STATISTICAL ANALYSIS PLAN
PHASE II-III

VERSION: 1.0

DATE OF PLAN: 26 February 2019

BASED ON:

Protocol Version 5.0 (US only): 7 February 2019
Protocol Version 4.0: 5 October 2018
Protocol Version 3.0: 6 December 2017
Protocol Version 2.0: 5 December 2017
Protocol Version 1.0: 20 September 2017

STUDY TITLE:

An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema

STUDY DRUG:

BCX7353

PROTOCOL NUMBER:

BCX7353-204

SPONSOR:

BioCryst Pharmaceuticals, Inc.
4505 Emperor Blvd., Suite 200
Durham, NC 27703
(919) 859-1302

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

CONFIDENTIAL

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

Jennifer A. Elder, PhD
Project Statistician
PharPoint Research, Inc.

Signature

26 Feb 2019
Date

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

Sharon C. Murray
Signature

26 FEB 2019
Date

This document has been reviewed and accepted by:

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

Signature

26 FEB 2019
Date

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

M Cornpropst
Signature

26 Feb 2019
Date

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

Signature

26 FEB 2019
Date

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company **BioCryst Pharmaceuticals, Inc.**	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: BCX7353	**Page:**	
Name of Active Ingredient: (R)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride		
Title of Study: An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema		
Investigators: Study Centers: Global, multiple study centers		
Studied period (years): 2	**Phase of development:** 2	

Objectives:

Primary:

- To evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 in subjects with hereditary angioedema (HAE)

Secondary:

- To assess the effectiveness (ie, HAE attack frequency, severity, and disease activity over time) of BCX7353 during long-term administration
- To evaluate quality of life (QoL) during long-term administration of BCX7353
- To evaluate subject's satisfaction with medication during long-term administration of BCX7353

Methodology:

This is a 2-arm, open-label study to evaluate the long-term safety and effectiveness of 2 dose levels of orally administered BCX7353 in subjects with HAE who either have participated in a previous study of BCX7353 or who are expected to derive benefit from an oral treatment to prevent angioedema attacks.

Subjects who meet the inclusion and exclusion criteria will be enrolled into the study. Subjects will be allocated to 1 of 2 treatment groups:

- Group 1: BCX7353 110 mg administered orally
- Group 2: BCX7353 150 mg administered orally

Subjects will receive 96 weeks of daily BCX7353. Study visits will occur at Screening, Baseline/Day 1, and at Weeks 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. Telephone contact will occur at Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92. An independent Data Monitoring Committee (DMC) will review the safety data from this study in concert with accumulating safety information generated across the BCX7353 clinical development program. For this study, the DMC will convene and review safety data once the first 10 subjects enrolled complete 12 weeks of dosing and approximately every 12 weeks thereafter until the last enrolled subject completes Week 48. After the last subject completes Week 48, the DMC will be provided with data every 6 months until the last subject completes Week 96, although a formal meeting of DMC members may not be required.

Subjects who have previously been treated with BCX7353 are not required to undergo a screening visit if the last dose of study drug was < 84 days ago. If the subject is directly rolling over from another BCX7353 study either without treatment interruption or with < 14 days of study drug interruption, the final study visit assessments in the prior BCX7353 study will serve as the baseline values for this study; however, relevant baseline assessments for this study will be performed at the final on-treatment visit for the prior study visit. Enrollment without treatment interruption into the current study will obviate the requirement for a follow-up visit in the previous BCX7353 study.

Subjects will be eligible to receive study drug (BCX7353) for 96 weeks or until the Sponsor discontinues development of the product, whichever comes first. Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related adverse event (AE). The study will be discontinued if ongoing regulatory or institutional review board/ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the ongoing conduct of the study. Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology and urinalysis), vital signs, electrocardiograms (ECGs), and physical examinations. The main study will be comprised of adult subjects (≥ 18 years of age); a substudy in participating regions will be included that allows adolescent subjects ≥ 12 to 17 years of age to screen and enroll. Subjects will document all angioedema attacks that occur while on study drug. Angioedema attacks will be treated in accordance with the subject's normal standard of care. Treatments for angioedema attacks will not be provided by the Sponsor.

Subject-reported outcomes will be completed by subjects for the disease-specific Angioedema Quality of Life (AE-QoL) questionnaire and Treatment Satisfaction Questionnaire for Medication (TSQM), where validated translations are available. Additionally, subjects will be asked about time away from work or school.

Number of Subjects (planned and analyzed):

Approximately 225 subjects

Diagnosis and main criteria for inclusion (see protocol section 8.2):

Inclusion Criteria:

1) Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy)

2) Subjects with Type I or Type II HAE who either have:

a) Participated in a BCX7353 study OR

b) In countries open to recruitment of treatment-naïve subjects under a prior version of Protocol BCX7353-204:
In the opinion of the Investigator, subjects are expected to benefit from an oral treatment for the prevention of angioedema attacks and have a clinical diagnosis of HAE Type I or II, defined as having a C1 esterase inhibitor (C1-INH) functional level below 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 intercritical period (ie, subject is not having an HAE attack), 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 I or II assessed during the screening period; 2) a confirmed family history of C1-INH deficiency; 3) a C4 redrawn and retested during an attack with the results below the LLN reference range measured during the screening period

For subjects with a C1-INH function ≥ 50% but less than the assay LLN, a SERPING-1 gene mutation known or likely to be associated with HAE Type I or II, assessed during the screening period OR a repeat C1-INH functional test < 50% will be considered acceptable for enrollment.

3) Subject weight ≥ 40 kg

4) Access to appropriate medication for the treatment of acute HAE attacks

5) Agreement to use acceptable effective contraception

6) Able to provide written, informed consent. Subjects aged ≥ 12 to 17 years who are screening for the substudy must be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent

7) In the opinion of the Investigator, the subject is able 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 including diary recording of HAE attacks

Exclusion Criteria:

1) Pregnancy or breast feeding or planned pregnancy during the study period.

2) Any clinically significant medical condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's safety or ability to participate in the study.

3) Discontinuation of study drug due to hypersensitivity reaction to BCX7353 in a prior study. This includes subjects who had a rash of any severity identified as possibly, probably, or definitely related to active BCX7353 in the previous study.

4) Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or participation in the study.

5) Clinically significant abnormal ECG including but not limited to, a corrected QT interval using Fridericia's method (QTcF) > 470 msec for women, a QTcF > 450 msec for men, a PR interval > 220 msec (both sexes), or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.

6) Unacceptable noncompliance in a previous BCX7353 study as assessed by the Sponsor or Investigator.

7) Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other cardiovascular disease.

8) Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.

9) History of or current implanted defibrillator or pacemaker.

10) Use of concomitant medications that are metabolized by CYP2D6, CYP2C9, CYP2C19, or CYP3A4 and that have a narrow therapeutic range, including those known to prolong the QT interval within 7 days of the baseline visit or planned initiation during the study.

11) 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.

12) Any laboratory parameter abnormality that, in the opinion of the Investigator, is clinically significant and relevant for this study.

13) Calculated creatinine clearance ≤ 30 mL/min or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value ≥ 3 times the upper limit of the normal (ULN) reference range value at screening or last available visit prior to enrollment.

14) Investigational drug exposure, other than BCX7353, within 30 days prior to the screening visit (or baseline if no screening visit).

15) Severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.

16) History of alcohol or drug abuse within the previous year, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 units of alcohol/day).

17) For subjects undergoing a screening visit, a positive drugs of abuse screen (unless used as a medical treatment [eg, with a prescription]).

18) For subjects undergoing a screening visit, current infection with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus.

19) Subjects with an immediate family relationship to either Sponsor employees, the Investigator or employees of the study site who are named on the delegation log.

20) Subjects who are held in an institution by a government or judicial order.

Test product, dose and mode of administration:

BCX7353 capsules, to be administered orally. Subjects will receive a dose of 110 mg or 150 mg once per day.

Duration of treatment:

Subjects will be eligible to receive BCX7353 for 96 weeks or until the Sponsor discontinues development of the product; whichever comes first. Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related AE.

Reference therapy, dose and mode of administration:

Not applicable.

Criteria for evaluation (see protocol section 13.3.5 and 13.3.6):

Effectiveness:

Effectiveness will be evaluated by the number of angioedema attacks and related details (timing, duration of symptoms, anatomical location, treatment), number of days with angioedema symptoms, assessment of attack severity, discontinuations due to lack of efficacy, and number of hospitalizations and clinic visits.

Safety:

Safety will be evaluated by 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 DMC will review safety data in accordance with a separate DMC Charter.

Subject Reported Outcomes/Quality of Life:

QoL will be assessed using the AE-QoL questionnaire and subject's satisfaction with their medication using the TSQM. The number of days lost from school and/or work will also be assessed.

Statistical methods:

Analysis of Safety: Safety endpoints will be summarized by treatment group and will include the proportion of subjects with treatment-emergent AEs (TEAEs); who discontinue due to a TEAE; who experience a treatment-emergent serious adverse event (SAE); who experience a Grade 3 or 4 TEAE; who experience a treatment-emergent, treatment-related AE consistent with a drug rash as identified by investigator as an event of special interest; who experience treatment-emergent, abdominal-related gastrointestinal AEs; and who experience Grade 3 or 4 laboratory abnormalities.

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ classification (SOC). The occurrence of TEAEs will be summarized using MedDRA PT, SOC, and severity. In addition to severity, AEs and SAEs will also be summarized based on Investigator assessment of relationship to study drug.

Time to discontinuation due to a TEAE, and time to development of drug-related rash will be estimated using the Kaplan-Meier method. For those with a drug-related rash, clinical and lab findings will be summarized and the proportion of subjects who successfully continued therapy following onset of rash.

