concentration and PD analysis[n]											X[n]

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

[a] Period 3 study drug is to be initiated upon administration of study drug, dispensed at the Week 52 visit.

[b] The investigator (or designee) must call and talk to the subject during Weeks 56, 64, 68, 76, 80, 88, 92, and 100; 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 angioedema event details (if applicable), or any usability issues with the e-diary.

[c] Adolescent subjects will have height measured at Weeks 48 and 96.

[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] Protocol Table 5 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 1 to 2 × at Weeks 60, 72, 84, 96, and 104. 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 angioedema event experienced since the last study visit. If the subject has not had an angioedema event since the last study visit, the subject is not required to fill out the second, angioedema event-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, they will enter angioedema events (attacks, symptoms or swelling due to HAE) and relevant details (as applicable) at least once per day. Subjects are not required to enter dosing information in the e-diary in this part.

[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 through the Week 48 visit only. 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 eCRF). PK and PD blood samples will be drawn at the ET visit, only if the ET visit occurs prior to Week 48.

5. PLANNED ANALYSES

5.1. Interim Analyses

Interim safety analyses may be conducted while Parts 2 and 3 ongoing to support regulatory filings.

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 (24-week assessment).

This is a double-blind study throughout both Parts 1 and 2. As such, study drug assignment will be blinded to the investigator, study staff, study subjects, and clinical research organization (CRO) staff involved with study operations. Part 3 is open-label and all subjects will receive BCX7353 150 mg.

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 frozen for the primary analysis at the end of Part 1.

As much as possible, sponsor and CRO employees who interact with sites will remain blinded during Part 2 of the study; however, unblinding of these staff may occur out of necessity during document preparation for regulatory filings of the study.

5.3. Combined Efficacy Analysis at the End of Part 1

The sample size considered feasible for enrollment in Japan has limited statistical power. Therefore, a supplemental statistical analysis will be conducted using combined data from Studies 302 and 301 in the comparison of efficacy and other selected endpoints for Part 1 of both studies. Investigator-confirmed attacks from Study 302 and expert-confirmed events from Study 301 will be considered equivalent for the combined analysis.

5.4. Final Analysis

The final analysis will occur after the last subject completes Part 3 of the study, the data are cleaned, and the database is locked for analysis. Analysis of the 104-week data will be comprised of data from the current study alone.

5.5. 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. Other interim analyses to support regulatory filings may be required.

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 (Alberti, Pontisso et al. 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
- SAS® program name, including the path where the program is stored
- Any other output specific details that require further elaboration

V9.4 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 Part 1 treatment, subject identification (ID), and visit, if applicable. Listings for the entire study period will include all parts and will generally be sorted by Part 1 treatment, Part 2 treatment, subject ID and visit, if applicable.

Adjusted visit (as described in Table 9) 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 to first dose of Part 2 treatment, if applicable.

One exception to the sort order is that laboratory listings will be sorted by laboratory parameter, Part 1 treatment, Part 2 treatment (for listings that include the entire study period), subject ID, visit, and adjusted visit, if applicable.

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 6).

Table 6: 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 7. The descriptors shown in Table 7 also apply to any displays specific to Part 3; footnotes will be provided detailing the transition from 110 to 150 mg at Week 52 (ie, Part 3).

Table 7: Treatment Descriptors for Part 2 Only Displays

Sort Order	Part 2 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 Part 2 with continuation to 150 mg in Part 3.[a]
4	150 mg after placebo	For subjects who were originally randomized to placebo and were randomized to 150 mg for Part 2 with continuation to 150 mg in Part 3.[a]

[a] Footnotes will be provided to detail the transition from 110 to 150 mg at Week 52 (ie, Part 3).

For tables that cover the entire study period, 110 and 150 mg data in Part 2 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 only or in both Parts 1 and 2. Treatment descriptors are provided in Table 8.

Table 8: Treatment Descriptors for Displays for Entire Study

Sort Order	Treatment Descriptor	Notes
1	110 mg	110 mg (originally randomized)
2	110 mg after placebo	Part 2 data from subjects in Part 2 who were originally randomized to placebo and were randomized to 110 mg for Part 2
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	Data from subjects in Part 2 who were originally randomized to placebo and were randomized to 150 mg for Part 2
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 9). This will allow for combining data from active treatments in Part 1 (either 110 or 150 mg) with active treatment in Part 2 that followed 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). Subjects who changed from 110 to 150 mg beginning in Part 3 will continue to be summarized in the same treatment to which they were assigned as in Part 2; a footnote will detail the transition from 110 to 150 mg at Week 52.

Table 9: 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 52	Week 28
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 or Week 26 visit in Part 1. There is no visit in Part 3 that corresponds to the Week 52 Visit in Part 2.

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 Drug Dictionary (WHODD) version from March 2017. AE preferred terms (PT) and system organ classifications (SOC) are coded using Medical Dictionary for Regulatory Affairs (MedDRA) v19.1.

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 PK, and 6 for PD. The third level of numbering represents the type of endpoint within the data type, the fourth level 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 analysis at the end of Part 3 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 v9.4 or higher 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, gender) 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 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. Intent-to-Treat Population

The intent to treat (ITT) population will include all subjects who are randomized, regardless of whether study treatment was administered. The ITT population will be used as the primary population for efficacy and health outcomes analyses. Subjects will be analyzed based on the treatment to which they were randomized.

6.5.3. Safety Population

The safety population will include all subjects who received at least 1 capsule of study drug. This population will be used for all analyses of accountability, demographics, BCX7353 drug concentrations, and safety. Subjects will be analyzed based on the actual treatment received at first dose for all subjects for Part 1 or at first dose of Part 2 for subjects originally randomized to placebo. **Per-Protocol Population**

The per protocol (PP) population will include a subset of subjects in the safety population that complete Part 1 and have ≥ 85% treatment compliance without any major protocol deviations that could impact efficacy measures. 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 on study Day 1 for Part 1. The PP population may be used as a secondary population for efficacy analyses.

6.5.5. Completers Population

The subset of subjects in the ITT population who complete Part 1 of the study (as evidenced by the completion of the Week 24 visit in the eCRF) 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.**Pharmacodynamic Population**

The PD population for plasma kallikrein inhibition 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 all analyses of plasma kallikrein inhibition.

6.5.7. Pharmacokinetic Concentration/Pharmacodynamic Population

The PK concentration/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 all correlation analyses and figures involving 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.

6.6.1. Baseline Event Rate

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

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

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

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

6.6.2. Categorized Baseline Event Rate

The categorized baseline event rate will be determined using the calculated baseline event rate (See Section 6.6.1) and will be categorized similarly to the stratification factor: ≥ 2 events/month vs. < 2 events/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

CFB is calculated as (post-baseline result – baseline result).Percent CFB is calculated as ((change from baseline/baseline result) * 100).

If either the baseline or the post-baseline result is missing, the CFB and/or percentage CFB 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 10. All information collected at an unscheduled visit will be identified as such in the listings.

Table 10: Visit Windows (Days)

Visit	Relative Target Day	Protocol-Specified Visit Window	Analysis Visit Window
Screening visit		-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 351
Week 52	365	364 to 368	352 to 406
Week 60	421	415 to 427	407 to 463
Week 72	505	499 to 511	464 to 547
Week 84	589	583 to 595	548 to 631
Week 96	673	667 to 679	632 to 683
Week 104	729	723 to 735	≥684

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. Event Rate

General Formula for Event Rate

In general, the formula for computing an event rate is the number of events meeting the event criteria divided by the duration of treatment during the reporting period of interest. Duration of treatment during the reporting period of interest = the last day in the reporting period – first day in the reporting period + 1.

$$Event\ Rate\ \left(\frac{events}{month}\right)\ During\ Reporting\ Period\ of\ Interest = \frac{\text{Number of Events} * 28}{\text{Duration of Treatment During Reporting Period in Days}}$$

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

Subject-Reported Event Rate

Diary entries for events and investigator-collected events that are not captured in the diary are considered subject-reported events. The expert reviews each event and either confirms it as an event or rejects it as an event. For Part 3, there is no expert review of attacks, but an adjusted subject-reported attack rate will be computed based on a list of programmable requirements.

Subject-reported event rates will be computed for the entire dosing period only (ie, not for the effective dosing period or by month) for Parts 1, 2, and 3.

Adjusted Subject-Reported Attack Rate for Part 3

Because there is no expert-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 Event Rate

Confirmed event rates will be computed based on the number of expert-confirmed events that occur during the reporting period of interest.

Confirmed event rates will be computed for the following reporting periods and expressed in units of events/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 event rates will be computed for Part 1 and at the end of Part 2. For confirmed event 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 the first dose for Part 3. Expert confirmation is not done in Part 3 and so confirmed event 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 events that occur within 24 hours after last dose will be counted in the calculation of events rate. If there are confirmed events in the eCRF without corresponding diary information, as may happen if a subject verbally reports an event to an investigator but does not enter it into the e-diary, the event will be counted.

For sensitivity analyses for missing data for the Part 1 primary analysis, confirmed event 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 event rate and an imputed event rate for periods of missing data post-treatment discontinuation. Details are provided in Section 6.8.1.

Expert-Confirmed Event Rate by Location

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

Adjusted Expert-Confirmed Event Rate

An adjusted expert-confirmed event rate will be computed for use in the determination of the 50%, 70%, and 90% responder endpoints comparing post-baseline event rates to baseline event rates. For the adjusted expert-confirmed event rate, the 2 additional requirements for confirmation of event rates used during screening will be applied to post-baseline expert-confirmed events to determine the number of confirmed events meeting the additional requirements. The additional requirements are:

- The events are unique, which is defined as an event that does not begin within 48 hours of the end of a previous event.
- The events 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 event).

6.7.5.2. Number and Percentage of Subjects Who Are Event Free Over Entire Dosing Period and Effective Dosing Period

The following event-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 events during the period of interest. Subjects with no confirmed events who discontinue before the end of the planned treatment period are not considered event-free.

The event-free rate for active treatment for subjects originally randomized to placebo will be based on the initial 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 entire dosing period prior to discontinuation of treatment for which at least 1 symptom is reported during an expert-confirmed HAE event.

This endpoint will be determined for Parts 1 and 2 as expert-confirmation will not be calculated for Part 3. As with the calculation of event 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 events during study treatment represents at least a 50% relative reduction compared with the baseline event rate as defined in Section 6.6.1.

The relative reduction is calculated for Part 1 as:

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

where the adjusted confirmed event 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 event rate for Part 1 is ≥ 50%. Otherwise, the subject is classified as a non-responder.

Responder analysis will be conducted for Part 1 only. Additional responder analyses will be conducted for 70% and 90% relative reduction, defined similarly.

6.7.5.5. Event Duration

The duration of each confirmed on-treatment event will be calculated in hours, based on the start and stop date and time of the confirmed event (time the event finished). Experts have the option to count more than one subject-reported event as a single confirmed event. For a confirmed event that includes more than 1 subject-reported event, the duration is calculated from the start of the first subject-reported event to the end of the last subject-reported event that has been combined into 1 event. 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 event from start of the event to time that the worst was over will also be calculated and summarized.

6.7.5.6. Event Onset Relative to Prior Dose of Study Drug

For each confirmed on-treatment event, the time to event 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 event, the event onset time relative to prior dose will be missing. The event onset time relative to prior dose of study drug information is used in the listing of event data only.

6.7.5.7. Medications to Treat HAE Events

The following medications reported taken as acute treatment in the subject diary will be classified in the analyses as targeted medications to treat subject-reported HAE events: Berinert, Cinryze, Kalbitor, Firazyr, Ruconest, and fresh frozen plasma. Of these, Berinert and Firazyr are approved for use in Japan. Other medications listed in the diary for treatment of HAE events will be considered non-targeted medications to treat subject-reported HAE events.

6.7.5.8. Event Symptoms

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

6.7.5.9. Event Location

The location of each subject-reported and confirmed event will be determined based on the symptoms indicated in the e-diary as shown in Table 11.

Table 11: Determination of Event Location Using Symptoms Collected in the e-Diary

Abdominal-only event	**Mixed Event**	**Peripheral event (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 event 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 event

[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 event.

6.7.5.10. Laryngeal Events

Laryngeal events are those events that have visible swelling in the mouth/tongue/lips or any of the following internal swelling symptoms: lump in throat (tightness), difficulty swallowing, change in voice, or difficulty breathing, as recorded in the e-diary.