Descriptive statistics for vital signs, weight, and clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded and flagged automatically with a reference range scale. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized. Laboratory toxicity shifts from baseline to the worst post-baseline value as well as the last visit will be summarized. The number and percentage of subjects having elevations in ALT, AST, or bilirubin abnormalities in relation to fold above the ULN will be summarized according to the Food and Drug Administration's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry.

Clinically significant abnormal ECG findings will be summarized by study visit. Changes from baseline in ECG parameters will also be summarized by study visit. The number and proportion of subjects with clinically important absolute and change from baseline thresholds in QTcF will be summarized.

Analysis of Effectiveness: Effectiveness endpoints will be analyzed by treatment group and will include angioedema attack rate, durability of response, number and proportion of days with angioedema symptoms, angioedema attack medication administrations, discontinuations due to lack of efficacy, and disease severity. The durability of response assessment will be based on attack rate trend over time, and the attack rate change from observed values for each subject in their respective previous efficacy study (where applicable) over time.

Additional related details of HAE attacks (eg, symptoms, anatomical location, hospitalizations, emergency room visits, attack severity, attack duration) and number of days lost from work and/or school due to attacks will be listed and summarized using descriptive statistics.

No formal tests of hypotheses will be conducted.

Quality of Life Analyses: The baseline, follow-up and change from baseline in the domain scores of the AE-QoL as well as the composite score of each instrument will be calculated and summarized by treatment group. Individual items will be analyzed to understand their contribution to the domain sub-scores. A TSQM global satisfaction score will be calculated as validated. Data on the global score as well as relevant subscales will be listed and summarized.

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AE-QoL	Angioedema Quality of Life
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
BCX7353	Study Drug
BMI	Body Mass Index
C1-INH	C1 Esterase Inhibitor
C1-INHf	Functional C1 Esterase Inhibitor
C3	Complement Component 3
C4	Complement Component 4
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
EOSI	Event of Special Interest
GI	Gastrointestinal
HAE	Hereditary Angioedema
HLGT	High Level Group Term
ICH	International Council for Harmonisation
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities Terminology
N	Total Sample Size
PBMC	Peripheral Blood Mononuclear Cells
PK	Pharmacokinetic
PT	Preferred Term
QD	Daily, Every Day
QTcF	Fridericia's Corrected QT Interval
SAE	Serious Adverse Event

Abbreviation	Term
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TSQM	Treatment Satisfaction Questionnaire for Medications
ULN	Upper Limit of Normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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 Protocol BCX7353-204. A summary of protocol revisions is provided in Table 2.

Table 2: Protocol Revision Chronology

Protocol	Date	Key Information
Protocol Version 1.0	20 September 2017	Original
Protocol Version 2.0	5 December 2017	Made administrative clarifications, changed design to include 2 dose groups, increased sample size, removed option to reduce dose, AECT assessment removed, updated prohibited medications
Protocol Version 3.0	6 December 2017	Made administrative clarifications, expanded inclusion criteria to include subjects naïve to BCX7353 in selected countries
Protocol Version 4.0	5 October 2018	Made administrative clarifications, expanded subject numbers, expanded inclusion criteria, extended study duration to 96 weeks, added study data, and clarified discontinuation criteria
Protocol Version 5.0	7 February 2019	Expanded subject numbers, added US sites, added subjects with recent androgen use.

Abbreviations: AECT = Angioedema Control Test; US = United States.

This SAP was developed in accordance with 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 effectiveness for Study BCX7353-204. Study population definitions, derivations of variables, handling of missing data, and other information necessary for analysis of study data are provided. Planned tables, figures, and listings are specified. All decisions regarding final analysis, as defined in this SAP document, will be made prior to database lock of the study data. Further information can be found in the protocol and electronic Case Report Forms (eCRFs).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 in subjects with hereditary angioedema (HAE).

3.1.2. Secondary Objective

The secondary objectives are as follows:

- To assess the effectiveness (ie, HAE attack frequency, severity and disease activity over time) of BCX7353 during long-term administration
- To evaluate quality of life during long-term administration of BCX7353
- To evaluate subject's satisfaction with medication during long-term administration of BCX7353

3.2. Study Endpoints

3.2.1. Safety Endpoints

The safety endpoints will include the following:

- The proportion of subjects with treatment-emergent adverse events (TEAEs)
- The proportion of subject with treatment-emergent, treatment-related adverse events (AEs) consistent with a drug rash
- The proportion of subjects who discontinue BCX7353 due to a TEAE
- The proportion of subjects with treatment-emergent serious adverse events (TESAEs)
- The proportion of subjects Grade 3 or 4 TEAEs
- The proportion of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities.

3.2.2. Effectiveness Endpoints

Effectiveness endpoints will include the following:

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Subject-reported outcomes (HAE disease-specific Angioedema Quality of Life [AE-QoL] questionnaire scores and Treatment Satisfaction Questionnaire for Medication [TSQM]) global satisfaction scores
- Number of attacks requiring attack medication
- Discontinuations due to lack of efficacy
- Severity of attacks

4. STUDY DESIGN

4.1. Summary of Study Design

This is a 2-arm, open-label study to evaluate the long-term safety and effectiveness of 2 dose levels of orally administered BCX7353 in subjects with HAE who either have participated in a previous study of BCX7353, or who are expected to derive benefit from an oral treatment to prevent angioedema attacks.

Subjects who meet the inclusion and exclusion criteria will be enrolled into the study. Subjects will be allocated to 1 of 2 treatment groups:

Group 1: BCX7353 110 mg administered orally

Group 2: BCX7353 150 mg administered orally

Subjects will receive 96 weeks of daily BCX7353. Study visits will occur at Screening, Baseline/Day 1, and at Weeks 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. Telephone contact will occur at Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92. An independent data monitoring committee (DMC) will review the safety data from this study in concert with accumulating safety information generated across the BCX7353 clinical development program. For this study, the DMC will convene and review safety data once the first 10 subjects enrolled complete 12 weeks of dosing and approximately every 12 weeks thereafter until the last enrolled subject completes the study. After the last subject completes Week 48, the DMC will be provided with data every 6 months until the last subject completes Week 96, although formal meeting of the DMC members will not be required.

Subjects who have previously been treated with BCX7353 are not required to undergo a screening visit if the last dose of study drug was < 84 days ago; however, these subjects are required to have a baseline visit. If the subject is directly rolling over from another BCX7353 study either without treatment interruption or with < 14 days of study drug interruption, the final study visit assessments in the prior BCX7353 study will serve as the baseline values for this study; however, relevant baseline assessments for this study will be performed at the final on-treatment visit for the prior study visit. Enrollment without treatment interruption into the current study will obviate the requirement for a follow-up visit in the previous BCX7353 study.

Subjects will be eligible to receive BCX7353 for 96 weeks or until the Sponsor discontinues development of the product; whichever comes first. Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related AE. The study will be discontinued if ongoing regulatory or institutional review board/ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the ongoing conduct of the study. Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology and urinalysis), vital signs, electrocardiograms (ECGs), and physical examinations.

The main study will be comprised of adult subjects (≥ 18 years of age); a substudy in participating regions will be included that allows adolescent subjects ≥ 12 to 17 years of age to screen and enroll. Subjects will document all angioedema attacks that occur while on study drug. Angioedema attacks will be treated in accordance with the subject's normal standard of care. Treatments for angioedema attacks will not be provided by the Sponsor.

Subject-reported outcomes will be completed by subjects for the disease-specific AE-QoL questionnaire and TSQM, where validated translations are available. Additionally, subjects will be asked about time away from work or school.

4.2. Definition of Study Drugs

Only the investigational product BCX7353 will be used as a study drug in this trial. Two dose levels will be examined.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

No sample size calculations were conducted for this open-label, long-term safety study. The purpose of the study is to characterize the safety profile of 110 and 150 mg daily doses of BCX7353.

Approximately 225 subjects (approximately 110 subjects at each dose level) may be enrolled in this study, to allow continued access to BCX7353 following a subject's participation in a prior BCX7353 study, or to provide access to BCX7353 for additional subjects who, in the opinion of the Investigator, are expected to benefit from treatment with an oral treatment for the prevention of angioedema attacks.

4.4. Allocation to Treatment Group

This is an open-label study. Subjects will be centrally allocated to 1 of 2 treatment groups:

- Group 1: BCX7353 110 mg administered orally once daily (QD)
- Group 2: BCX7353 150 mg administered orally QD

Sites will request a treatment allocation for eligible subjects in the Interactive Response System, preferably after all baseline assessments to reconfirm eligibility have completed. If required by site procedures (ie, dispensing of allocated study drug must occur through a pharmacy), the treatment allocation request may be made on the business day prior to the planned baseline visit.

Version 1 of the protocol included only the BCX7353 150 mg dose for those in previous BCX7353 clinical trials. As Version 1 of the protocol only utilized the 150 mg dose, sites initiated under protocol Version 1 have all subjects allocated to the 150 mg dose. Protocol Version 2 allowed for subjects to be treated with either the 110 or 150 mg dose. Protocol Version 3 broadened the inclusion criteria to allow for inclusion of subjects who had not previously participated in clinical trials of BCX7353. Sites initiated under Protocol Versions 2 or 3, or who were initially included under Protocol Version 1 and later changed versions, may have subjects allocated to 150 or 110 mg.

No changes to the allocation scheme were made in Protocol Versions 4 and 5.

4.5. Assessments

The schedule of assessments is provided in Table 3.

Table 3: Schedule of Clinical Assessments

Assessment	***Screening Period***	***Baseline Visit[a]***	***Treatment Period (Visit schedule)***					***End of Study Assessment***
	Screening Visit (Up to Day -28)	**(Day 1)**	**Week 2 (Day 15 ± 2 days)[b]**	**Week 4 (Day 29 ± 2 days)**	**Week 8 (Day 57 ± 2 days)**	**Week 12 (Day 85 ± 2 days)**	**Visits every 12 weeks until 96 weeks (± 6 days)**	**3 weeks (± 3 days) after last dose of study drug**
Informed consent[c]	X	X						
Clinic staff phone call/ communication							X[d]	
Inclusion-exclusion criteria	X	X						
Medical and medication history, HAE medical and medication history[e]	X	X						
Weight/height/BMI[f]	X	X		X	X	X	X	X
Drugs of abuse screen[g]	X							
Physical examination[h]	X	X		X	X	X	X	X
Pregnancy test[i]	X	X		X	X	X	X	X
Vital signs[j]	X	X		X	X	X	X	X
FSH[k]	X	X						
HIV, HCV, HBV serology	X							
Diagnosis of HAE established[l]	X							
Clinical chemistry/ hematology/coagulation[g]	X	X	X[b]	X	X	X	X	X
Troponin I and Troponin T, CK-MB		X		X	X	X	X	X
NGAL and ACR		X				X	X	X
Urinalysis[g]	X	X	X[b]	X	X	X	X	X

Sample for HLA analysis and C3[m]		X						
Assessment	***Screening Period***	***Baseline Visit[a]***	***Treatment Period (Visit schedule)***					***End of Study Assessment***
	Screening Visit (Up to Day -28)	**(Day 1)**	**Week 2 (Day 15 ± 2 days)[b]**	**Week 4 (Day 29 ± 2 days)**	**Week 8 (Day 57 ± 2 days)**	**Week 12 (Day 85 ± 2 days)**	**Visits every 12 weeks until 96 weeks (± 6 days)**	**3 weeks (± 3 days) after last dose of study drug**
Optional sample for exploratory PG[n]		X						
ECG[o]	X	X		X	X	X	X	X
AE-QoL, assessment of days lost from work and/or school and TSQM[p]		X		X	X	X	X	X
Concomitant medications[q]	X	X	X	X	X	X	X	X
PK plasma sample[r]		X		X	X	X	X	X
AEs	X	X	X	X	X	X	X	X
Diary instruction/ review/set-up[s]	X	X		X	X	X	X	X
Allocation to study drug[t]		X						
Diary completion[u]	←	—	—	—	—	—	→	
Study drug dosing		←	—	—	—	—	→	
Study drug accountability/ dispensing		X		X	X	X	X	X

Abbreviations: ACR = spot urine microalbumin to creatinine ratio; AE = adverse event; AE-QoL = Angioedema Quality of Life; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; C1-INH = C1 esterase inhibitor; C3 = complement 3; C4 = complement 4; CK-MB = creatine kinase MB isoenzyme; CRF = case report form; ECG = electrocardiogram; 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 response system; LLN = lower limit of normal; NGAL = neutrophil gelatinase-associated lipocalin; PG = pharmacogenomic; PK = pharmacokinetic; QoL = quality of life; QTcF = QT interval corrected using Fridericia's method; TSQM = Treatment Satisfaction Questionnaire for Medication.

[a] The baseline visit should be within 28 days of the screening visit. Subjects who have interrupted study drug from a previous BCX7353 study for < 84 days are not required to undergo a screening visit. For subjects directly rolling over from another BCX7353 study without treatment interruption or subjects who interrupt study drug for < 14 days, the final on-treatment visit in the prior BCX7353 study will be considered the baseline visit for this study.

[b] The Week 2 visit will consist of monitoring liver function tests only [ALT, AST, GGT, total and direct bilirubin, ALP]; urine and additional tubes of blood may be required to accommodate reflex testing for abnormal GGT (see protocol Table 7). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.
[c] Informed consent will be signed at the screening visit for subjects requiring a screening visit and will be signed for all other subjects at the baseline visit or final on treatment visit in the parent study (which serves as the subject's baseline visit in this study).
[d] After the Week 12 visit, clinic staff must contact the subjects at least once every 4 weeks between clinic visits to assess the subject's overall wellbeing and any issues with regards to study drug tolerability. During all calls, sites will also discuss study drug compliance and any issues with the diary or study drug.
[e] Medical history and medication history will be completed at screening (for subjects requiring a screening visit) and at baseline. At the Screening visit (or baseline for those with no screening visit), the HAE Medical and Medication history form will be updated from the previous HAE study, as applicable, with additional questions to be answered if provided.
[f] BMI calculation and height at screening; weight is to be recorded at each in-clinic visit.
[g] Please see protocol Table 7 for analytes to be assessed. The lipid panel as part of clinical chemistry will only be measured at baseline, Week 12 and then every 12 weeks.
[h] Full physical examinations will be performed at screening and baseline; symptom-directed physical examinations will be performed at all post-baseline visits.
[i] For women of childbearing potential, 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 dispensing study drug.
[j] To include blood pressure and pulse rate. Temperature and respiratory rate will be captured at screening and baseline only. Prior to obtaining vital signs, subjects should rest in a supine position for at least 5 minutes.
[k] For a woman who declares that they have been post-menopausal ≤ 2 years or was considered a woman of childbearing potential in the previous study. The sample may be drawn at baseline for those who those who do not undergo a screening visit; however, the subject must have a negative urine pregnancy test at baseline prior to receiving study drug.
[l] For subjects that have not participated in a previous BCX7353 study, a clinical diagnosis of hereditary angioedema Type 1 or Type 2, defined as having a C1-INH functional level below 50% and a C4 level below the lower LLN reference range, as assessed during the Screening period. In the absence of a low C4 value drawn during the inter-critical period, one of the following is acceptable to confirm the diagnosis of HAE assessed during the Screening period: 1) a SERPING-1 gene mutation known or likely to be associated with HAE Type I or II; 2) a confirmed family history of C1-INH deficiency; 3) a C4 redrawn and retested during an attack with the results below the LLN reference range.
[m] A sample for HLA analysis will be drawn on subjects who have not donated one in a previous study. The sample may be drawn at baseline or at any subsequent visit.
[n] All ECGs during the study will be single assessments with the exception of baseline which will be obtained in triplicate. An ECG should be repeated for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec. Prior to obtaining an ECG, subjects should rest quietly in a supine position for at least 10 minutes.
[o] AE-QoL and TSQM will be administered once at baseline and at Weeks 4, 8, 12, and every 12 weeks thereafter. Additional questions regarding loss of time from work/school will be instituted at each visit to more fully characterize QoL.
[p] Concomitant medications will be reviewed at each visit and on treatment, new concomitant medications will be reviewed to determine whether there are any contraindications or dosage adjustments required.
[q] The actual date and time of PK blood draw, and time of last study drug dose (relative to PK sample draw) will be captured in the CRF.
[r] Site staff will review the diary instructions with the subjects at the first clinic visit. Subjects will be instructed to bring the completed diary with them to their visits. Any issues with the entered data in the diary will be discussed with the subject and corrections will be made by the subject as required.
[s] Sites will request a treatment allocation in the IXRS for eligible subjects at the Day 1 visit
[t] At any time the diary is in a subject's possession, they will enter HAE attacks and relevant details and dosing information (as applicable) once per day.

5. PLANNED ANALYSES

5.1. Interim Analyses

DMC meetings will occur after the first 10 subjects have completed 12 weeks of treatment and every 12 weeks thereafter until the last enrolled subject completes 48 weeks, or as DMC meetings are conducted in concert for related BCX7353 studies.

Before each scheduled DMC meeting, a packet of summary materials will be prepared and distributed for the Committee's review. The packet will include study disposition, demographic, and safety information by treatment group. Study disposition will consist of the number of subjects screened, the number of subjects allocated to treatment, the number of subjects who received treatment, the number of subjects who completed the study, the number of subjects who were withdrawn from the study and the primary reasons for withdrawal, the number of subjects ongoing in the study, the number of subjects who completed dosing in the entire study, the number of subjects withdrawn from the study medication, and the primary reasons for withdrawal, and the number of subjects ongoing on study medication. Demographic information will consist of age, gender, race, ethnicity, weight, height, and body mass index (BMI).

Safety summaries will include an overall summary of TEAEs (overall numbers of subjects with TESAEs, TEAEs, drug-related TEAEs, TEAEs leading to discontinuation of study drug, Grade 3 or 4 TEAEs, and drug-related TEAEs of Grade 3 or 4), summaries of TEAEs by system organ class (SOC) and preferred term (PT), which include TESAEs, TEAEs, Grade 3 or 4 TEAEs, TEAEs leading to discontinuation of study drug, and summaries of subjects with treatment-emergent laboratory abnormalities overall and for each laboratory panel by parameter and grade. Relevant review materials will normally be sent to DMC members and open session participants 5 business days before each scheduled meeting.

All summary materials will be distributed via email.

An internal analysis will be conducted at the time of the BCX7353-302, Part 1 analysis. This analysis will be used to write the draft report for the BCX7353-204 study.

An interim analysis will be performed when approximately 100 subjects at either the 110 or 150 mg dose from a combination of studies BCX7353-204 and BCX7353-302 complete 48 weeks. Additionally, an integrated analysis of safety and effectiveness involving data from both studies will be performed. This analysis will be used for regulatory submissions.

Other interim analyses may be performed as needed during the course of the study to support regulatory filings and safety updates at the request of the Sponsor.