6.7.5.11. Event Triggers

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

6.7.5.12. AE-QoL

The AE-QoL (Wechsler, Fulkerson 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:

$$(\Sigma \text{ items})/(\max \Sigma \text{ items}) \times 100$$

where

Σ items = Sum of answered item scores per CRF

max Σ items = Sum of the maximum possible score for the answered items (ie 4 × the number of completed items)

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 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as shown in Table 12. 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 event since their last visit, starting at Week 4, they complete it a second time reflecting back on their health status during a *"usual event*". On summary tables, the "*today"* and *"usual event*" questionnaire results should appear in different rows.

Table 12: 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 analog 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 United States (US) value set (Besari, Md Noor et al. 2014). 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, one 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 13.

Table 13: 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 clearly, 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 seven-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)

Note that higher scores indicate higher satisfaction as the seven-point scale for the individual items goes from 1 = extremely dissatisfied to 7 = extremely satisfied.

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

Effectiveness

([(Item 1 + Item 2 + Item 3) − 3] ÷ 18) × 100.
If 1 item is missing: ([(Sum of Available Items) − 2] ÷ 12) × 100.

Side Effects

If Item 4 answer is "No" then score = 100.
Else…
([(Sum of Item 5 to Item 8) − 4] divided by 16) × 100.
If 1 item is missing: ([(Sum of Available Items) − 3] ÷ 12) × 100.

Convenience

([(Sum of Item 9 to Item 11) − 3] ÷18) × 100.
If 1 item is missing: ([(Sum of Available Items) − 2] ÷ 12) × 100.

Global Satisfaction

([(Sum of Item 12 to Item 14) − 3] ÷ 14) × 100.
If Item 12 or Item 13 is missing:
([(Sum (the two completed items)) – 2] ÷ 10) × 100
If Item 14 is missing:
([(Sum of Available Items) − 2] ÷ 8) × 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*[Q2/(Q2+Q4)].
2. Presenteeism: Percent impairment while working due to health: 100*[Q5/10].
3. Work productivity loss: Percent overall work impairment due to problem: 100*{Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]}.
4. Activity impairment: Percent activity impairment due to health: 100*(Q6/10).

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 event rate used in the 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 2 ways:

1. Using observed post-treatment discontinuation data where available without imputation for missing data. For this analysis, the event 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 event 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 event 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 event 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:

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

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

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

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

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

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

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

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 14. Data missing at random will be imputed using multiple imputation with 10 separate founds of imputations, randomly selecting from observed confirmed event 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 event rate of subjects in the worst quartile of performance (ie, highest event 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 14: 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.

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 event 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 in order to identify medication as occurring during treatment or not. For the purpose 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.

- Completely missing start date:

  For HAE medications, the date will be set to corresponding HAE event date. For all other concomitant medications, a completely missing date will be set to the treatment start date (if prior to the medication end date) or otherwise will be set to the medication end date.

- 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.

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 Event

For HAE events reported with missing start date and/or time, stop date and/or time, or date and/or time reported that the worst symptoms of the event were over (“worst over”), 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 worst over time, but worst over date present:
  The worst over time will be set to 11:59PM.
- Missing worst over date and time:
  The worst over date will be set to the start date, the worst over time will be set to 11:59PM
- 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 worst over date, or if missing, the event 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 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 study report, starting with the number of subjects screened.

A summary of enrollment by 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, complement 4 (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 Part 2 will be conducted prior to database lock for the final study report after the last subject has completed Part 2. Protocol deviations for Part 2 will be summarized by Part 2 treatment (Table 7) 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 Treatment and Part 2 Treatment (Table 7). 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.

Baseline C1-INH antigenic levels will be summarized using descriptive statistics for the continuous measure and categorized into < lower limit of normal (LLN) and ≥ LLN; subjects who take Cinryze or Berinert within 72 hours or Ruconest within 24 hours will be excluded from

the categorization but included in the continuous summary. A scatter plot of baseline C1-INH antigenic levels vs. screening C1-INH functional levels will be produced.

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), and fresh frozen plasma. The summary of androgens will include androgens (unspecified), oxandrolone, danazol (brand name = Danocrine), and stanozolol.

All HAE medical and medication history collected on the CRF will be listed. Summaries will include a grouping of any C1-INH medication as well as displays of individual medications.

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 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 WHODD, 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 6 and Table 8, 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 event-level summary will also be provided showing the number of expert-confirmed events for which the various HAE-related medications were taken based on the subject diary.

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 events will be listed. The baseline event rate and the categorized baseline event rate will be summarized by Part 1 treatment using descriptive statistics for baseline event rate and n [%] for the categorized baseline event rate. The proportion of days with HAE symptoms during the baseline period 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 for the primary efficacy endpoint for Part 1 of the current study and the combined Studies 301 and 302 using the ITT populations. Analyses of Part 2 data will be descriptive and will be reported for the current study only. No hypotheses will be tested for Part 2 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 subgroup membership for the current study and for the combined Studies 301 and 302 will be provided by Part 1 treatment. Subgroups are listed in Section 8.4. In addition, the duration of baseline period, baseline event rate, categorized baseline event rate ($\geq$ 2 events/month vs. < 2 events/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 expert-confirmed HAE events
- H_A: $R_A \neq R_P$; active treatment does have a differential effect on the rate of expert-confirmed HAE events

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

Secondary hypotheses are (in order of hierarchical testing):

1. 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.
2. Rate of expert-confirmed HAE events during the effective dosing 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 expert-confirmed HAE events during the effective dosing period
   - H_A: $R_A \neq R_P$; active treatment does have a differential effect on the rate of expert-confirmed HAE events during the effective dosing period

   where R_A is the monthly event rate for active treatment and R_P is the monthly event rate for placebo treatment during the effective dosing period.
3. 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).

8.4. Subgroup Analyses for Combined Study Analysis

For the combined study analysis, subgroup analyses for the primary and secondary endpoints will be provided by:

1. Sex

2. Race (white vs. other)
3. Baseline event rate (≥ 2 events/month vs. < 2 events/month)
4. Age group (12 - 17, 18 to 64, ≥ 65 years)
5. Region (North America vs. Japan vs. rest of world)
6. Weight (< median vs. ≥ median)
7. BMI (18.5 to 24.9 kg/m^2 vs. 25 to 29.9 kg/m^2 vs. ≥ 30 kg/m^2)
8. Prior androgen use (yes vs. no)

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

8.5. Multiple Comparisons and Multiplicity

There are 4 endpoints being tested in the combined analysis, the primary endpoint and 3 secondary endpoints. For each endpoint, there are 2 potential doses to be tested. 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 expert-confirmed angioedema events 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 angioedema events 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 hypothesis for the next endpoint in the hierarchy will not be tested.

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

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

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 one dose is being tested, the single test is conducted with $\alpha = 0.025$.

The sample size considered feasible for enrollment in Japan has limited statistical power. Therefore, a supplemental statistical analysis will be conducted in the same manner as above using the combined data from Studies 301 and 302. The combined rate of HAE events will utilize investigator-confirmed attacks from Study 302 and expert-confirmed events from Study 301.

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 expert-confirmed HAE events during dosing in the entire 24-week dosing 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 expert-confirmed HAE events for Part 1 will be analyzed by treatment group using appropriate descriptive statistics for the confirmed event rate (expressed as events/month) based on the 24-week dosing period or until study treatment discontinuation, if applicable. An additional summary of confirmed event rate by month, including CFB event rate and percentage CFB event 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 angioedema event rate and the treatment comparisons between each BCX7353 dose and placebo in the rate of expert-confirmed angioedema events during the entire dosing period will be analyzed using a negative binomial regression model. The number of expert-confirmed angioedema events will be included as the dependent variable, the treatment will be included as a fixed effect, the stratification variable (baseline monthly angioedema event rate) and study (for the combined study analysis) will be included as covariates, and the logarithm of duration on treatment will be included as an offset variable. The estimated rate of angioedema events for each treatment group, the treatment differences expressed as the angioedema event rate ratio (BCX7353 over placebo rate ratio), and their associated 95% confidence intervals (CIs) will be provided from the negative binomial regression model. Monthly will be defined as 28 days.

The percentage reduction from placebo will be calculated for each dose as:

$$Percentage\ rate\ reduction = (\ 1 - event\ rate\ ratio) * 100 = (1 - \frac{R_A}{R_P}) * 100$$

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

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

```
proc genmod data = datasetname;
  class trt01p /param=glm;
  model ecevents = trt01p blatk /dist=negbin link=log offset=logdurtrt;
run;
```

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

Plots of mean confirmed event rate by month and scatter plots of baseline event rate vs. 24-week event rate will be produced with a different color for each treatment. Plots of mean event rate per month will be updated to include the Part 2 data at the end of Part 2. Adjusted subject-reported event rate data per month will be plotted separately for Part 3, as Part 3 does not include expert confirmation of events. A scatterplot will be produced for the difference between the baseline confirmed event rate and the confirmed event rate for Part 1 vs. the baseline confirmed event rate. This scatterplot will also be produced by gender. A plot of confirmed events by study day for Part 1 will be presented for individual subjects by treatment group and will display the length of each event and will include the use of on-demand medication. A plot of individual event rates showing the baseline and the Part 1 confirmed event rate will be presented by treatment group. A plot of individual event rates showing the baseline and confirmed event rates for each month will be presented by treatment group.

The sample size considered feasible for enrollment in Japan has limited statistical power. Therefore, a supplemental statistical analysis will be conducted in the same manner as above using the combined monthly angioedema event rate (investigator-confirmed attacks in Study 302 and expert-confirmed events in Study 301) in the entire treatment period in the ITT population.

The relationship of selected baseline characteristics with the expert-confirmed events will be explored using an appropriate model-building method for Part 1.

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 expert-confirmed events will also be conducted.

In addition, there will be 2 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 event rate determination. The estimand for this analysis is referred to as the de facto estimand. Details on the determination of the event 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 event 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.

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

Sensitivity analyses will also be conducted for the combined study.

8.7. Analysis of the Secondary Efficacy Endpoints

Analysis of the secondary efficacy endpoints will be conducted for the combined study.

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

CFB 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 Part 2.

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 event 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 one 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 Part 2 will also include data from visits at Weeks 28, 32, 36, 48, and 52. Summaries will be updated to include the additional information. An additional descriptive summary of change from Week 24 will be provided for Part 2 visits for subjects originally randomized to placebo treatment.

A summary and analysis of the number and percent of subjects with at least a six-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 Part 2. The analysis for Part 1 will be based on a logistic model with response of achievement of the MCID (yes/no), baseline event 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 Part 2. 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 event 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 Part 2 will include a summary of the number and proportion of days with angioedema symptoms through Week 52 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 one 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 the end of the study. 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 Expert-Confirmed HAE Events during Dosing in the Effective Dosing Period

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

Summaries and analysis of the expert-confirmed event rate using the ITT population for the effective dosing period (Day 8 through Week 24, inclusive) will be conducted using negative binomial 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 Event Medications

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

A Kaplan-Meier (KM) plot of time to first use of targeted HAE rescue medication to treat an expert-confirmed event and corresponding summary table will be produced for Part 1.

The rate of the use of any HAE medications (ie medication rate) used to treat expert-confirmed events will be calculated as doses taken for expert-confirmed events per month (28 days), similar to the calculation of the event rate. This will be analyzed using a negative binomial regression analysis in the same manner as the primary endpoint, with the number of rescue medication doses included as the dependent variable, treatment included as a fixed effect, baseline expert-confirmed event rate included as a covariate, and the logarithm of duration on treatment included as an offset variable. This analysis will also be conducted for the medication rate for subject-reported events.

A summary of expert-confirmed events requiring treatment with targeted HAE medications that will display the first medication taken and number of uses of any other targeted medications for each attack will be presented.

8.7.5. Discontinuations due to Lack of Efficacy

Discontinuation due to lack of efficacy is a secondary endpoint for Part 2.

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 and Part 2 as well as overall.

8.8. Analysis of Additional Exploratory Efficacy Endpoints

8.8.1. Number and Proportion of Subjects with No Events

The number and proportion of subjects with no events 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 events over the entire dosing period of 52 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 events 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 event-free. A separate summary of the number and proportion of subjects with no adjusted subject-reported events 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 events 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 KM plot and corresponding summary of time to first event 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 expert-confirmed HAE events meeting the stricter screening criteria during treatment compared with the baseline event 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 event 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. This analysis will also be conducted for responders with at least 70% and 90% relative reduction and conducted by subgroups for 50%, 70%, and 90% relative reduction. Forest plots will be produced to accompany the subgroup analyses.

A waterfall plot of relative reduction by treatment will be produced. For the combined study, this plot will include differentiation in the bar fill for Japan and the rest of the world.

A listing of expert-confirmed events that are not included in any adjusted expert-confirmed events will be provided.

The relationship of selected baseline characteristics with the proportion of responders with at least 50% and 70% relative reduction, respectively, will be explored using an appropriate model-building method for Part 1.

8.8.3. Event Characteristics

Characteristics of events including location of event (see Section 6.7.5.9), laryngeal events (see Section 6.7.5.10), duration of events from start to finish and from start to the time the worst symptoms of the event were over, time since last dose, triggers, swelling, other symptoms, whether the event was treated, severity as assessed by the patient 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 event for abdominal, peripheral, and mixed events will also be provided (see Table 11).

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 Part 2. 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 event 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 event*". On summary tables, the "*today"* and *"usual event*" 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 CFB 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 event 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 Part 2 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 event*" will be provided.

Plots of VAS and EQ-5D-5L index mean scores over time and CFB mean scores will be provided for Part 1 analysis and at end of Part 2 analysis using the health status "*today*". For Part 2, 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 Part 2. 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 CFB score of interest will be included as the dependent variable in the model with fixed effects for treatment, baseline event 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 one line per treatment group will be provided. There will be one set of figures for Part 1 and another for the entire study period. For the analysis at the end of Part 2, 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 Part 2. 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 CFB WPAI score of interest will be included as the dependent variable in the model with fixed effects for treatment, baseline event 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 CFB mean scores over time with one line per treatment group will be provided. There will be one set of figures for Part 1 and another for

the entire study period. For the plots produced at the end of Part 2, the figure will have separate lines for active treatment for subjects originally randomized to placebo.

10. SAFETY AND TOLERABILITY

Analysis of safety data will be conducted for the current study alone.

The safety analyses will be analyzed separately for Part 1; available data from all parts of the study will be combined for a long-term safety assessment.

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

The following are Part 1 safety endpoints and 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.

In addition, the proportion of subjects with a treatment-emergent, treatment-related AE consistent with a drug rash will also be summarized

AEs will be mapped to the MedDRA version 19.1 preferred term (PT) and 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 or Part 2, and will be assigned to the relevant treatment depending on when the TEAE began (Part 1 or Part 2 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 will be considered as TEAEs and will be associated with Part 1 or Part 2 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 a TEAE, 4) had any TESAE, 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, or 8) had a drug-related TESAE. This summary will be reproduced for TEAEs by month (1 month = 28 days) for the first 7 months of the study, eg Month 1 will include events which have a start date between Day 1 and Day 28 of the study, Month 2 will include events between Day 29 and Day 56, etc. Subjects at risk for each month will include those who are receiving drug in the period of interest or who have discontinued drug within 30 days of the start of the period. Figures presenting the categories by month will also be produced.

AEs 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 AEs will be provided by PT (not by SOC and PT), in decreasing order of frequency. Frequent AEs will be defined as events that occur in 2 or more subjects in the clinical trial.

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 risk difference will be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome).

A listing of subjects for whom narratives are required will be provided and will include the reason for the narrative.

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

The following is a Part 2 primary endpoint:

- 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 (EOSIs) 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 EOSIs for investigator reporting purposes. There are no appropriate standardized MedDRA queries in MedDRA to evaluate GI abdominal-related AEs that are appropriate to assess potential AEs 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 v19.1 hierarchy under the high-level group terms (HLGTs) of 1) gastrointestinal signs and symptoms and 2) gastrointestinal motility and defaecation conditions. See Section 17.3 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
- A 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 KM method. The results will be displayed in summary tables as well as in a KM 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 AE.

A KM plot and summary of duration of event will be provided for the investigator-identified rashes and GI abdominal 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 event 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 Person-Year 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 AE 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 100 person-years 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-years of exposure
- Summary of drug-related, TEAE rate per 100 person-years of exposure
- Summary of TESAEs per 100 person-years of exposure

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

10.2. Exposure to Study Treatment and Treatment Compliance

The number of subjects exposed to study treatment, the number of subjects who discontinue treatment early, and the reasons for early discontinuation 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 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. KM 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*(date of the last dose-date of the first dose+1)

If the number of capsules taken per day changes due to formulation or lot changes at any time (eg, from 2 per day to 1 per day), the expected number of capsules will be adjusted accordingly at the date of the change.

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

$$\text{Treatment compliance (dispensing)} = \frac{Number\ of\ capsules\ taken}{Expected\ number\ of\ capsules\ taken} * 100$$

Treatment compliance will be listed and summarized for Part 1 for all subjects and for Day 1 to Week 24, Day 1 to Week 48, and Day 1 to Week 52, for subjects who have completed the respective visit. For subjects initially assigned to placebo, treatment compliance will be computed for placebo treatment and separately for the active treatment received in Part 2.

A categorical summary of treatment compliance will be produced with the following categories shown in Table 15.

Table 15: 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 CFB event rate by % compliance will be produced for Part 1, with treatment groups overlaid.

Treatment compliance will also be calculated between scheduled visits (or between the final dispense date and the final return date) similar to above with the following changes. The expected number of capsules will be computed as the number of capsules expected between scheduled dispense dates. Drug will be assumed to have been taken during the period after the

drug was dispensed, as long as the bottle is returned, regardless of the return date. Visits for which no bottles are returned at any time are considered missing data and compliance is not calculated in these cases. Note that this calculation does not take into account any protocol-allowable study drug interruptions.

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 Part 2 primary endpoint:

- 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 one-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 US Food and Drug Administration's (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

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

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 vs. 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 KM plots of time to event for a Grade 3 or higher ALT, AST, or bilirubin will be produced.

A listing of AEs of nausea, vomiting, anorexia, abdominal pain, or fatigue occurring within 24 hours of an elevation of 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-INH antigenic level, C1-INH functional level, complement 3 (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 will be collected for analysis of possible drug-specific immune responses and possible drug-responsive T cells.

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.

A scatter plot of baseline values vs. all observed changes relative to baseline recorded at any time will be produced.

10.7. 12-lead Electrocardiograms

Baseline (pre-dose) and Week 24 ECGs will be obtained in triplicate (ie, three 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 CFB in corrected QT interval using Fridericia's method (QTcF) > 60 msec or a QTcF interval > 500 msec.

ECGs and corresponding CFB will be summarized by treatment group and visit using descriptive statistics.

ECG findings will be summarized.

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

Δik= (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.

A scatter plot of baseline values vs. all observed changes relative to baseline recorded at any time will be produced.

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 for the entire study period at the end of Part 2. Note that PK concentration data collected at each visit will not be summarized by visit as the timing 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 concentration data will be performed using the PD population. The baseline amidolytic activity mean will be summarized by treatment for all subjects and for males and females separately.

Plasma kallikrein inhibition (KKI) data will be expressed as percent inhibition compared to subject baseline activity (%KKI). The formula for percent inhibition is:

$$\%KKI = 100 - (\text{postbaseline value})$$

where the values are the mean amidolytic activity (%) at each time point. The mean amidolytic activity is set as 100% at baseline. 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.

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, using the PK/PD population for the current study alone. Note the division by 4 of the concentration corrects for the dilution of the plasma required for the PD assay. This analysis will be conducted for the current study alone and for combined Studies 301 and 302.

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 may be evaluated in a separate cross-study analysis.

15. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The following changes from protocol-specified analyses are as follows:

- The definition of the screen failure population has changed from subjects not dispensed treatment to those who are not randomized and are reported as screen failures in the eCRF.
- The definition of the PP population has been altered to include ≥ 85% treatment compliance as an inclusion requirement.
- Part 1 is defined as Day 1 to first dose of Part 2 rather than Day 1 through Day 168.
- The entire dosing period for Part 1 is defined as Day 1 to first dose of Part 2 rather than Day 1 through Day 168 and Day 1 through Day 168 + 24 hours.
- The negative binomial regression model will be used instead of the Poisson regression model for all applicable analyses. The Poisson regression that was originally proposed is a special case of the negative binomial regression model. For Study 302, the required assumptions of the Poisson model were not met, and the negative binomial model was used instead. For this reason and because there will be a combined analysis of the current study with Study 302, the negative binomial model results for the current study will be provided.

16. REFERENCES

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17. APPENDIX

17.1. Table of Contents for Data Display Specifications

17.1.1. Tables

17.1.1.1. BCX7353-301 Only

Output Number	Population Title	Output Title
14.1.1.1	All Subjects	Summary of Subject Disposition by Site, Part 1
14.1.1.1.ES	All Subjects	Summary of Subject Disposition by Site, Entire Study
14.1.2.1	ITT Population	Summary of Analysis Populations
14.1.2.2	ITT Population	Summary of Subgroups
14.1.2.3.1	ITT Population	Summary of Inclusion/Exclusion Criteria Violations
14.1.2.3.2	Screen Failures	Summary of Inclusion/Exclusion Criteria Violations
14.1.2.4	ITT Population	Summary of Protocol Deviations, Part 1
14.1.2.4.ES	ITT Population	Summary of Protocol Deviations that Occurred During Part 2
14.1.2.5	All Subjects	Summary of Confirmation of Diagnosis of HAE Type I or II
14.1.3.1.1	ITT Population	Summary of Demographic Characteristics
14.1.3.1.1.ES	ITT Population	Summary of Demographic Characteristics - Subjects Who Transitioned to Part 2
14.1.3.1.2	PP Population	Summary of Demographic Characteristics
14.1.3.1.3	Screen Failures	Summary of Demographic Characteristics
14.1.3.2	ITT Population	Summary of Subject-Reported HAE Baseline Characteristics - HAE Medical History
14.1.3.3	ITT Population	Summary of Past Prophylactic Treatments of HAE
14.1.3.4	ITT Population	Summary of Primary Reason for Discontinuation of Past Prophylactic Treatments of HAE
14.1.3.5	ITT Population	Summary of Current On-Demand Treatments of HAE
14.1.3.6	ITT Population	Summary of Subject-Reported HAE Baseline Characteristics - Primary Acute Event Treatment Information
14.1.3.7	ITT Population	Summary of Pre-Treatment Expert-Confirmed Event Rates and Angioedema Symptoms
14.1.3.8	ITT Population	Summary of C1-INH Antigenic Levels
14.1.4.1	ITT Population	Summary of Medications Taken within 30 Days Prior to Screening and Discontinued Prior to Dosing
14.1.4.2	ITT Population	Summary of Concomitant Medications, Part 1
14.1.4.2.ES	ITT Population	Summary of Concomitant Medications, Entire Study
14.1.4.3	ITT Population	Summary of Concomitant Medications for HAE, Part 1
14.1.4.3.ES	ITT Population	Summary of Concomitant Medications for HAE, Entire Study
14.1.4.3.P3	ITT Population	Summary of Concomitant Medications for HAE, Part 3
14.1.4.4	ITT Population	Summary of Concomitant Medications for Acute Treatment of Angioedema Events - Event Level [1]
14.1.4.4.ES	ITT Population	Summary of Concomitant Medications for Acute Treatment of Angioedema Events - Event Level [1], Entire Study
14.1.4.4.P3	ITT Population	Summary of Concomitant Medications for Acute Treatment of Angioedema Events – Event Level, Part 3
14.1.4.5	ITT Population	Summary of Expert-Confirmed Events Requiring Treatment with Targeted HAE Medications, Part 1
14.1.4.5.ES	ITT Population	Summary of Expert-Confirmed Events Requiring Treatment with Targeted HAE Medications, Entire Study