5.2. Final Analyses

The final analysis will be completed after the last subject completes the final study visit or discontinues the study and the resulting clinical database has been cleaned, quality checked, locked, and authorized for analysis.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Tables and listings will be prepared in accordance with the current ICH Guidelines (ICH E3 Structure and Content of Clinical Study Reports 1996). The information and explanatory notes in the "footer" or bottom of each table and listing will include the following information:

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

In general, tables will be formatted with columns displaying findings for all subjects by treatment group and all subjects across treatment groups.

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

These listings will generally be sorted by treatment group, subject identifier, and visit, if applicable.

Summary displays will be presented by treatment. A column that combines both active treatments will also be included. Table 4 shows treatment descriptors for displays.

Table 4: Treatment Descriptors for Displays

Sort Order	Treatment	Notes
1	BCX7353 110 mg	110 mg
2	BCX7353 150 mg	150 mg
3	Total	Combined 110 mg and 150 mg groups

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

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

Tables, listings, and figures will be numbered using a decimal system to indicate the main levels of unique displays and sub-levels of replicate displays. The first level represents the appendix within which the tables, figures, and listings will appear. This will be 14 for tables and figures and 16 for listings. For tables, the second level of the numbering represents the type of data; 1 for Study Population, 2 for Effectiveness, 3 for Safety, 4 for Health Outcomes, and 5 for pharmacokinetics (PK). The third level of numbering represents the type of endpoint within the data type, the fourth represents a count of displays for the endpoint, and the fifth level is used for repeated tables. For example, tables may be repeated using a different population or for a subset of subjects.

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

Listings will be numbered starting with 16.2.1 and with sequential numbering in the third level in accordance with ICH guidelines. Listings will be sorted and presented by dose, subject number, and visit, if applicable.

6.3. Data Management

A data management plan will be developed and approved prior to 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. PharPoint standard operating procedures (SOPs) will be used.

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

6.4. Data Presentation Conventions

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

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 as HH:MM for presentation.
- Wherever possible, data will be decimal aligned.

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

6.5. Analysis Populations

6.5.1. Screen Failures

Subjects who give informed written consent, but are not allocated to study treatment, and are noted as screen failures in eCRF are considered screen failures. These subjects will not be treated with study drug and will not be summarized other than on the disposition table. Data collected from screen failures may be presented on corresponding data listings.

6.5.2. Safety Population

The safety population will include all subjects who receive at least 1 dose of study drug. This population will be used in the assessment and reporting of demographic information, baseline disease characteristics, safety data, and PK concentrations. Data will be analyzed according to the actual treatment received on Day 1 of the study.

6.6. Baseline Definition

Baseline is the last available assessment prior to the time of first dose unless otherwise specified.

6.6.1. Baseline Attack Rate

No baseline attack rate is calculated for the following reasons:

- Not all subjects entering the study have baseline measures collected as some subjects are rolling over from previous studies.
- Some subjects are on other prophylactic HAE medications
- Some subjects are discontinuing androgens that were used as HAE prophylaxis

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Age in years will be reported as recorded on the demographics form.

6.7.2. Study Day

Study Day 1 is defined as the date of first dose.

If the date of interest occurs on or after the first dose date, study day will be calculated as (date of interest – date of first dose + 1). If the date of interest occurs prior to the first dose date, study day will be calculated as (date of interest – date of first dose). There is no study day 0.

6.7.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as ((change from baseline/baseline result) × 100).

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

6.7.4. Prior Androgen Use

Subgroup analyses for prior androgen use (latency and duration) are described in Section 9.2. Details of calculations for latency and duration are described in this section.

Any medications classified as androgens or androgen derivatives (based on WHODD, March 2017) used prior to the study treatment start date will be considered "prior androgens". These medications will include androgens (unspecified), oxandrolone, danazol (brand name = Danocrine), and stanozolol.

Total duration of prior androgen use includes days from beginning of first date of each androgen used to last dosing date of each androgen. Any days of overlapping multiple androgen use will be counted once for total duration.

Total duration of prior androgen use within the 12 months prior to treatment start date will be calculated similarly to total duration of prior androgen use. The prior 12-month window will include days from treatment start date minus 365 up to treatment start date. For androgens started prior to treatment start date minus 365, start date of androgen will be considered treatment start date minus 365 for this analysis. Duration will be calculated as stop date – start date + 1. If androgen was started and stopped on the same day, duration will be 1 day.

Days since stopping last androgen use (latency) are calculated as date of last androgen use - treatment start date.

6.7.5. Subjects Entering the Study on Prophylactic HAE Medications

Any subject who took Berinert, Ruconest, Haegarda, or Cinryze (all C1-inhibitors or C1-esterase inhibitors [C1-INH]) on Study Day 1 with regular frequency of administration (eg, once weekly, twice weekly, etc.) or tranexamic acid taken daily and *not* flagged on the concomitant medications eCRF as 'PRN' are considered to be on current prophylactic medication.

6.7.6. Visit Windows

For summary purposes in general, records will be assigned to the scheduled visit collected on the eCRF. 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 5. All information collected at an unscheduled visit will be identified as such in the listings.

Table 5: Visit Windows (Days)

Visit	Relative Target Day	Protocol-Specified Visit Window	Analysis Visit Window
Screening visit		-28 to -1	-28 to -1
Baseline visit	1	1	1
Week 2 (Day 15)	15	12 – 18	2 – 22
Week 4 (Day 29)	29	27 – 31	23 – 43
Week 8 (Day 57)	57	55 – 59	44 – 71
Week 12 (Day 85)	85	83 – 87	72 – 127
Week 24 (Day 169)	169	163 – 175	128 – 211
Week 36 (Day 253)	253	247 – 259	212 – 295
Week 48 (Day 337)	337	331 – 343	296 – 379
Week 60 (Day 421)	421	415 – 427	380 – 463
Week 72 (Day 505)	505	499 – 511	464 – 547
Week 84 (Day 589)	589	583 – 595	548 – 631
Week 96 (Day 673)	673	667 – 679	≥ 632

In certain presentation, the HAE attack rates are analyzed by month. The HAE attack will be assigned to an analysis month according to the study day of the actual HAE attack using the following conventions:

Attack Day	Analysis Month for Display
1 – 28	Month 1 (Day 1 – 28)
29 – 56	Month 2 (Day 29 – 56)
57 – 84[a]	Month 3 (Day 57 – 84)

[a] Continues for additional months (28-day blocks) through the end of the study.

6.7.7. Multiple Assessments

Where multiple scheduled measurements are recorded for a given time point (ie, triplicate ECGs or repeated blood pressure assessments), 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 the analysis if available. If no scheduled visit occurs within the window and unscheduled visit(s) and/or an 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 regardless of their use for 'by visit' displays.

Listings will display all visits as recorded on the eCRF, including the date and study day. All available data including any totals, domains, or subscales of scale assessments summarized will be listed.

6.7.8. Derived Efficacy Endpoints

6.7.8.1. Subject-Reported Attack

A subject-reported attack is any attack reported on the HAE Attack Details eCRF page. Each reported attack will count as a separate attack, even if the time periods for the attacks are overlapping.

6.7.8.2. Adjusted Attack

Subject-reported attacks reported must meet the following criteria (applied in order) for inclusion in effectiveness analyses:

- 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 began > 24 hours from the end of the prior attack).
- Any attack that begins within 24 hours from the end of a prior attack will be combined with the prior attack.
- If the entire adjusted attack is untreated, it must have a duration > 24 hours

Using the above criteria, adjusted attacks will be determined programmatically. For adjusted attacks that span 2 or more subject-reported attacks, attack triggers, locations, symptoms, duration, and other characteristics will be based on the information from each component subject-reported attack. Additionally, the start date/time of the adjusted attack will be the start date/time from the first attack and then end date/time of the adjusted attack will be the end date/time from the last attack being collapsed programmatically.

6.7.8.3. Attack Rate

The observed attack rate will be computed as the number of attacks per month, where 1 month is defined as a 4-week period (28 days).

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

$$Attack\ Rate\ (\frac{attacks}{month}) = \frac{\text{Number of Attacks} * 28}{\text{Duration of Treatment Period of Interest}}$$

For subjects who complete the reporting period of interest, duration of reporting period of interest is defined as the last day in the reporting period – first day in reporting period + 1. For subjects who discontinue treatment prematurely in the reporting period of interest, the duration of reporting period of interest is defined as (last day of treatment +1) – first day in reporting period + 1. For example, if a subject receives the last treatment on Day 13 of Month 3 with 2 attacks between Day 1 and Day 14, that subject will be considered to have had a rate of 4 attacks/month (2 × 28/14 = 4) for Month 3. Both the reporting period and the treatment period have been adjusted to include an additional day as the subject prematurely discontinued dosing in Month 3.

Subject-Reported Attack Rate

Subject-reported attack rates will be computed for the entire dosing period.

Adjusted Attack Rate

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

- By month
- Entire dosing period

For adjusted attack rates by month, months will be defined in blocks of 28 days, beginning on Day 1, the day of first dose. Should a subject prematurely discontinue treatment at the end of the monthly reporting period (ie, Day 28), any attacks any attacks that occur within 24 hours after last dose will be counted in the calculation of attack rate of the prior month and the additional 24-hour period will be included in the duration of the reporting period. For example, if a subject has 1 attack from Day 1 to 28, discontinues drug on Day 28, and has an attack on Day 29, the Month 1 (Day 1 to Day 28) attack rate will be 0.55 attacks/month (2 × 28/29 = 0.55).

No imputation will be performed for missing data.

Adjusted Attack Rate by Location

Adjusted Abdominal-only, Peripheral, and Mixed attack rates will be computed using the location definitions provided in Section 6.7.8.12.

6.7.8.4. Number and Proportion of Days with Angioedema Symptoms

The number of days with angioedema symptoms is the sum of the days during the reporting period for which at least one symptom is reported during an adjusted HAE attack. The definition of the reporting period will be defined for subjects who discontinue in the same manner as for the attack rate calculation (see Section 6.7.8.3).

The percentage of days with angioedema symptoms is derived as the number of days with angioedema symptoms divided by the duration of the reporting period of interest. The calculation will be performed similarly to the calculation of the attack rate (see Section 6.7.8.3).

6.7.8.5. Durability of Response

The durability of response is defined as the adjusted attack rate trend over time. Adjusted attack rates by month (28-day blocks of time, starting with Day 1) will be calculated and summarized.

6.7.8.6. Subjects Who Are Attack Free

A subject who completes dosing in the reporting period of interest and has no adjusted attacks during this same period is considered attack free. Subjects with no adjusted attacks in the reporting period but who discontinue before the end of the period or who experience adjusted attacks in the period are not considered attack-free. For the purposes of this analysis, the reporting period is zero to 24 weeks zero to 48 weeks, and for the entire study.

6.7.8.7. Attack Duration

The duration of each subject-reported attack will be calculated in hours, based on the start and stop date and time of the subject-reported attack (time the attack finished). For an adjusted attack that includes more than one subject-reported attack, the duration is calculated from the start of the first subject-reported attack to the end of the last subject-reported attack that has been combined into one adjusted attack. Similarly, the duration of the attack from start of the attack to time that the worst was over will also be calculated.

All subject-reported attack durations will be included in listings and those included in adjusted attacks will be denoted. Adjusted attack duration will be summarized.

6.7.8.8. Attack Onset Relative to Initial Dose of Study Drug

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

6.7.8.9. Medications to Treat HAE Attacks

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 attacks: Berinert, Cinryze, Kalbitor, Firazyr, Ruconest, and fresh frozen plasma.

The following medications, also recorded in the subject diary as HAE treatments, will be classified as non-targeted medications: pain medication, nausea medication, intravenous fluids, other.

6.7.8.10. Time to First Use of HAE Rescue Targeted Medication for an Adjusted Attack

For each subject, the time to first use of HAE targeted rescue medication to treat an adjusted attack will be calculated as the number of days from the first dose of study drug to the first use of rescue medication.

6.7.8.11. Attack Symptoms

Symptoms reported for adjusted attacks will be included in summaries of attack characteristics. In addition, listings of diary data will show symptoms for all subject reported attacks.

6.7.8.12. Attack Location

The anatomical location of each subject-reported and adjusted attack will be determined based on the symptoms indicated in the diary as shown in Table 6.

Table 6: Determination of Attack Location Using Symptoms Collected in the Diary

Abdominal-Only Attack	**Mixed Attack**	**Peripheral Attack (Inclusive of Skin and Airway Swelling)**
Symptoms checked must only come from this box: Internal swelling or symptoms of internal swelling in the abdomen: Nausea Abdominal discomfort Cramps (colicky pain) Vomiting Abdominal pain Diarrhea	Must have at least 1 symptom from left and right box (from abdominal and peripheral attack characterization)	Symptoms checked must only come from this box: Visible swelling: face/head neck (outer swelling) legs, buttocks/genitals eyes arms feet stomach (outside) mouth/tongue/lips hands chest/back joints Internal swelling or symptoms of internal swelling of the airways: lump in throat/tightness change in voice difficulty swallowing difficulty breathing Pink rings (erythema marginatum)

Note: Symptoms of headache and substantial fatigue may be checked by the subject but play no role in the characterization of the location of a subject-reported attack.

6.7.8.13. Attack Triggers

Attack triggers for adjusted attacks will be summarized with the attack characteristics for adjusted attacks. In addition, attack triggers for each subject-reported attack will be included in the listings.

6.7.8.14. AE-QoL

The AE-QoL (Weller, Groffik et al. 2012) consists of 4 domains and a total score. Each item answered by the subject scores between 0 and 4 points depending on the answer option chosen by the subject. The first answer option gets 0 points, the second option 1 point, the third option 2 points, etc. Dimensions of the AE-QoL are shown in Table 7.

Table 7: Dimensions of the AE-QoL

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

Abbreviations: AE-QoL = angioedema quality of life questionnaire.

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

$$\text{AE-QoL Domain Score} = \frac{\sum items}{\max(\sum items)} * 100$$

where

$\sum items$ = Sum of reported item scores per case report form

$\max(\sum items)$ = Sum of the Maximum possible score for each domain

The calculated AE-QoL domain scores range from 0 (best) to 100 (worst).

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 or only little influenced by missing items. An AE-QoL domain scores will not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score will not be calculated if more than 25% of items (ie, > 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.

6.7.8.15. TSQM

The TSQM consists of 14 items of which 13 items are made up of 3 specific scales (Effectiveness, Side Effects, and Convenience) and 1 global satisfaction scale (Global Satisfaction). In addition, 1 item (Item 4) questions whether as a result of taking this medication, the subject experienced any side effects at all, which can be answered by yes and no. Table 8, reproduced from (Atkinson, Sinha et al. 2004), details the individual items in the TSQM.

Table 8: List of Questions from 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.

At baseline, TSQM questionnaires were presented to subjects with instructions that they complete the questionnaire based on their usual medications. At all other time points for collection of TSQM, subjects are asked to think about their level of satisfaction or dissatisfaction with the medication they are taking in this clinical trial.

Scale scores are calculated for each scale and are transformed into scores ranging from 0 to 100 (Quintiles IMS 2017). Of note, a score can be computed for a domain only if no more than 1 item is missing from that domain. The calculations specific to each domain are presented in detail below.

- **Global Satisfaction**

([(Sum(Item 12 to Item 14)) – 3] divided by 14) * 100

  - *If Item 12 or 13 is missing*

  ([(Sum(the 2 completed items)) – 2] divided by 10) * 100

  - *If Item 14 is missing*

  ([(Sum(Item 12 and Item 13)) – 2] divided by 8) * 100

- **Effectiveness**

([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100

  - *If 1 item is missing*

  ([Sum(the 2 completed items)) – 2] divided by 12) * 100

- **Side Effects**

If Question 4 is answered 'No' then score = 100

Else…

([Sum(Item 5 to Item 8) – 4] divided by 16) * 100

  - *If 1 item is missing*

  ([(Sum(the 3 completed items)) – 3] divided by 12) * 100

- **Convenience**

([Sum(Item 9 to Item 11) – 3] divided by 18) * 100

  - *If 1 item is missing*

  ([(Sum(the 2 completed items)) – 2] divided by 12) * 100

6.8. Handling of Missing Data

6.8.1. Missing Effectiveness Endpoints

For subjects who prematurely discontinue the study, all available data will be included for the key safety and effectiveness analyses. No imputation for missing data will occur.

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

For analysis of medications, a complete date should be established in order to identify whether a medication was taken during the study treatment period 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 event/medication will be assigned to the day of first dose of trial medication.

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

- Missing start day and month, but year present:

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

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

- Missing end day, but month and year present:

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

- Missing end day and month, but year present:

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

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

- Completely missing start date:

  For HAE medications collected on subject diaries, the date will be set to the corresponding HAE attack date. For all other concomitant medications, a completely missing start 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.

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

6.8.3. Missing Start and Stop Dates for Adverse Events

The same conventions for addressing incomplete dates for prior and concomitant medications will also be used for AEs.

6.8.4. Missing Time of First and Last Dose

In case of missing time for first dose, it will be assumed that baseline pre-dose 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 on the diary, 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.

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

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

- Missing start time but start date present:

The start time will be set to 12:00PM.

- Missing start date and time:

The start date will be set to the diary date for which the question was answered "Yes". The start time will be set to 12:00PM

- Missing stop time, but stop date present:

The stop time will be set to 11:59PM

- Missing stop date and time:

The stop date will be set to the attack start date, the stop time will be set to 11:59PM

7. STUDY POPULATION

7.1. Subjects Disposition

Subject disposition will be presented for all subjects. The number of subjects who completed through each study visit and those that discontinued from the study will be provided. The primary reasons for early discontinuation will also be presented by dose. Reasons for exclusion from the safety population will be tabulated. Days on study will be summarized by treatment group.

Subject status at the end of the study will be listed and summarized based on the safety 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. 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 consolidated standards of reporting trials (CONSORT) diagram will be created based on the summary tables for the study report. This will include summary tables assessed for eligibility, subjects excluded (not meeting entrance criteria, declining to participate, and other reasons for exclusion), subjects enrolled, subjects allocated to either treatment group, including subjects who did and did not receive intended treatment (with reasons given for not receiving intended treatment), subjects lost to follow-up or discontinuing treatment (with reasons given), and subjects analyzed vs. not analyzed (with reasons given for subjects who are not included in an analysis).

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

Summaries of prior androgen use will be provided by overall duration of prior use, duration of use within 12 months prior to treatment start date, and time since stopping androgen use to treatment start date (latency).

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 on the disposition table. A listing of demographic information for screen failures will be provided.

7.3. Protocol Deviations

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. It will also detail a list of categories of protocol deviations.

7.4. Demographic and Baseline Characteristics

Demographics, including age, gender, race, ethnicity, childbearing potential, weight, height, and BMI will be summarized using descriptive statistics by treatment group. Time from last BCX7353 dose to baseline will be summarized and listed for subjects who were enrolled in previous clinical trials of BCX7353.

Age (in years) will be reported as the age at consent or assent, as collected in the eCRF.