Output Number	Population Title	Output Title
14.1.5.1	Safety Population	Summary of Treatment Exposure, Part 1
14.1.5.1.ES	Safety Population	Summary of Treatment Exposure, Entire Study
14.1.5.3	Safety Population	Summary of Treatment Compliance, Part 1
14.1.5.3.ES	Safety Population	Summary of Treatment Compliance, Entire Study
14.2.1.1	ITT Population	Summary of Hierarchical Testing for Efficacy Endpoints
14.2.1.2.1	ITT Population	Overall Event Summary During Part 1
14.2.1.2.1.ES	ITT Population	Overall Event Summary During Entire Study
14.2.1.2.2	PP Population	Overall Event Summary During Part 1
14.2.1.3.1	ITT Population	Overall Event Summary During the Effective Dosing Period, Part 1
14.2.1.3.1.ES	ITT Population	Overall Event Summary During the Effective Dosing Period, Entire Study
14.2.1.3.2	PP Population	Overall Event Summary During the Effective Dosing Period, Part 1
14.2.1.4.1	ITT Population	Summary of Rate of Expert-Confirmed Events During Part 1
14.2.1.4.1.ES	ITT Population	Summary of Rate of Expert-Confirmed Events During Entire Study
14.2.1.4.2	PP Population	Summary of Rate of Expert-Confirmed Events During Part 1
14.2.1.4.3	Completers Population	Summary of Rate of Expert-Confirmed Events During Part 1
14.2.1.4.4	ITT Population	Summary of Rate of Expert-Confirmed Events During Part 1, Including Observed Data Post Treatment Discontinuation
14.2.1.4.5	ITT Population	Summary of Rate of Expert-Confirmed Events During Part 1, Including Observed Data Post Treatment Discontinuation and Missing Data Post Treatment Discontinuation are Imputed
14.2.1.11.1	ITT Population	Summary of Rate of Expert-Confirmed Events During Effective Dosing Period, Part 1
14.2.1.11.1.ES	ITT Population	Summary of Rate of Expert-Confirmed Events During Effective Dosing Period, Entire Study
14.2.1.11.2	PP Population	Summary of Rate of Expert-Confirmed Events During Effective Dosing Period, Part 1
14.2.1.14	ITT Population	Summary of Rate of Expert-Confirmed Events Requiring Treatment During Part 1
14.2.1.14.ES	ITT Population	Summary of Rate of Expert-Confirmed Events Requiring Treatment During Entire Study
14.2.1.15	ITT Population	Summary of Rate of Expert-Confirmed Abdominal-Only Events During Part 1
14.2.1.15.ES	ITT Population	Summary of Rate of Expert-Confirmed Abdominal-Only Events During Entire Study
14.2.1.16	ITT Population	Summary of Rate of Expert-Confirmed Peripheral-Only Events During Part 1
14.2.1.16.ES	ITT Population	Summary of Rate of Expert-Confirmed Peripheral-Only Events During Entire Study
14.2.1.17	ITT Population	Summary of Rate of Expert-Confirmed Mixed Location Events During Part 1
14.2.1.17.ES	ITT Population	Summary of Rate of Expert-Confirmed Mixed Location Events During Entire Study
14.2.1.18	ITT Population	Summary of Rate of Subject-Reported Events During Part 1
14.2.1.18.ES	ITT Population	Summary of Rate of Subject-Reported Events During Entire Study
14.2.1.18.P3	ITT Population	Summary of Rate of Subject-Reported Events During Part 3
14.2.1.19.P3	ITT Population	Summary of Rate of Subject-Reported Events Requiring Treatment During Part 3
14.2.1.20	ITT Population	Subject-Reported and Expert-Confirmed Events During Part 1
14.2.1.20.ES	ITT Population	Subject-Reported and Expert-Confirmed Events During Entire Study
14.2.1.22	ITT Population	Relationship of Baseline Characteristics and the Rate of Expert-Confirmed Events, Part 1
14.2.2.1	ITT Population	Summary of Rate of Expert-Confirmed Events by Month During Part 1
14.2.2.1.ES	ITT Population	Summary of Rate of Expert-Confirmed Events by Month During Entire Study

Output Number	Population Title	Output Title
14.2.2.1.P3	ITT Population	Summary of Rate of Adjusted Events By Month During Part 3
14.2.3.1.1	ITT Population	Summary of AE-QoL Scores by Visit, Part 1
14.2.3.1.1.ES	ITT Population	Summary of AE-QoL Scores by Visit, Entire Study
14.2.3.1.2	PP Population	Summary of AE-QoL Scores by Visit, Part 1
14.2.3.7	ITT Population	Number and Percent of Subjects Achieving the MCID (Decrease in Total AE-QoL Score), Part 1
14.2.3.7.ES	ITT Population	Number and Percent of Subjects Achieving the MCID (Decrease in Total AE-QoL Score), Entire Study
14.2.4.1	ITT Population	Summary of Number and Proportion of Subjects Who are Expert-Confirmed Event-Free, Part 1
14.2.4.1.ES	ITT Population	Summary of Number and Proportion of Subjects Who are Expert-Confirmed Event-Free, Entire Study
14.2.4.2	ITT Population	Summary of Number and Proportion of Subjects Who are Expert-Confirmed Event-Free in the Effective Dosing Period, Part 1
14.2.4.2.ES	ITT Population	Summary of Number and Proportion of Subjects Who are Expert-Confirmed Event-Free in the Effective Dosing Period, Entire Study
14.2.5.1.1	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert-Confirmed Events, Part 1
14.2.5.1.1.ES	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert-Confirmed Events, Entire Study
14.2.5.1.1.P3	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Adjusted Events, Part 3
14.2.5.1.2	PP Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert-Confirmed Events, Part 1
14.2.5.1.3	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert-Confirmed Events During Effective Dosing Period, Part 1
14.2.5.1.3.ES	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert-Confirmed Events During Effective Dosing Period, Entire Study
14.2.6.1.1	ITT Population	Summary of Relative Reduction from Baseline in Adjusted Expert-Confirmed Event Rate, Part 1
14.2.6.1.2	PP Population	Summary of Relative Reduction from Baseline in Adjusted Expert-Confirmed Event Rate, Part 1
14.2.6.3	ITT Population	Relationship of Baseline Characteristics and the Proportion of Subjects with at least a 50% Relative Reduction in Adjusted Expert- or Investigator-Confirmed Events, Part 1
14.2.6.4	ITT Population	Relationship of Baseline Characteristics and the Proportion of Subjects with at least a 70% Relative Reduction in Adjusted Expert- or Investigator-Confirmed Events, Part 1
14.2.7.1	ITT Population	Event-Level Duration of Expert-Confirmed Events (hours) from Start of Event to the Time the Event Finished, Part 1
14.2.7.1.ES	ITT Population	Event-Level Duration of Expert-Confirmed Events (hours) from Start of Event to the Time the Event Finished, Entire Study
14.2.7.2	ITT Population	Event-Level Duration of Expert-Confirmed Events (hours) from Start of Event Until Worst Was Over, Part 1
14.2.7.2.ES	ITT Population	Event-Level Duration of Expert-Confirmed Events (hours) from Start of Event Until Worst Was Over, Entire Study
14.2.8.1	ITT Population	Summary of Time (Days) to First Expert-Confirmed Event
14.2.9.1	ITT Population	Summary of Time (Days) to First Use of Targeted HAE Rescue Medication to Treat an Expert-Confirmed Event
14.2.10.1	ITT Population	Summary of Event Characteristics for Expert-Confirmed Events, Part 1
14.2.10.1.ES	ITT Population	Summary of Event Characteristics for Expert-Confirmed Events, Entire Study
14.2.11.1	ITT Population	Summary of Event Locations for Expert-Confirmed Events, Part 1

Output Number	Population Title	Output Title
14.2.11.1.ES	ITT Population	Summary of Event Locations for Expert-Confirmed Events, Entire Study
14.2.12.1	ITT Population	On-demand Rescue Medication Rate for Expert-Confirmed Events, Part 1
14.2.12.2	ITT Population	On-demand Rescue Medication Rate for Subject-Reported Events, Part 1
14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events, Part 1
14.3.1.1.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events, Entire Study
14.3.1.2	Safety Population	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.2.ES	Safety Population	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.3	Safety Population	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.3.ES	Safety Population	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.4	Safety Population	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.4.ES	Safety Population	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.5	Safety Population	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.5.ES	Safety Population	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.6	Safety Population	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.6.ES	Safety Population	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.7	Safety Population	Drug-Related Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.7.ES	Safety Population	Drug-Related Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.8	Safety Population	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 Population	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 Population	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 Population	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 Population	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity, Part 1
14.3.1.10.ES	Safety Population	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity, Entire Study
14.3.1.12	Safety Population	Summary of Frequent Adverse Events, Part 1
14.3.1.12.ES	Safety Population	Summary of Frequent Adverse Events, Entire Study
14.3.1.14	Safety Population	Summary of Drug-Related Frequent Adverse Events, Part 1
14.3.1.14.ES	Safety Population	Summary of Drug-Related Frequent Adverse Events, Entire Study
14.3.1.15	Safety Population	Overall Summary of Treatment-Emergent Investigator-Identified Rash (Event of Special Interest), Part 1

Output Number	Population Title	Output Title
14.3.1.15.ES	Safety Population	Overall Summary of Treatment-Emergent Investigator-Identified Rash (Event of Special Interest), Entire Study
14.3.1.16	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Part 1
14.3.1.16.ES	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Entire Study
14.3.1.17	Safety Population	Drug-Related Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Part 1
14.3.1.17.ES	Safety Population	Drug-Related Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Entire Study
14.3.1.18	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.18.ES	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.19	Safety Population	Drug-Related Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.19.ES	Safety Population	Drug-Related Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Serious Adverse Events by System Organ class and Preferred Term, Entire Study
14.3.1.20	Safety Population	Treatment-Emergent Grade 3 or Grade 4 Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Part 1
14.3.1.20.ES	Safety Population	Treatment-Emergent Grade 3 or Grade 4 Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Entire Study
14.3.1.21	Safety Population	Drug-Related Treatment-Emergent Grade 3 or 4 Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Part 1
14.3.1.21.ES	Safety Population	Drug-Related Treatment-Emergent Grade 3 or 4 Investigator-Identified Rash (Event of Special Interest) by System Organ Class and Preferred Term, Entire Study
14.3.1.22	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Leading to the Interruption of the Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.22.ES	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Leading to the Interruption of the Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.23	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Part 1
14.3.1.23.ES	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term, Entire Study
14.3.1.24	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Requiring the Use of Concomitant Medication by System Organ Class and Preferred Term, Part 1
14.3.1.24.ES	Safety Population	Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) Requiring the Use of Concomitant Medication by System Organ Class and Preferred Term, Entire Study
14.3.1.25	Safety Population	Summary of Time (Days) to Development of Investigator-Identified Rash (Event of Special Interest), Part 1
14.3.1.25.ES	Safety Population	Summary of Time (Days) to Development of Investigator-Identified Rash (Event of Special Interest), Entire Study
14.3.1.27	Safety Population	Summary of Duration (Days) of Investigator-Identified Rash (Event of Special Interest), Part 1
14.3.1.27.ES	Safety Population	Summary of Duration (Days) of Investigator-Identified Rash (Event of Special Interest), Entire Study

Output Number	Population Title	Output Title
14.3.1.29	Safety Population	Overall Summary of Treatment-Emergent GI Abdominal-Related Adverse Events, Part 1
14.3.1.29.ES	Safety Population	Overall Summary of Treatment-Emergent GI Abdominal-Related Adverse Events, Entire Study
14.3.1.30	Safety Population	Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.30.ES	Safety Population	Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.31	Safety Population	Drug-Related Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.31.ES	Safety Population	Drug-Related Treatment-Emergent GI Abdominal-Related Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.32	Safety Population	Treatment-Emergent GI Abdominal-Related Events Serious Adverse Events by System Organ Class and Preferred Term, Part 1
14.3.1.32.ES	Safety Population	Treatment-Emergent GI Abdominal-Related Events Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.33	Safety Population	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 Population	Drug-Related Treatment-Emergent GI Abdominal-Related Serious Adverse Events by System Organ Class and Preferred Term, Entire Study
14.3.1.34	Safety Population	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 Population	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 Population	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 Population	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 Population	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 Population	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 Population	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 Population	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 Population	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 Population	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 Population	Summary of Time (Days) to Development of GI Abdominal-Related Adverse Events, Part 1
14.3.1.39.ES	Safety Population	Summary of Time (Days) to Development of GI Abdominal-Related Adverse Events, Entire Study
14.3.1.41	Safety Population	Duration (Days) of GI Abdominal-Related Adverse Events, Part 1
14.3.1.41.ES	Safety Population	Duration (Days) of GI Abdominal-Related Adverse Events, Entire Study
14.3.1.44	Safety Population	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Events with Abdominal-Only Symptoms, Part 1
14.3.1.44.ES	Safety Population	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Events with Abdominal-Only Symptoms, Entire Study