Body mass index (kg/m^2) will be calculated using the standard formula:

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

7.5. Listing of Subject Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be listed for each subject.

7.6. HAE Medical and Medication History

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

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

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

include androgens (unspecified), oxandrolone, danazol (brand name = Danocrine), and stanozolol.

For subjects who are not rolling over from a previous BCX7353 study, a summary of screening complement 4 (C4) and functional C1 esterase inhibitor (C1-INHf) will be provided in categories showing how subjects met the inclusion criteria confirming diagnosis of Type I or II HAE. Confirmation by SERPING, if required, will be included in the summary. Categories for C4 will be C4 < lower limit of normal (LLN) and C4 ≥ LLN and for C1-INHf will be < 50%, 50% to < 74%, and ≥ 74%. Where the C4 test has been repeated, the test result for the repeat will be used in this summary.

In addition, detailed SERPING data will be 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, with the exception of contraceptives, which are collected from 60 days prior to Screening. Medications 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 started more than 30 days post discontinuation of study drug will not be considered concomitant medications.

Medication verbatim text will be coded using the WHODD, March 2017. The number and percentages of subjects taking each medication will be summarized by World Health Organizaton (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 listed in subject diaries as taken for subject-reported attacks will be listed and summarized separately from HAE-related medications identified as concomitant medications. An attack-level summary will also be provided showing the number of attacks for which the various HAE-related medications were taken based on the subject diary and the concomitant medication form (androgens) in the eCRF.

Subjects who enter the study on prophylactic HAE medications will be summarized by treatment group. The time to discontinuation of prophylactic HAE medications will be estimated by the Kaplan-Meier method. Subjects who enter on prophylactic HAE medications and do not discontinue prophylactic medication will be censored at their last assessment.

All medication data will be listed.

7.8. Baseline Physical Examination

Physical examination findings, including baseline, will be listed.

7.9. Baseline Primary and Secondary Effectiveness Evaluations

All attacks (subject-reported and adjusted) will be listed.

Similarly, a summary of baseline AE-QoL total and domain scores will be presented in an appropriate summary table.

8. EFFECTIVENESS

8.1. General Considerations

As the primary nature of this study is to evaluate the safety of BCX7353, effectiveness is considered of secondary importance. No formal testing will be conducted.

8.2. Subgroup Analyses

Subgroup analyses for effectiveness endpoints will not be performed.

8.3. Analysis of the Effectiveness Endpoints

8.3.1. Effectiveness Analysis

The effectiveness analysis is comprised of multiple endpoints (Section 3.2.2) and will be conducted on the safety population.

8.3.1.1. HAE Attack Rate

The number of subject-reported and adjusted HAE attacks will be analyzed by treatment group using appropriate descriptive statistics. The adjusted attack rate (expressed as attacks/month) will be presented by month as well as for the entire study dosing period.

8.3.1.2. Number and Proportion of Days with Angioedema Symptoms

The number and proportion of days with angioedema symptoms reported from adjusted attacks will be summarized by month as well as for the entire study dosing period using descriptive statistics by treatment group.

8.3.1.3. Number and Proportion of Subjects Attack Free

The number and proportion of subjects adjusted attack free will be summarized using descriptive statistics by treatment group.

8.3.1.4. Discontinuations Due to Lack of Efficacy

The number of subjects who discontinue due to lack of efficacy will be provided with subject disposition and will be summarized by treatment group.

8.3.1.5. Attack Characteristics

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

The time to first adjusted attack will be estimated using Kaplan-Meier. Subjects who do not experience an adjusted attack will be censored at the time of study treatment discontinuation.

A summary of duration of attack for abdominal, peripheral, and mixed attacks will also be provided for subject-reported and adjusted HAE attacks.

8.3.1.6. Use of HAE Attack Medications

Use of HAE medications as noted in the diary will be summarized separately from concomitant medications as noted in Section 7.7 . In addition, summaries of the number of subject-reported HAE attacks requiring treatment will be provided.

The time to first use of HAE targeted rescue medication for an adjusted attack will be estimated using Kaplan-Meier estimates. Subjects who do not use HAE rescue medication will be censored at the time of study treatment discontinuation.

8.3.1.7. AE-QoL

Subject-reported outcomes including the AE-QoL questionnaire domain scores (total, functioning, fatigue/mood, fears/shame, and nutrition) will be calculated as discussed in Section 6.7.8.14. The AE-QoL will be summarized by domain/subscale, visit and treatment group using descriptive statistics.

8.3.1.8. TSQM

TSQM is measured at baseline and represents satisfaction with their usual medication. The baseline scores may be reflective of satisfaction with the subject's previous treatment or with no treatment.

TSQM scores for Effectiveness, Side Effects, Convenience, and Global Satisfaction and corresponding change from baseline values will be calculated for each visit as discussed in Section 6.7.8.15. The TSQM scores will be summarized by score, treatment and visit.

9. SAFETY AND TOLERABILITY

9.1. Overall Summary of Tolerability

The summaries of tolerability will be presented in the tables described in Section 9.3 and Section 9.4.

9.2. Subgroup Analyses

The following subgroup analyses for selected safety endpoints will be performed:

- Prior androgen use (latency: time between stopping androgen and starting BCX7353: < 2 weeks, 2 weeks to < 1 month, 1 month to < 2 months, and ≥ 2 months)
- Duration of prior androgen use (never used, < 6 month, 6 months to < 1 year, 1 year to < 5 years, 5 years to < 10 years, ≥ 10 years).

9.3. Adverse Event Preferred Term and Body/Organ System Summary Tables

The following are safety endpoints:

- Proportion of subjects with TEAEs
- Proportion of subjects with TESAEs
- Proportion of subjects who discontinue BCX7353 due to a TEAE
- Proportion of subjects with treatment-emergent Grade 3 or 4 AEs
- Proportion of subjects with treatment-emergent, treatment-related AE consistent with a drug rash
- Proportion of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities

AEs will be mapped to a MedDRA version 19.1 SOC and PT. If a subject experiences multiple events that map to a single preferred term, the greatest severity grade according to the Division of Microbiology and Infectious Diseases (DMID) November 2007 criteria and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication. 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 through 30 days post-discontinuation of study treatment. All AEs that occurred prior to the initiation of study treatment or those recorded after 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.

9.3.1. Summaries of Adverse Event Incidence Rates for All Subjects and Adverse Incidence Rates for Serious Adverse Events, Adverse Event Dropouts, and Death

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

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 treatment-emergent adverse events by severity
- Summary of Grade 3 or Grade 4 TEAEs
- Summary of drug-related, Grade 3 or Grade 4 TEAEs
- 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, summaries of frequent TEAEs and drug-related TEAEs will be provided by preferred term (not by SOC and PT), in decreasing order of frequency. Frequent TEAEs will be defined as TEAEs that occur in at least 5% of the total number of subjects in the clinical trial. The number of events will be displayed on all summary tables except the overall summary of TEAEs. All TEAE analyses will be repeated using subgroups.

A single presentation of the summary of TEAEs for subjects entering on prophylactic medications will be presented. For this presentation, only TEAEs occurring while the subject was simultaneously taking BCX7353 and prophylactic medication will be summarized.

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)

9.3.2. Investigator-Identified Rash Events of Special Interest

All rashes, regardless of assess causality or severity are reported as events of special (EOSI) interest by investigators in a protocol defined manner. However, the endpoint of interest is the proportion of subjects with a treatment-emergent, treatment-related AE consistent with drug rash. These events are marked as EOSI on the AE eCRF page and will be referred to as investigator-identified drug rash.

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

- A TEAE

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

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

A Kaplan-Meier plot and summary of duration of event will be provided for the investigator-identified rashes. 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.

9.3.3. Gastrointestinal Abdominal-Related AEs

Gastrointestinal (GI) abdominal-related AEs are also of interest, although these are not AEs of special interest for investigator reporting purposes. There are no appropriate standard MedDRA queries (SMQs) to evaluate abdominal-related AEs that are appropriate to assess potential adverse events associated with BCX7353 use. In order to create a list of PTs that are pertinent, the events to be analyzed have been prospectively defined as all PTs within the MedDRA 19.1 hierarchy under the High Level Group Terms (HLGTs) of 1) gastrointestinal signs and symptoms and 2) gastrointestinal motility and defaecation conditions (See Section 13.3 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 GI abdominal-related events, separate listings will be provided. In addition, for GI abdominal-related events there will be a summary that shows, by treatment group, the number and percentage of subjects with:

- A TEAE
- A drug-related TEAE
- Permanent discontinuation from study drug due to the TEAE
- An AE that was considered an TESAE
- Any Grade 3 or higher TEAE
- Any Grade 3 or higher drug-related TEAE

- Any TEAE leading to interruption of study drug
- An TEAE that was considered a drug-related TESAE
- A TEAE that required use of concomitant medication

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

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

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

9.3.4. Missing and Partial AE Onset Dates

See Section 6.8.3.

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

For this study, the duration of exposure to study treatment may vary due to differential follow-up. Because of this, certain AE tables will be repeated using the number of AEs per 100 person-years of exposure instead of as a count, where 1 year = 365.25 days.

To determine 100 person-years of exposure, the duration of treatment exposure will be computed for each subject and then summed across subjects to obtain the 100 person-years exposure per treatment group. The table will then display the rate per 100 person-years of exposure (count of AEs reported/total exposure for the treatment group in 100 person-years) values for each treatment group and for each AE.

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 exposure
- Summary of TESAEs

A listing of 100 person-years of exposure to study treatment will be provided.

9.4. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

The number of subjects exposed to study drug will be presented on the disposition table, and the duration of exposure will be presented on the exposure table. Treatment adherence, dose interruptions, and reasons for dose interruptions will be provided as summaries and listed.