Output Number	Population Title	Output Title
14.3.1.45.ES	Safety Population	Summary of Treatment-Emergent Adverse Event Rate Per 100 Person-Years of Exposure, Entire Study
14.3.1.46.ES	Safety Population	Summary of Drug-Related Treatment-Emergent Adverse Event Rate Per 100 Person-Years of Exposure, Entire Study
14.3.1.47.ES	Safety Population	Summary of Treatment-Emergent Serious Adverse Event Rate Per 100 Person-Years of Exposure, Entire Study
14.3.1.48.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 1, Part 1
14.3.1.48.1.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 1, Entire Study
14.3.1.48.2	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 2, Part 1
14.3.1.48.2.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 2, Entire Study
14.3.1.48.3	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 3, Part 1
14.3.1.48.3.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 3, Entire Study
14.3.1.48.4	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 4, Part 1
14.3.1.48.4.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 4, Entire Study
14.3.1.48.5	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 5, Part 1
14.3.1.48.5.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 5, Entire Study
14.3.1.48.6	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 6, Part 1
14.3.1.48.6.ES	Safety Population	Overall Summary of Treatment-Emergent Adverse Events Occurring in Month 6, Entire Study
14.3.5.1	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Clinical Chemistry, Part 1
14.3.5.1.ES	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Clinical Chemistry, Entire Study
14.3.5.2	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Hematology and Coagulation, Part 1
14.3.5.2.ES	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Hematology and Coagulation, Entire Study
14.3.5.3	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Complement Factors, Part 1
14.3.5.3.ES	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Complement Factors, Entire Study
14.3.5.4	Safety Population	Summary of Observed and Change from Baseline Laboratory Data: Additional Tests, Part 1
14.3.5.4.ES	Safety Population	Summary of Observed and Change from Baseline Laboratory Data: Additional Tests, Entire Study
14.3.5.5	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Continuous Urinalysis Parameters, Part 1
14.3.5.5.ES	Safety Population	Summary of Observed and Change from Baseline in Laboratory Data: Continuous Urinalysis Parameters, Entire Study
14.3.5.6	Safety Population	Summary of Observed Laboratory Data: Categorical Urinalysis Parameters, Part 1

Output Number	Population Title	Output Title
14.3.5.6.ES	Safety Population	Summary of Observed Laboratory Data: Categorical Urinalysis Parameters, Entire Study
14.3.5.7	Safety Population	Shift from Baseline to Worst Post-Baseline Assessment: Clinical Chemistry, Part 1
14.3.5.7.ES	Safety Population	Shift from Baseline to Worst Post-Baseline Assessment: Clinical Chemistry, Entire Study
14.3.5.8	Safety Population	Shift from Baseline to Worst Post-Baseline Assessment: Hematology and Coagulation, Part 1
14.3.5.8.ES	Safety Population	Shift from Baseline to Worst Post-Baseline Assessment: Hematology and Coagulation, Entire Study
14.3.5.9	Safety Population	Shift from Baseline to Worst Post-Baseline Assessment: Urinalysis, Part 1
14.3.5.9.ES	Safety Population	Shift from Baseline to Worst Post-Baseline Assessment: Urinalysis, Entire Study
14.3.5.10	Safety Population	Summary of Treatment-Emergent Graded Laboratory Abnormalities, Part 1
14.3.5.10.ES	Safety Population	Summary of Treatment-Emergent Graded Laboratory Abnormalities, Entire Study
14.3.5.11	Safety Population	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities, Part 1
14.3.5.11.ES	Safety Population	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities, Entire Study
14.3.5.12	Safety Population	Summary of Treatment-Emergent Laboratory Toxicity Grade Increases from Baseline, Part 1
14.3.5.12.ES	Safety Population	Summary of Treatment-Emergent Laboratory Toxicity Grade Increases from Baseline, Entire Study
14.3.5.13	Safety Population	Summary of Fold x ULN for Liver Function Tests, Part 1
14.3.5.13.ES	Safety Population	Summary of Fold x ULN for Liver Function Tests, Entire Study
14.3.5.14	Safety Population	Summary of Fold Change from Baseline for Liver Function Tests, Part 1
14.3.5.14.ES	Safety Population	Summary of Fold Change from Baseline for Liver Function Tests, Entire Study
14.3.5.15	Safety Population	Summary of Elevations in Post-Baseline Liver Function Tests, Part 1
14.3.5.15.ES	Safety Population	Summary of Elevations in Post-Baseline Liver Function Tests, Entire Study
14.3.5.16	Safety Population	Summary of Elevations in Post-Baseline Liver Function Tests, Part 1 - Subjects with Prior Androgen Use
14.3.5.16.ES	Safety Population	Summary of Elevations in Post-Baseline Liver Function Tests, Entire Study - Subjects with Prior Androgen Use
14.3.5.17	Safety Population	Summary of Elevations in Post-Baseline Liver Function Tests, Part 1 - Subjects with No Prior Androgen Use
14.3.5.17.ES	Safety Population	Summary of Elevations in Post-Baseline Liver Function Tests, Entire Study - Subjects with No Prior Androgen Use
14.3.5.18	Safety Population	Summary of Treatment-Emergent Elevations in Post-Baseline Liver Function Tests, Part 1
14.3.5.18.ES	Safety Population	Summary of Treatment-Emergent Elevations in Post-Baseline Liver Function Tests, Entire Study
14.3.5.24	Safety Population	Summary of Time (Days) to First Occurrence of Grade 3 or 4 ALT, Part 1

Output Number	Population Title	Output Title
14.3.5.26	Safety Population	Summary of Time (Days) to First Occurrence of Grade 3 or 4 AST, Part 1
14.3.5.28	Safety Population	Summary of Time (Days) to First Occurrence of Grade 3 or 4 Total Bilirubin, Part 1
14.3.5.30	Safety Population	Summary of Treatment-Emergent Graded Laboratory Abnormalities by Greatest Post-Baseline Severity, Part 1
14.3.5.30.ES	Safety Population	Summary of Treatment-Emergent Graded Laboratory Abnormalities by Greatest Post-Baseline Severity, Entire Study
14.3.5.31	Safety Population	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities by Greatest Post-Baseline Severity, Part 1
14.3.5.31.ES	Safety Population	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities by Greatest Post-Baseline Severity, Entire Study
14.3.6.1	Safety Population	Summary of Observed and Change from Baseline in Vital Signs, Part 1
14.3.6.1.ES	Safety Population	Summary of Observed and Change from Baseline in Vital Signs, Entire Study
14.3.6.3	Safety Population	Summary of Diastolic and Systolic Blood Pressure, Part 1; Baseline and All Post-Baseline Observations
14.3.6.3.ES	Safety Population	Summary of Diastolic and Systolic Blood Pressure, Part 2; Baseline and All Post-Baseline Observations
14.3.7.1	Safety Population	Summary of Observed and Change from Baseline in ECG Interval Values, Part 1
14.3.7.1.ES	Safety Population	Summary of Observed and Change from Baseline in ECG Interval Values, Entire Study
14.3.7.2	Safety Population	Summary of QTcF Baseline and All Post-Baseline Observations, Part 1
14.3.7.2.ES	Safety Population	Summary of QTcF Baseline and All Post-Baseline Observations, Part 1
14.3.7.3	Safety Population	Summary of ECG Findings, Part 1
14.3.7.3.ES	Safety Population	Summary of ECG Findings, Entire Study
14.3.7.4	Safety Population	Summary of QTcF Observed and Change from Baseline in Categorical Findings, Part 1
14.3.7.4.ES	Safety Population	Summary of QTcF Observed and Change from Baseline in Categorical Findings, Entire Study
14.3.7.5	Safety Population	Summary of QTcF Observed and Change from Baseline in Categorical Findings, Part 1; Baseline and All Post-Baseline Observations
14.3.7.5.ES	Safety Population	Summary of QTcF Observed and Change from Baseline in Categorical Findings, Entire Study; Baseline and All Post-Baseline Observations
14.4.1.1	ITT Population	Summary of WPAI Scores, Part 1
14.4.1.1.ES	ITT Population	Summary of WPAI Scores, Entire Study
14.4.1.4	ITT Population	Summary of Responses to WPAI Individual Questions, Part 1
14.4.1.4.ES	ITT Population	Summary of Responses to WPAI Individual Questions, Entire study
14.4.2.1	ITT Population	Summary of EQ-5D-5L VAS Scores, Part 1
14.4.2.1.ES	ITT Population	Summary of EQ-5D-5L VAS Scores, Entire Study
14.4.2.11	ITT Population	Summary of Responses to EQ-5D-5L Individual Questions, Part 1
14.4.2.11.ES	ITT Population	Summary of Responses to EQ-5D-5L Individual Questions, Entire study
14.4.2.12	ITT Population	Summary of Responses to EQ-5D-5L Individual Questions from Usual Event, Part 1
14.4.2.12.ES	ITT Population	Summary of Responses to EQ-5D-5L Individual Questions from Usual Event, Entire study
14.4.2.4	ITT Population	Summary of EQ-5D-5L VAS Scores from Usual Event, Part 1

Output Number	Population Title	Output Title
14.4.2.4.ES	ITT Population	Summary of EQ-5D-5L VAS Scores from Usual Event, Entire Study
14.4.2.6	ITT Population	Summary of EQ-5D-5L Index Scores, Part 1
14.4.2.6.ES	ITT Population	Summary of EQ-5D-5L Index Scores, Entire Study
14.4.2.9	ITT Population	Summary of EQ-5D-5L Index Scores from Usual Event, Part 1
14.4.2.9.ES	ITT Population	Summary of EQ-5D-5L Index Scores from Usual Event, Entire Study
14.4.3.1	ITT Population	Summary of TSQM Scores, Part 1
14.4.3.1.ES	ITT Population	Summary of TSQM Scores, Entire Study
14.4.3.4	ITT Population	Summary of Responses to TSQM Individual Questions, Part 1
14.4.3.4.ES	ITT Population	Summary of Responses to TSQM Individual Questions, Entire study
14.5.1.1	Safety Population	Summary of Plasma BCX7353 Concentration (ng/mL), Part 1
14.5.1.1.ES	Safety Population	Summary of Plasma BCX7353 Concentration (ng/mL), Entire Study
14.5.2.1	Safety Population	Plasma BCX7353 Concentration (ng/mL) Samples above Kallikrein Inhibition EC50, Part 1
14.5.2.1.ES	Safety Population	Plasma BCX7353 Concentration (ng/mL) Samples above Kallikrein Inhibition EC50, Entire Study
14.6.1.1	PD Population	Summary of Plasma Kallikrein Inhibition (%), Part 1
14.6.1.1.ES	PD Population	Summary of Plasma Kallikrein Inhibition (%), Entire Study
14.6.2.1	PD Population	Plasma Kallikrein Inhibition Samples above 50% and 80%, Part 1
14.6.2.1.ES	PD Population	Plasma Kallikrein Inhibition Samples above 50% and 80%, Entire Study
14.6.2.2	PD Population	Summary of Baseline Mean Amidolytic Activity Overall and by Gender

17.1.1.2. BCX7353-301 and BCX7353-302 Combined Study Output

Output Number	Population Title	Output Title
14.1.1.1.C	All Subjects	Summary of Subject Disposition by Country and Site, Part 1
14.1.2.1.C	ITT Population	Summary of Analysis Populations
14.1.2.2.C	ITT Population	Summary of Subgroups
14.1.2.3.1.C	ITT Population	Summary of Inclusion/Exclusion Criteria Violations
14.1.2.4.C	ITT Population	Summary of Protocol Deviations, Part 1
14.1.2.5.C	All Subjects	Summary of Confirmation of Diagnosis of HAE Type I or II
14.1.3.1.1.C	ITT Population	Summary of Demographic Characteristics
14.1.3.1.2.C	PP Population	Summary of Demographic Characteristics
14.1.3.2.C	ITT Population	Summary of Subject-Reported HAE Baseline Characteristics - HAE Medical History
14.1.3.3.C	ITT Population	Summary of Past Prophylactic Treatments of HAE
14.1.3.4.C	ITT Population	Summary of Primary Reason for Discontinuation of Past Prophylactic Treatments of HAE
14.1.3.5.C	ITT Population	Summary of Current On-Demand Treatments of HAE
14.1.3.6.C	ITT Population	Summary of Subject-Reported HAE Baseline Characteristics - Primary Acute Event Treatment Information
14.1.3.7.1.C	ITT Population	Summary of Pre-Treatment Expert- or Investigator-Confirmed Event Rates and Angioedema Symptoms
14.1.3.7.2.C	ITT Population	Summary of Pre-Treatment Expert- or Investigator-Confirmed Event Rates and Angioedema Symptoms by Subgroups
14.1.3.8.C	ITT Population	Summary of C1-INH Antigenic Levels
14.1.4.1.C	ITT Population	Summary of Medications Taken within 30 Days Prior to Screening and Discontinued Prior to Dosing
14.1.4.2.C	ITT Population	Summary of Concomitant Medications, Part 1
14.1.4.3.C	ITT Population	Summary of Concomitant Medications for HAE, Part 1

Output Number	Population Title	Output Title
14.1.4.4.C	ITT Population	Summary of Concomitant Medications for Acute Treatment of Angioedema Events - Event Level [1]
14.1.5.1.C	Safety Population	Summary of Treatment Exposure, Part 1
14.1.5.3.C	Safety Population	Summary of Treatment Compliance, Part 1
14.2.1.1.C	ITT Population	Summary of Hierarchical Testing for Efficacy Endpoints
14.2.1.2.1.C	ITT Population	Overall Event Summary During Part 1
14.2.1.2.2.C	PP Population	Overall Event Summary During Part 1
14.2.1.3.1.C	ITT Population	Overall Event Summary During the Effective Dosing Period, Part 1
14.2.1.3.2.C	PP Population	Overall Event Summary During the Effective Dosing Period, Part 1
14.2.1.4.1.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Part 1
14.2.1.4.2.C	PP Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Part 1
14.2.1.4.3.C	Completers Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Part 1
14.2.1.4.4.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Part 1, Including Observed Data Post Treatment Discontinuation
14.2.1.4.5.C	ITT Population	Summary of Rate of Expert-Confirmed Events During Part 1, Including Observed Data Post Treatment Discontinuation and Missing Data Post Treatment Discontinuation are Imputed
14.2.1.6.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Part 1 by Subgroups
14.2.1.11.1.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Effective Dosing Period, Part 1
14.2.1.11.2.C	PP Population	Summary of Rate of Expert- or Investigator-Confirmed Events During Effective Dosing Period, Part 1
14.2.1.14.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Events Requiring Treatment During Part 1
14.2.1.15.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Abdominal-Only Events During Part 1
14.2.1.16.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Peripheral-Only Events During Part 1
14.2.1.17.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Mixed Location Events During Part 1
14.2.1.18.C	ITT Population	Summary of Rate of Subject-Reported Events During Part 1
14.2.1.19.C	ITT Population	Subject-Reported and Expert- or Investigator-Confirmed Events During Part 1
14.2.1.21.C	ITT Population	Relationship of Baseline Characteristics and the Rate of Expert- or Investigator-Confirmed Events, Part 1
14.2.2.1.C	ITT Population	Summary of Rate of Expert- or Investigator-Confirmed Events by Month During Part 1
14.2.3.1.1.C	ITT Population	Summary of AE-QoL Scores by Visit, Part 1
14.2.3.1.2.C	PP Population	Summary of AE-QoL Scores by Visit, Part 1
14.2.3.2.C	ITT Population	Summary of AE-QoL Total Scores, Part 1 by Subgroups
14.2.3.7.C	ITT Population	Number and Percent of Subjects Achieving the MCID (Decrease in Total AE-QoL Score), Part 1
14.2.4.1.C	ITT Population	Summary of Number and Proportion of Subjects Who are Expert- or Investigator-Confirmed Event-Free, Part 1
14.2.4.2.C	ITT Population	Summary of Number and Proportion of Subjects Who are Expert- or Investigator-Confirmed Event-Free in the Effective Dosing Period, Part 1
14.2.5.1.1.C	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert- or Investigator-Confirmed Events, Part 1

Output Number	Population Title	Output Title
14.2.5.1.2.C	PP Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert- or Investigator-Confirmed Events, Part 1
14.2.5.1.3.C	ITT Population	Summary of Number and Proportion of Days with Angioedema Symptoms from Expert- or Investigator-Confirmed Events During Effective Dosing Period, Part 1
14.2.6.1.1.C	ITT Population	Summary of Relative Reduction from Baseline in Adjusted Expert- or Investigator-Confirmed Event Rate, Part 1
14.2.6.1.2.C	PP Population	Summary of Relative Reduction from Baseline in Adjusted Expert- or Investigator-Confirmed Event Rate, Part 1
14.2.6.3.C	ITT Population	Relationship of Baseline Characteristics and the Proportion of Subjects with at least a 50% Relative Reduction in Adjusted Expert- or Investigator-Confirmed Events, Part 1
14.2.6.4.C	ITT Population	Relationship of Baseline Characteristics and the Proportion of Subjects with at least a 70% Relative Reduction in Adjusted Expert- or Investigator-Confirmed Events, Part 1
14.2.6.5.C	ITT Population	Summary of Relative Reduction from Baseline in Adjusted Expert- or Investigator-Confirmed Event Rate by Subgroups, Part 1
14.2.7.1.C	ITT Population	Event-Level Duration of Expert- or Investigator-Confirmed Events (hours) from Start of Event to the Time the Event Finished, Part 1
14.2.7.2.C	ITT Population	Event-Level Duration of Expert- or Investigator-Confirmed Events (hours) from Start of Event Until Worst Was Over, Part 1
14.2.8.1.C	ITT Population	Summary of Time (Days) to First Expert- or Investigator-Confirmed Event
14.2.9.1.C	ITT Population	Summary of Time (Days) to First Use of Targeted HAE Rescue Medication to Treat an Expert- or Investigator-Confirmed Event
14.2.10.1.C	ITT Population	Summary of Event Characteristics for Expert- or Investigator-Confirmed Events, Part 1
14.2.11.1.C	ITT Population	Summary of Event Locations for Expert- or Investigator-Confirmed Events, Part 1
14.2.12.1.C	ITT Population	On-demand Rescue Medication Rate for Expert or Investigator-Confirmed Events, Part 1
14.2.12.2.C	ITT Population	On-demand Rescue Medication Rate for Subject-Reported Events, Part 1

17.1.2. Listings (BCX7353-301 Only)

Output Number	Population Title	Output Title
16.2.1.1	All Subjects	Informed Consent and Screen Failures
16.2.1.2	All Subjects	Subject Randomization and Site
16.2.1.3	Safety Population	Planned and Actual Treatment Assignments for Subjects with Incorrect Treatment, Part 1
16.2.1.3.ES	Safety Population	Planned and Actual Treatment Assignments for Subjects with Incorrect Treatment, Entire Study
16.2.1.4	ITT Population	Subject Disposition, Part 1
16.2.1.5	All Subjects	Confirmation of Clinical Diagnosis of HAE
16.2.1.6	ITT Population	Analysis Populations
16.2.1.7	ITT Population	Subgroups Based on Baseline Characteristics
16.2.1.8	ITT Population	IXRS Reported Event Rate and Baseline Event Rate
16.2.2.1	ITT Population	Protocol Deviations, Part 1
16.2.2.1.ES	ITT Population	Protocol Deviations Occurring During Part 2 of the Study
16.2.2.2	Safety Population	Subjects for Whom the Treatment Blind Was Broken, Part 1
16.2.2.2.ES	Safety Population	Subjects for Whom the Treatment Blind Was Broken, Entire Study
16.2.4.1	ITT Population	Inclusion/Exclusion Criteria Not Met
16.2.4.2.1	All Subjects	Demography

Output Number	Population Title	Output Title
16.2.4.2.2	All Subjects	Demography - Contraception
16.2.4.3.1	ITT Population	Medical History
16.2.4.3.2	ITT Population	HAE Baseline Characteristics - HAE Medical History
16.2.4.3.3	Safety Population	HAE Medication History: Past and Current On-Demand HAE Treatment
16.2.4.3.4	Safety Population	HAE Medication History: Past Prophylactic HAE Treatment
16.2.4.4.1	Safety Population	Medications Taken within 30 Days Prior to Screening and Discontinued Prior to Dosing
16.2.4.4.2	Safety Population	Concomitant Medication Use, Part 1
16.2.4.4.2.ES	ITT Population	Concomitant Medication Use, Entire Study
16.2.4.4.3	Safety Population	Use of Concomitant Medications for HAE, Part 1
16.2.4.4.3.ES	ITT Population	Use of Concomitant Medications for HAE, Entire Study
16.2.4.5	ITT Population	Pre-Treatment Expert-Confirmed Event Rates and Angioedema Symptoms
16.2.5.1	Safety Population	Drug Accountability, Part 1
16.2.5.1.ES	Safety Population	Drug Accountability, Entire Study
16.2.5.2	Safety Population	Dosing Diary, Part 1
16.2.5.2.ES	Safety Population	Dosing Diary, Entire Study
16.2.5.3	Safety Population	Person-Years of Exposure, Part 1
16.2.5.3.ES	Safety Population	Person-Years of Exposure, Entire Study
16.2.5.4	Safety Population	Treatment Compliance, Part 1
16.2.5.5	Safety Population	Subjects Who Switched from 110 mg to 150 mg During the Study
16.2.6.1.1	ITT Population	HAE Event Diary and Investigator Confirmation for All Events, Part 1
16.2.6.1.1.ES	ITT Population	HAE Event Diary and Investigator Confirmation for All Events, Entire Study
16.2.6.1.2	ITT Population	HAE Event Diary and Investigator Confirmation (Expert-Confirmed Events Only), Part 1
16.2.6.1.2.ES	ITT Population	HAE Event Diary and Investigator Confirmation (Expert-Confirmed Events Only), Entire Study
16.2.6.1.3	ITT Population	HAE Event Diary Detail - Subject-Reported Events, Part 1
16.2.6.1.3.ES	ITT Population	HAE Event Diary Detail - Subject-Reported Events, Entire Study
16.2.6.1.4	ITT Population	HAE Event Diary Detail - Expert-Confirmed Events, Part 1
16.2.6.1.4.ES	ITT Population	HAE Event Diary Detail - Expert-Confirmed Events, Entire Study
16.2.6.1.5	ITT Population	HAE Event Level Summary - Subject-Reported Events, Part 1
16.2.6.1.5.ES	ITT Population	HAE Event Level Summary - Subject-Reported Events, Entire Study
16.2.6.1.6	ITT Population	HAE Event Level Summary - Expert-Confirmed Events, Part 1
16.2.6.1.6.ES	ITT Population	HAE Event Level Summary - Expert-Confirmed Events, Entire Study
16.2.6.1.7	ITT Population	Event Rate, Part 1
16.2.6.1.7.ES	ITT Population	Event Rate, Entire Study
16.2.6.1.8	ITT Population	Imputed Expert-Confirmed Event Rates for Subjects with Missing Data, Part 1
16.2.6.1.9	ITT Population	Subjects Who Are Expert-Confirmed Event-Free During Entire Dosing Period and Effective Dosing Period, Part 1

Output Number	Population Title	Output Title
16.2.6.1.9.ES	ITT Population	Subjects Who Are Expert-Confirmed Event-Free During Entire Dosing Period and Effective Dosing Period, Entire Study
16.2.6.1.10	ITT Population	Days with Angioedema Symptoms from Expert-Confirmed Events, Part 1
16.2.6.1.10.ES	ITT Population	Days with Angioedema Symptoms from Expert-Confirmed Events, Entire Study
16.2.6.1.11.1	ITT Population	Subject-Level Efficacy Endpoint Profile, Part 1
16.2.6.1.11.2	ITT Population	Subject-Level Additional Derived Endpoint Profile, Part 1
16.2.6.1.12	ITT Population	HAE Event Diary Detail - Expert-Confirmed Laryngeal Events, Part 1
16.2.6.1.13	ITT Population	Expert-Confirmed Attacks Not Included in Adjusted Expert-Confirmed Attacks
16.2.6.2.1	ITT Population	AE-QoL: Individual Question Responses and Days Missed, Part 1
16.2.6.2.1.ES	ITT Population	AE-QoL: Individual Question Responses and Days Missed, Entire Study
16.2.6.2.2	ITT Population	AE-QoL: Domain Scores, Part 1
16.2.6.2.2.ES	ITT Population	AE-QoL: Domain Scores, Entire Study
16.2.6.3.1	ITT Population	TSQM Global Satisfaction Individual Responses, Part 1
16.2.6.3.1.ES	ITT Population	TSQM Global Satisfaction Individual Responses, Entire Study
16.2.6.3.2	ITT Population	TSQM Global Satisfaction, Effectiveness, Side Effects, and Convenience Subscale Scores, Part 1
16.2.6.3.2.ES	ITT Population	TSQM Effect, Side Effect, Convenience and Global Satisfaction Scores, Entire Study
16.2.6.4.1	ITT Population	EQ-5D-5L Individual Question Responses, Part 1
16.2.6.4.1.ES	ITT Population	EQ-5D-5L Individual Question Responses, Entire Study
16.2.6.4.2	ITT Population	EQ-5D-5L Descriptive, VAS, and Index Scores, Part 1
16.2.6.4.2.ES	ITT Population	EQ-5D-5L Descriptive, VAS, and Index Scores, Entire Study
16.2.6.4.3	ITT Population	EQ-5D-5L for Usual Event Individual Question Responses, Part 1
16.2.6.4.3.ES	ITT Population	EQ-5D-5L for Usual Event Individual Question Responses, Entire Study
16.2.6.4.4	ITT Population	EQ-5D-5L for Usual Event Descriptive, VAS, and Index Scores, Part 1
16.2.6.4.4.ES	ITT Population	EQ-5D-5L for Usual Event Descriptive, VAS, and Index Scores, Entire Study
16.2.6.5.1	ITT Population	WPAI Individual Question Responses, Part 1
16.2.6.5.1.ES	ITT Population	WPAI Individual Question Responses, Entire Study
16.2.6.5.2	ITT Population	WPAI Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment Scores, Part 1
16.2.6.5.2.ES	ITT Population	WPAI Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment Scores, Entire Study
16.2.7.1	Safety Population	Adverse Events, Part 1
16.2.7.1.ES	Safety Population	Adverse Events, Entire Study
16.2.7.2	Safety Population	Serious Adverse Events, Part 1
16.2.7.2.ES	Safety Population	Serious Adverse Events, Entire Study
16.2.7.3	Safety Population	Grade 3 or 4 Adverse Events, Part 1
16.2.7.3.ES	Safety Population	Grade 3 or 4 Adverse Events, Entire Study
16.2.7.4	Safety Population	Adverse Events Leading to Permanent Discontinuation of Study Drug, Part 1
16.2.7.4.ES	Safety Population	Adverse Events Leading to Permanent Discontinuation of Study Drug, Entire Study
16.2.7.5	Safety Population	Fatal Serious Adverse Events, Part 1