A summary and listing of dose reductions will be produced. The listing will include information of study day of dose reduction.

The number of subjects exposed to study treatment and number of subjects who discontinue treatment early will be presented on the disposition table. A summary of exposure to study treatment will be also be presented and will include a summary of 100 person-years of exposure to study treatment as described in Section 9.3.5. Listings of exposure to study treatment and of drug accountability will be provided by subject and treatment. Kaplan-Meier plots of duration of study treatment will be provided.

Treatment compliance, based on drug accountability information as collected in the eCRF, will be calculated for each study treatment that the subject received as follows:

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

The number of capsules taken is derived from the number of capsules dispensed (30 per bottle dispensed) – the number of capsules returned as reported in the eCRF. For those on the 150 mg dose level, the expected number of capsules taken is defined relative to the lot of drug received as the number of pills taken × the duration of study treatment (eg, date of the last dose – date of the first dose + 1). The number of pills taken is either 3 or 1 depending on lot number. If a subject receives drug from different lots, the expected number of capsules taken is calculated relative to the dispense and return dates for a given lot and then summed across lots. On a date of return, the dose is assumed to be taken from the newly dispensed bottle. For subjects on the 110-mg dose level, the expected number is defined as 1 × the duration of study treatment.

A categorical summary of treatment compliance will be produced with the following categories shown in Table 9.

Table 9: Definition of Compliance Categories

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

9.5. Concomitant and Other Medications

Medications received and discontinued prior to the date of first dose are considered as 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 for the treatment period of interest 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.

Medication verbatim text will be coded using the WHODD, DDE B2 March 2017 version. Concomitant medications will be summarized by treatment and WHO preferred name. 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.

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

See Section 6.8.2.

9.6. Laboratory Data

The following is a safety 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 protocol Section 11.1.6.

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 post-baseline assessments will be summarized.

The number and percentage of subjects having elevations in liver enzyme abnormalities (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or bilirubin) in relation to fold above the upper limit of normal (ULN) will be summarized by treatment group.

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 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 for prior androgen use subgroups as defined in Section 9.2. 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 versus maximum bilirubin, the liver test safety panel over time and the distribution of ALT by time and treatment. The distribution plots for AST, ALP, bilirubin, cholesterol and triglycerides will use the same format as is used for ALT.

Separate Kaplan-Meier plots of time to event for a Grade 3 or higher ALT, AST, or total bilirubin will be produced. The results will also be displayed in a summary table. Subjects who do not experience the event of interest will be censored at the date of the last dose.

In addition, a listing of all liver function test results for subjects experiencing a treatment-emergent Grade 3 or 4 liver function test will be provided.

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

9.6.1. Complement Factors and HAE Diagnosis

Laboratory results related to HAE diagnosis, including complement factors C1-INHAg, C1-INHf, complement 3 (C3), and C4 will be included in summaries of laboratory data. Criteria used to confirm diagnosis of HAE Type I or II will be summarized and listed as described in Section 7.6.

9.6.2. Laboratory Assessments for Rash

For subjects with rash marked as possibly, probably, or definitely related to study drug, peripheral blood mononuclear cells (PBMCs) may be collected for analysis of possible drug-specific immune responses and possible drug-responsive T-cells. The data from PBMC analysis, if collected, may be listed.

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

9.7. Pregnancy

A listing of positive pregnancy test results, if applicable, will be provided.

9.8. 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.

9.9. 12-lead Electrocardiograms

Baseline (predose) ECGs will be obtained in triplicate (ie, 3 separate readings) at 1- to 5-minute intervals, with baseline values calculated from an average of the 3 readings. All other ECGs will be single assessments. For subjects who are directly rolling over from a previous study or those with a treatment interruption of < 14 days from a previous study, the pretreatment ECG values obtained in the previous study will serve as the baseline ECG values.

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

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

ECG findings will be summarized.

The change from baseline in QTcF will be summarized at each time point where ECGs are analyzed. An individual subject's change from baseline will be calculated as:

Δ_{ik}= (QTcF for subject i at time point k – Baseline QTcF)

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

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, dose, and visit.

Additionally, 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.

9.10. Physical Examination

A full physical examination is conducted at screening (if applicable) and baseline, with symptom-directed examinations at all post-baseline assessments. Physical examination data will be listed by subject and dose.

9.11. Study Termination Status

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

10. PHARMACOKINETICS

Analyses of PK concentration data will be based on the safety population. PK concentration data will be listed by subject, treatment, day, and time. Note that PK concentration data collected at each visit will not be summarized by visit as the timing of PK sampling with respect to previous dose was not pre-specified.

The value of half-maximal effective concentration (EC_{50}) is 9 ng/mL.

The following summary displays will be produced:

- Summary of number and percentage of collected samples $> 4 \times EC_{50}$, $> 6 \times EC_{50}$, and $> 8 \times EC_{50}$ at each visit and overall
- Summary of number and percentage of samples within a subject $> 4 \times EC_{50}$, $> 6 \times EC_{50}$, and $> 8 \times EC_{50}$

PK concentration data will be combined with data from other studies as part of a population PK analysis. A separate SAP will be written for that analysis.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Changes from protocol-specified analyses include: removal of the intent-to-treat population, removal of analysis of disease severity, removal of comparison of effectiveness endpoints between subjects who received the indicated dose and a reduced dose, removal of comparison of effectiveness endpoints for those that received concomitant C1-INH and those who did not.

12. REFERENCES

Atkinson, M. J., A. Sinha, S. L. Hass, S. S. Colman, R. N. Kumar, M. Brod and C. R. Rowland (2004). "Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease." Health Qual Life Outcomes **2**: 12.

Quintiles IMS (2017). "User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.0."

Weller, K., A. Groffik, M. Magerl, N. Tohme, P. Martus, K. Krause, M. Metz, P. Staubach and M. Maurer (2012). "Development and construct validation of the angioedema quality of life questionnaire." Allergy **67**(10): 1289-1298.

13. APPENDIX

13.1. Table of Contents for Data Display Specifications

Title		Population
Study Population Section		
Figures		
14.1.1.2	CONSORT Diagram	All Subjects
14.1.6.2	Kaplan-Meier: Time to Discontinuation of Study Drug	Safety
Tables		
14.1.1.1	Summary of Subject Disposition	All Subjects
14.1.1.3	Summary of Subject Disposition by Country and Site	All Subjects
14.1.1.4	Analysis Populations	Safety Population
14.1.1.5	Confirmation of Clinical Diagnosis	All Subjects
14.1.1.6.1	Summary of Inclusion/Exclusion Criteria Not Met	Safety Population
14.1.1.6.2	Summary of Inclusion/Exclusion Criteria Not Met	Screen Failures
14.1.1.7	Summary of Protocol Deviations	Safety Population
14.1.2.1	Summary of Demographic Characteristics	Safety
14.1.2.2	Summary of Demographic Characteristics	Safety
14.1.3.1	Summary of Medications Taken within 30 Days of Screening and Discontinued Prior to Dosing	Safety
14.1.3.2	Summary of Concomitant Medications	Safety
14.1.3.3	Summary of Concomitant Medications for HAE	Safety
14.1.3.4	Summary of Concomitant Medications for HAE – Attack Level	Safety
14.1.3.5	Summary of Medications Discontinued During the Study	Safety
14.1.4.1	Summary of Baseline HAE Characteristics - HAE History	Safety
14.1.4.2.1	Past Prophylactic Medications for HAE	Safety
14.1.4.2.2	Current Prophylactic Medications for HAE	Safety
14.1.4.3	Summary of Current On-Demand Treatments of HAE	Safety
14.1.4.4	Summary of Subjects Entering on Prophylactic Medications for HAE	Safety
14.1.4.5	Summary of Subject-Reported Baseline HAE Characteristics – Primary Acute Attack Treatment Information	Safety

Title		Population
14.1.5.1	Summary of Treatment Exposure and Treatment Compliance	Safety
Effectiveness Section		
Figures		
14.2.1.2	Plot of Individual Adjusted Attack Rate	Safety
14.2.1.3	Plot of Individual Subject-Reported Attack Rate	Safety
14.2.1.4	Cumulative Distribution Plot of Adjusted Attack Rate	Safety
14.2.1.5	Cumulative Distribution Plot of Subject-Reported Attack Rate	Safety
14.2.1.6	Histogram of Adjusted Attack Rate	Safety
14.2.1.7	Histogram of Subject-Reported Attack Rate	Safety
14.2.1.10	Plot of Mean Adjusted Attack Rate by Month	Safety
14.2.1.11	Plot of On Study Adjusted Attack Rate by Baseline Adjusted Attack Rate	Safety
14.2.1.17	Kaplan-Meier Plot of Time (Days) to First Adjusted Attack after First Dose of Study Treatment	Safety
14.2.1.19	Kaplan-Meier Plot of Time (Days) to First Use of Targeted Rescue Medication for an Adjusted Attack	Safety
14.2.4.2	Plot of Mean AE-QoL Over Time	Safety
14.2.4.3	Plot of Mean Change from Baseline in AE-QoL Over Time	Safety
14.2.5.2	Plot of Mean TSQM Over Time	Safety
14.2.5.3	Plot of Mean Change from Baseline in TSQM Over Time	Safety
Tables		
14.2.1.1	Summary of HAE Attacks	Safety
14.2.1.8.1	Summary of Durability of Response – Adjusted Attacks	Safety
14.2.1.8.2	Summary of Durability of Response – Adjusted Attacks for Abdominal-Only Attacks	Safety
14.2.1.8.3	Summary of Durability of Response – Adjusted Attacks for Peripheral-Only Attacks	Safety
14.2.1.8.4	Summary of Durability of Response – Adjusted Attacks for Mixed Location Attacks	Safety
14.2.1.9	Summary of Durability of Response – Subject-Reported Attacks	Safety
14.2.1.12	Summary of Duration of Adjusted Attacks (hours)	Safety