Output Number	Population Title	Output Title
16.2.7.5.ES	Safety Population	Fatal Serious Adverse Events, Entire Study
16.2.7.6	Safety Population	Adverse Events Leading to Interruption of Study Drug, Part 1
16.2.7.6.ES	Safety Population	Adverse Events Leading to Interruption of Study Drug, Entire Study
16.2.7.7	Safety Population	Investigator-Identified Rash (Event of Special Interest), Part 1
16.2.7.7.ES	Safety Population	Investigator-Identified Rash (Event of Special Interest), Entire Study
16.2.7.8	Safety Population	GI Abdominal-Related Adverse Events, Part 1
16.2.7.8.ES	Safety Population	GI Abdominal-Related Adverse Events, Entire Study
16.2.7.9	Safety Population	Adverse Events Occurring with 24 Hours of an LFT Elevation for Subjects with an LFT Elevation, Part 1
16.2.7.9.ES	Safety Population	Adverse Events For Subjects with Elevated LFTs Occurring within 24 hours of the Elevation, Entire Study
16.2.7.10	ITT Population	Listing of GI Abdominal-Related Adverse Events and Unconfirmed HAE Events with Abdominal-Only Symptoms, Part 1
16.2.7.10.ES	ITT Population	Listing of GI Abdominal-Related Adverse Events and Unconfirmed HAE Events with Abdominal-Only Symptoms, Entire Study
16.2.7.11	ITT Population	Listing of Subjects For Whom Narratives are Required, Part 1
16.2.7.11.ES	ITT Population	Listing of Subjects For Whom Narratives are Required, Entire Study
16.2.7.12.ES	Subjects Randomized to BCX7353 110 mg who Switch to BCX7353 150 mg	Adverse Events Occurring Following 110 mg Switch to 150 mg, Entire Study
16.2.8.1	Safety Population	Clinical Chemistry, Part 1
16.2.8.1.ES	Safety Population	Clinical Chemistry, Entire Study
16.2.8.2	Safety Population	Hematology, Part 1
16.2.8.2.ES	Safety Population	Hematology, Entire Study
16.2.8.3	Safety Population	Coagulation, Part 1
16.2.8.3.ES	Safety Population	Coagulation, Entire Study
16.2.8.4	Safety Population	Urinalysis, Part 1
16.2.8.4.ES	Safety Population	Urinalysis, Entire Study
16.2.8.5	Safety Population	Other Laboratory Tests, Part 1
16.2.8.5.ES	Safety Population	Other Laboratory Tests, Entire Study
16.2.8.6	Safety Population	Complement Factors C3, C4, and C1-INH, Part 1

Output Number	Population Title	Output Title
16.2.8.6.ES	Safety Population	Complement Factors C3, C4, and C1-INH, Entire Study
16.2.8.7	ITT Population	SERPING Results
16.2.8.8	ITT Population	Pregnancy Tests, Part 1
16.2.8.8.ES	ITT Population	Pregnancy Tests, Entire Study
16.2.8.9	Safety Population	Laboratory Abnormalities, Part 1
16.2.8.9.ES	Safety Population	Laboratory Abnormalities, Entire Study
16.2.8.10	Safety Population	Grade 3 or Grade 4 Laboratory Abnormalities, Part 1
16.2.8.10.ES	Safety Population	Grade 3 or Grade 4 Laboratory Abnormalities, Entire Study
16.2.8.11	Safety Population	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 Population	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.ES	Subjects Randomized to BCX7353 110 mg who Switch to BCX7353 150 mg	Grade 3 or 4 Liver Function Test Results Occurring Following 110 mg Switch to 150 mg, Entire Study
16.2.8.14	Safety Population	Vital Signs, Part 1
16.2.8.14.ES	Safety Population	Vital Signs, Part 1, Entire Study
16.2.8.15	Safety Population	12-Lead Electrocardiogram, Part 1
16.2.8.15.ES	Safety Population	12-Lead Electrocardiogram, Entire Study
16.2.8.16	Safety Population	QTcF Values > 450 msec or QTcF Change from Baseline Values > 30 msec, Part 1
16.2.8.16.ES	Safety Population	QTcF Values > 450 msec or QTcF Change from Baseline Values > 30 msec, Entire Study
16.2.8.17	Safety Population	Physical Exam, Part 1
16.2.8.17.ES	Safety Population	Physical Exam, Entire Study
16.2.8.18	Safety Population	Pharmacokinetic Sample Collection, Part 1
16.2.8.18.ES	Safety Population	Pharmacokinetic Sample Collection, Entire Study
16.2.8.19	PD Population	Plasma Kallikrein Inhibition (%), Part 1
16.2.8.19.ES	PD Population	Plasma Kallikrein Inhibition (%), Entire Study

17.1.3. Figures

17.1.3.1. BCX7353-301 Only

Output Number	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
14.1.3.9	Safety Population	Plot of Baseline C1-INH Antigenic Levels vs. Screening C1-INH Functional Levels
14.1.5.2	Safety Population	Plot of Duration of Exposure to Study Drug [1], Part 1
14.1.5.2.ES	Safety Population	Plot of Duration of Exposure to Study Drug, Entire Study
14.1.5.4	Safety Population	Histogram Plot of Treatment Compliance, Part 1
14.1.5.4.ES	Safety Population	Histogram Plot of Treatment Compliance, Entire Study
14.2.1.7	ITT Population	Box Plot of Expert-Confirmed Event Rate By Dose for Entire Dosing Period, Part 1
14.2.1.7.ES	ITT Population	Box Plot of Expert-Confirmed Event Rate By Dose for Entire Dosing Period, Entire Study
14.2.1.8	ITT Population	Cumulative Distribution Plot of Individual Expert-Confirmed Event Rate for Entire Dosing Period, Part 1
14.2.1.8.ES	ITT Population	Cumulative Distribution Plot of Individual Expert-Confirmed Event Rate for Entire Dosing Period, Entire Study
14.2.1.9	ITT Population	Forest Plot of Results of Sensitivity Analyses of Expert-Confirmed Event Rate for Entire Dosing Period, Part 1
14.2.1.10	ITT Population	Forest Plot of Results of Subgroup Analyses of Expert-Confirmed Event Rate for Entire Dosing Period, Part 1
14.2.1.12	ITT Population	Box Plot of Expert-Confirmed Event Rate By Dose for Effective Dosing Period, Part 1
14.2.1.12.ES	ITT Population	Box Plot of Expert-Confirmed Event Rate By Dose for Effective Dosing Period, Entire Study
14.2.1.13	ITT Population	Cumulative Distribution Plot of Individual Expert-Confirmed Event Rate for Effective Dosing Period, Part 1
14.2.1.13.ES	ITT Population	Cumulative Distribution Plot of Individual Expert-Confirmed Event Rate for Effective Dosing Period, Entire Study
14.2.1.21	ITT Population	Plot of Expert-Confirmed Events and Use of On-Demand Medication, Part 1
14.2.2.2	ITT Population	Histogram Plot of Baseline Expert-Confirmed Event Rate, Part 1
14.2.2.3	ITT Population	Plot of Mean Expert-Confirmed Event Rate by Month, Part 1
14.2.2.3.ES	ITT Population	Plot of Mean Expert-Confirmed Event Rate by Month, Entire Study
14.2.2.3.P3	ITT Population	Plot of Mean Adjusted Event Rate by Month, Part 3
14.2.2.4	ITT Population	Scatterplot of On-Study Expert-Confirmed Event Rate vs Baseline Expert-Confirmed Event Rate, Part 1
14.2.2.4.ES	ITT Population	Plot of On-Study Expert-Confirmed Event Rate vs Baseline Expert-Confirmed Event Rate, Entire Study
14.2.2.5	ITT Population	Plot of Change from Baseline Expert-Confirmed Event Rate vs. Baseline Expert-Confirmed Event Rate, Part 1
14.2.2.6	ITT Population	Plot of Change from Baseline Expert-Confirmed Event Rate vs. Percent Compliance, Part 1
14.2.2.7	ITT Population	Plot of Change from Baseline Expert-Confirmed Event Rate vs. Baseline Expert-Confirmed Event Rate by Gender, Part 1
14.2.2.8	ITT Population	Plot of Baseline and Expert-Confirmed Attack Rate By Subject
14.2.2.9	ITT Population	Plot of Individual Expert-Confirmed Attack Rate by Month

Output Number	Population Title	Output Title
14.2.2.10	ITT Population	Plot of Change from Baseline Expert-Confirmed Attack Rate vs. Baseline Expert-Confirmed Attack Rate, Part 1 By Gender
14.2.3.3	ITT Population	Plot of Mean AE-QoL Scores Over Time, Part 1
14.2.3.3.ES	ITT Population	Plot of Mean AE-QoL Scores Over Time, Entire Study
14.2.3.4	ITT Population	Plot of Mean Change from Baseline AE-QoL Scores Over Time, Part 1
14.2.3.4.ES	ITT Population	Plot of Mean Change from Baseline AE-QoL Scores Over Time, Entire Study
14.2.3.5	ITT Population	Cumulative Distribution of Total AE-QoL Change from Baseline at Week 24
14.2.3.6	ITT Population	Forest Plot of Results of Subgroup Analyses of Total AE-QOL Change from Baseline at Week 24, Part 1
14.2.6.2	ITT Population	Waterfall Plot of Relative Reduction from Baseline in Adjusted Expert-Confirmed Event Rate, Part 1
14.2.8.2	ITT Population	Kaplan-Meier Plot of Time to First Expert-Confirmed Event, Part 1
14.2.9.2	ITT Population	Kaplan-Meier Plot of Time to First Use of Targeted HAE Rescue Medication to Treat an Expert-Confirmed Event, Part 1
14.3.1.13	Safety Population	Forest Plot of Treatment-Emergent Adverse Events Sorted by Risk Difference, Part 1
14.3.1.13.ES	Safety Population	Forest Plot of Treatment-Emergent Adverse Events Sorted by Risk Difference, Entire Study
14.3.1.26	Safety Population	Kaplan-Meier Plot of Time to Development of Investigator-Identified Rash (Event of Special Interest), Part 1
14.3.1.26.ES	Safety Population	Kaplan-Meier Plot of Time to Development of Investigator-Identified Rash (Event of Special Interest), Entire Study
14.3.1.28	Safety Population	Kaplan-Meier Plot of Duration of Investigator-Identified Rash (Event of Special Interest), Part 1
14.3.1.28.ES	Safety Population	Kaplan-Meier Plot of Duration of Investigator-Identified Rash (Event of Special Interest), Entire Study
14.3.1.40	Safety Population	Kaplan-Meier Plot of Time to First Occurrence of a GI Abdominal-Related Adverse Event, Part 1
14.3.1.40.ES	Safety Population	Kaplan-Meier Plot of Time to First Occurrence of a GI Abdominal-Related Adverse Event Entire Study
14.3.1.42	Safety Population	Kaplan-Meier Plot of Duration of GI Abdominal-Related Adverse Events, Part 1
14.3.1.42.ES	Safety Population	Kaplan-Meier Plot of Duration of GI Abdominal-Related Adverse Events Entire Study
14.3.1.43	Safety Population	Plot of Occurrence of Treatment-Emergent GI Abdominal-Related Adverse Events, Part 1
14.3.1.43.ES	Safety Population	Plot of Occurrence of Treatment-Emergent GI Abdominal-Related Adverse Events, Entire Study
14.3.1.49	Safety Population	Plot of Treatment-Emergent Adverse Events by Study Month, Part 1
14.3.1.50	Safety Population	Plot of Drug-Related Treatment-Emergent Adverse Events by Study Month, Part 1
14.3.1.51	Safety Population	Plot of Treatment-Emergent Serious Adverse Events by Study Month, Part 1
14.3.1.52	Safety Population	Plot of Treatment-Emergent Grade 3 or Grade 4 Adverse Events by Study Month, Part 1
14.3.1.53	Safety Population	Plot of Drug-Related Treatment-Emergent Grade 3 or Grade 4 Adverse Events by Study Month, Part 1
14.3.1.54	Safety Population	Plot of Treatment-Emergent Adverse Events Leading to the Interruption of Study Drug by Study Month, Part 1
14.3.1.55	Safety Population	Plot of Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by Study Month, Part 1

Output Number	Population Title	Output Title
14.3.1.56	Safety Population	Plot of Treatment-Emergent Investigator-Identified Rash (Event of Special Interest) by Study Month, Part 1
14.3.1.57	Safety Population	Plot of Treatment-Emergent GI Abdominal-Related Adverse Events by Study Month, Part 1
14.3.1.58	Safety Population	Plot of Treatment-Emergent GI Abdominal-Related Adverse Events Leading to Discontinuation of Study Drug by Study Month, Part 1
14.3.5.19	Safety Population	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities, Part 1
14.3.5.20	Safety Population	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT, Part 1
14.3.5.20.ES	Safety Population	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT, Entire Study
14.3.5.21	Safety Population	Liver Test Safety Panel Over Time, Baseline vs. On-Study, Part 1
14.3.5.21.ES	Safety Population	Liver Test Safety Panel Over Time, Baseline vs. On-Study, Entire Study
14.3.5.22	Safety Population	Distribution of Liver Tests Over Time: ALP, ALT, AST, and Bilirubin, Part 1
14.3.5.22.ES	Safety Population	Distribution of Liver Tests Over Time: ALP, ALT, AST, and Bilirubin, Entire Study
14.3.5.23	Safety Population	Distribution of Cholesterol and Triglycerides Over Time, Part 1
14.3.5.23.ES	Safety Population	Distribution of Cholesterol and Triglycerides Over Time, Entire Study
14.3.5.25	Safety Population	Kaplan-Meier Plot of Time to First Occurrence of Grade 3 or 4 ALT, Part 1
14.3.5.27	Safety Population	Kaplan-Meier Plot of Time to First Occurrence of Grade 3 or 4 AST, Part 1
14.3.5.29	Safety Population	Kaplan-Meier Plot of Time to First Occurrence of Grade 3 or 4 Total Bilirubin, Part 1
14.3.6.2	Safety Population	Distribution of Diastolic and Systolic Blood Pressure Over Time, Part 1
14.3.6.2.ES	Safety Population	Distribution of Diastolic and Systolic Blood Pressure Over Time, Entire Study
14.3.6.4	Safety Population	Distribution of Diastolic and Systolic Blood Pressure, Part 1; Baseline and All Post-Baseline Observations
14.3.6.4.ES	Safety Population	Distribution of Diastolic and Systolic Blood Pressure, Entire Study; Baseline and All Post-Baseline Observations
14.3.7.6	Safety Population	Distribution of QTcF Observed Changes Relative to Baseline Over Time, Part 1
14.3.7.6.ES	Safety Population	Distribution of QTcF Observed Changes Relative to Baseline Over Time, Entire Study
14.3.7.7	Safety Population	Distribution of QTcF Observed Changes Relative to Baseline, Part 1; Baseline and All Post-Baseline Observations
14.3.7.7.ES	Safety Population	Distribution of QTcF Observed Changes Relative to Baseline, Entire Study; Baseline and All Post-Baseline Observations
14.4.1.2	ITT Population	Plot of Mean WPAI Scores Over Time, Part 1
14.4.1.2.ES	ITT Population	Plot of Mean WPAI Scores Over Time, Entire Study
14.4.1.3	ITT Population	Plot of Mean Change from Baseline WPAI Scores Over Time, Part 1
14.4.1.3.ES	ITT Population	Plot of Mean Change from Baseline WPAI Scores Over Time, Entire Study
14.4.2.2	ITT Population	Plot of Mean EQ-5D-5L VAS Scores Over Time, Part 1
14.4.2.2.ES	ITT Population	Plot of Mean EQ-5D-5L VAS Scores Over Time, Entire Study
14.4.2.3	ITT Population	Plot of Mean Change from Baseline EQ-5D-5L VAS Scores Over Time, Part 1

Output Number	Population Title	Output Title
14.4.2.3.ES	ITT Population	Plot of Mean Change from Baseline EQ-5D-5L VAS Scores Over Time, Entire Study
14.4.2.5	ITT Population	Plot of Mean EQ-5D-5L VAS Scores from Usual Event Over Time, Part 1
14.4.2.5.ES	ITT Population	Plot of Mean EQ-5D-5L VAS Scores from Usual Event Over Time, Entire Study
14.4.2.7	ITT Population	Plot of Mean EQ-5D-5L Index Scores Over Time, Part 1
14.4.2.7.ES	ITT Population	Plot of Mean EQ-5D-5L Index Scores Over Time, Entire Study
14.4.2.8	ITT Population	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Over Time, Part 1
14.4.2.8.ES	ITT Population	Plot of Mean Change from Baseline EQ-5D-5L Index Scores Over Time, Entire Study
14.4.2.10	ITT Population	Plot of Mean EQ-5D-5L Index Scores from Usual Event Over Time, Part 1
14.4.2.10.ES	ITT Population	Plot of Mean EQ-5D-5L Index Scores from Usual Event Over Time, Entire Study
14.4.3.2	ITT Population	Plot of Mean TSQM Scores Over Time, Part 1
14.4.3.2.ES	ITT Population	Plot of Mean TSQM Scores Over Time, Entire Study
14.4.3.3	ITT Population	Plot of Mean Change from Baseline TSQM Scores Over Time, Part 1
14.4.3.3.ES	ITT Population	Plot of Mean Change from Baseline TSQM Scores Over Time, Entire Study
14.6.1.2	PK-PD Population	Scatterplot of Kallikrein Inhibition (%) and BCX7353 Plasma Concentration/4 by Study Visit, Part 1
14.6.1.2.ES	PK-PD Population	Scatterplot of Kallikrein Inhibition (%) and BCX7353 Plasma Concentration/4 by Study Visit, Entire Study

17.1.3.2. BCX7353-301 and BCX7353-302 Combined Study Output

Output Number	Population Title	Output Title
14.1.1.2.C	All Subjects	CONSORT Diagram, Part 1
14.1.5.2.C	Safety Population	Plot of Duration of Exposure to Study Drug [1], Part 1
14.1.5.4.C	Safety Population	Histogram Plot of Treatment Compliance, Part 1
14.2.1.7.C	ITT Population	Box Plot of Expert- or Investigator-Confirmed Event Rate By Dose for Entire Dosing Period, Part 1
14.2.1.8.C	ITT Population	Cumulative Distribution Plot of Individual Expert- or Investigator-Confirmed Event Rate for Entire Dosing Period, Part 1
14.2.1.9.C	ITT Population	Forest Plot of Results of Sensitivity Analyses of Expert- or Investigator-Confirmed Event Rate for Entire Dosing Period, Part 1
14.2.1.10.C	ITT Population	Forest Plot of Results of Subgroup Analyses of Expert- or Investigator-Confirmed Event Rate for Entire Dosing Period, Part 1
14.2.1.12.C	ITT Population	Box Plot of Expert- or Investigator-Confirmed Event Rate By Dose for Effective Dosing Period, Part 1
14.2.1.13.C	ITT Population	Cumulative Distribution Plot of Individual Expert- or Investigator-Confirmed Event Rate for Effective Dosing Period, Part 1
14.2.1.20.C	ITT Population	Plot of Investigator-Confirmed Events and Use of On-Demand Medication, Part 1
14.2.2.2.C	ITT Population	Histogram Plot of Baseline Expert- or Investigator-Confirmed Event Rate, Part 1
14.2.2.3.C	ITT Population	Plot of Mean Expert- or Investigator-Confirmed Event Rate by Month, Part 1
14.2.2.4.C	ITT Population	Scatterplot of On-Study Expert- or Investigator-Confirmed Event Rate vs Baseline Expert- or Investigator-Confirmed Event Rate, Part 1
14.2.2.5.C	ITT Population	Plot of Change from Baseline Expert- or Investigator -Confirmed Event Rate vs. Baseline Expert-Confirmed Event Rate, Part 1
14.2.2.6.C	ITT Population	Plot of Change from Baseline Expert- or Investigator -Confirmed Event Rate vs. Percent Compliance, Part 1
14.2.2.7.C	ITT Population	Plot of Change from Baseline Expert- or Investigator-Confirmed Event Rate vs. Baseline Expert- or Investigator-Confirmed Event Rate by Gender, Part 1
14.2.2.8.C	ITT Population	Plot of Baseline and Expert- or Investigator-Confirmed Attack Rate By Subject

Output Number	Population Title	Output Title
14.2.2.9.C	ITT Population	Plot of Individual Expert-Confirmed Attack Rate by Month
14.2.2.10.C	ITT Population	Plot of Change from Baseline Expert- or Investigator-Confirmed Attack Rate vs. Baseline Expert- or Investigator-Confirmed Attack Rate, Part 1 By Gender
14.2.3.3.C	ITT Population	Plot of Mean AE-QoL Scores Over Time, Part 1
14.2.3.4.C	ITT Population	Plot of Mean Change from Baseline AE-QoL Scores Over Time, Part 1
14.2.3.5.C	ITT Population	Cumulative Distribution of Total AE-QoL Change from Baseline at Week 24
14.2.3.6.C	ITT Population	Forest Plot of Results of Subgroup Analyses of Total AE-QOL Change from Baseline at Week 24, Part 1
14.2.6.2.C	ITT Population	Waterfall Plot of Relative Reduction from Baseline in Adjusted Expert-Confirmed Event Rate, Part 1
14.2.6.4.C	ITT Population	Forest Plot of Results of Additional Subgroup Analysis for Proportion of Subjects with a 50% Relative Reduction from Baseline in Adjusted Expert-Confirmed Event Rate , Part 1
14.2.6.5.C	ITT Population	Forest Plot of Results of Additional Subgroup Analysis for Proportion of Subjects with a 70% Relative Reduction from Baseline in Adjusted Expert- or Investigator-Confirmed Event Rate , Part 1
14.2.6.6.C	ITT Population	Forest Plot of Results of Additional Subgroup Analysis for Proportion of Subjects with a 90% Relative Reduction from Baseline in Adjusted Expert- or Investigator-Confirmed Event Rate , Part 1
14.2.8.2.C	ITT Population	Kaplan-Meier Plot of Time to First Expert- or Investigator-Confirmed Event, Part 1
14.2.9.2.C	ITT Population	Kaplan-Meier Plot of Time to First Use of Targeted HAE Rescue Medication to Treat an Expert- or Investigator-Confirmed Event, Part 1
14.6.1.2.C	PK-PD Population	Scatterplot of Kallikrein Inhibition (%) and BCX7353 Plasma Concentration/4 by Study Visit, Part 1

17.2. Data Display Specifications

Table, Listing, and Figure shells will be stored in a separate document.

17.3. List of Preferred Terms, High Level Terms, and High Level Group Terms for GI Abdominal-Related AEs

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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
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
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
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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
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
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
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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
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 defaecation conditions	Gastrointestinal disorders
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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
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
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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
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
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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10067752	Oesophageal hypomotility	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
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