	Title	Population
14.2.1.13	Summary of Duration of Subject-Reported Attacks (hours)	Safety
14.2.1.14	Summary of Attack Characteristics for Adjusted Attacks	Safety
14.2.1.15	Summary of Attack Locations for Adjusted Attacks	Safety
14.2.1.16	Time to First Adjusted Attack (KM Estimates)	Safety
14.2.1.18	Time to First Use of Targeted Rescue Medication for an Adjusted Attack (KM Estimates)	Safety
14.2.2	Summary of Number and Proportion of Subjects Adjusted Attack Free	Safety
14.2.3	Summary of Days with Angioedema Symptoms from Adjusted Attacks	Safety
14.2.4.1	Summary of AE-QoL Scores	Safety
14.2.4.4	Summary of Number of Days Missed from School or Work	Safety
14.2.5.1	Summary of TSQM Global Satisfaction Scores	Safety
Safety Section		
Figures		
14.3.1.11.1	Kaplan-Meier: Time to Discontinuation Due to an AE	Safety
14.3.1.11.2	Kaplan-Meier: Time to Discontinuation Due to an AE by Time Since Discontinuation of Androgen Use	Safety
14.3.1.11.3	Kaplan-Meier: Time to Discontinuation Due to an AE by Duration of Prior Androgen Use	Safety
14.3.1.26.1	Kaplan-Meier: Time to Development of Investigator-Identified Rash	Safety
14.3.1.26.2	Kaplan-Meier: Time to Development of Investigator-Identified Rash by Time Since Discontinuation of Androgen Use	Safety
14.3.1.26.3	Kaplan-Meier: Time to Development of Investigator-Identified Rash by Duration of Prior Androgen Use	Safety
14.3.1.28	Kaplan-Meier: Duration of Investigator-Identified Rash	Safety
14.3.1.40.1	Kaplan-Meier: Time to First Occurrence of a GI Abdominal-Related Event	Safety
14.3.1.40.2	Kaplan-Meier: Time to First Occurrence of a GI Abdominal-Related Event by Time Since Discontinuation of Androgen Use	Safety
14.3.1.40.3	Kaplan-Meier: Time to First Occurrence of a GI Abdominal-Related Event by Duration of Prior Androgen Use	Safety

Title		Population
14.3.1.42.1	Kaplan-Meier: Duration of GI Abdominal-Related Event	Safety
14.3.1.42.2	Kaplan-Meier: Duration of GI Abdominal-Related Event by Time Since Discontinuation of Androgen Use	Safety
14.3.1.42.3	Kaplan-Meier: Duration of GI Abdominal-Related Event by Duration of Prior Androgen Use	Safety
14.3.1.43.1	Plot: Occurrence of Treatment-Emergent GI Abdominal-Related Events	Safety
14.3.1.43.2	Plot: Occurrence of Treatment-Emergent GI Abdominal-Related Events by Time Since Discontinuation of Androgen Use	Safety
14.3.1.43.3	Plot: Occurrence of Treatment-Emergent GI Abdominal-Related Events by Duration of Prior Androgen Use	Safety
14.3.4.15.1	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities	Safety
14.3.4.15.2	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities by Time Since Discontinuation of Androgen Use	Safety
14.3.4.15.3	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities by Duration of Prior Androgen Use	Safety
14.3.5.19.1	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 ALT	Safety
14.3.5.19.2	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 ALT by Time Since Discontinuation of Androgen Use	Safety
14.3.5.19.3	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 ALT by Duration of Prior Androgen Use	Safety
14.3.5.21.1	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 AST	Safety
14.3.5.21.2	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 AST by Time Since Discontinuation of Androgen Use	Safety
14.3.5.21.3	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 AST by Duration of Prior Androgen Use	Safety
14.3.5.23.1	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 Total Bilirubin	Safety
14.3.5.23.2	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 Total Bilirubin by Time Since Discontinuation of Androgen Use	Safety

Title		Population
14.3.5.23.3	Kaplan-Meier: Time to First Occurrence of Grade 3 or 4 Total Bilirubin by Duration of Prior Androgen Use	Safety
14.3.5.24.1	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities	Safety
14.3.5.24.2	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities by Time Since Discontinuation of Androgen Use	Safety
14.3.5.24.3	Plot of Liver Function Test Profiles for Subjects with Grade 3 or 4 Liver Abnormalities by Duration of Prior Androgen Use	Safety
14.3.5.25	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT	Safety
14.3.5.26	Liver Test Safety Panel Over Time, Baseline vs. On-Study	Safety
14.3.5.27	Distribution of Liver Tests Over Time: ALT, AST, ALP, and Bilirubin	Safety
14.3.5.28	Distribution of Cholesterol and Triglycerides Over Time	Safety
14.3.6.2	Distribution Plots for Diastolic and Systolic BP Over Time	Safety
14.3.7.2	Distribution Plots for QTcF Over Time	Safety
Tables		
14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
14.3.1.1.2	Overall Summary of Treatment-Emergent Adverse Events by Time Since Discontinuation of Androgen Use	Safety
14.3.1.1.3	Overall Summary of Treatment-Emergent Adverse Events by Duration of Prior Androgen Use	Safety
14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.2.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.3.1	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety

Title		Population
14.3.1.3.2	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.3.3	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.4.1	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.4.2	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.4.3	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.5.1	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.5.2	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.5.3	Drug-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.6.1	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.6.2	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.6.3	Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.7.1	Drug-Related Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.7.2	Drug-Related Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.7.3	Drug-Related Treatment-Emergent Grade 3 or Grade 4 Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.8.1	Treatment-Emergent Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term	Safety

Title		Population
14.3.1.8.2	Treatment-Emergent Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.8.3	Treatment-Emergent Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.9.1	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety
14.3.1.9.2	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.9.3	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.10.1	Time to Discontinuation Due to an AE (KM Estimates)	Safety
14.3.1.10.2	Time to Discontinuation Due to an AE (KM Estimates) by Time Since Discontinuation of Androgen Use	Safety
14.3.1.10.3	Time to Discontinuation Due to an AE (KM Estimates) by Duration of Prior Androgen Use	Safety
14.3.1.12.1	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity	Safety
14.3.1.12.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity by Time Since Discontinuation of Androgen Use	Safety
14.3.1.12.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity by Duration of Prior Androgen Use	Safety
14.3.1.13.1	Frequent Adverse Events by Preferred Term	Safety
14.3.1.13.2	Frequent Adverse Events by Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.13.3	Frequent Adverse Events by Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.14.1	Drug-Related Frequent Adverse Events by Preferred Term	Safety
14.3.1.14.2	Drug-Related Frequent Adverse Events by Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.14.3	Drug-Related Frequent Adverse Events by Preferred Term by Duration of Prior Androgen Use	Safety

Title		Population
14.3.1.15	Overall Summary of Treatment-Emergent Investigator-identified Rash	Safety
14.3.1.16	Treatment-Emergent Investigator-identified Rash by System Organ Class and Preferred Term	Safety
14.3.1.17	Drug-Related Treatment-Emergent Investigator-identified Rash by System Organ Class and Preferred Term	Safety
14.3.1.18	Treatment-Emergent Investigator-identified Rash Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.19	Drug-Related Treatment-Emergent Investigator-identified Rash Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.20	Treatment-Emergent Grade 3 or Grade 4 Investigator-identified Rash by System Organ Class and Preferred Term	Safety
14.3.1.21	Drug-Related Treatment-Emergent Grade 3 or Grade 4 Investigator-identified Rash by System Organ Class and Preferred Term	Safety
14.3.1.22	Treatment-Emergent Investigator-identified Rash Leading to the Interruption of Study Drug by System Organ Class and Preferred Term	Safety
14.3.1.23	Treatment-Emergent Investigator-identified Rash Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety
14.3.2.24	Treatment-Emergent Investigator-identified Rash Requiring the Use of Concomitant Medications	Safety
14.3.1.25	Time to Development of Investigator-identified Rash (KM Estimates)	Safety
14.3.1.27	Duration of Investigator-identified Rash	Safety
14.3.1.29.1	Overall Summary of Treatment-Emergent GI Abdominal-related Events	Safety
14.3.1.29.2	Overall Summary of Treatment-Emergent GI Abdominal-related Events by Time Since Discontinuation of Androgen Use	Safety
14.3.1.29.3	Overall Summary of Treatment-Emergent GI Abdominal-related Events by Duration of Prior Androgen Use	Safety
14.3.1.30.1	Treatment-Emergent GI Abdominal-related Events by System Organ Class and Preferred Term	Safety

Title		Population
14.3.1.30.2	Treatment-Emergent GI Abdominal-related Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.30.3	Treatment-Emergent GI Abdominal-related Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.31.1	Drug-Related Treatment-Emergent GI Abdominal-related Events by System Organ Class and Preferred Term	Safety
14.3.1.31.2	Drug-Related Treatment-Emergent GI Abdominal-related Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.31.3	Drug-Related Treatment-Emergent GI Abdominal-related Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.32.1	Treatment-Emergent GI Abdominal-related Events Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.32.2	Treatment-Emergent GI Abdominal-related Events Serious Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.32.3	Treatment-Emergent GI Abdominal-related Events Serious Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.33.1	Drug-Related Treatment-Emergent GI Abdominal-related Events Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.33.2	Drug-Related Treatment-Emergent GI Abdominal-related Events Serious Adverse Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.33.3	Drug-Related Treatment-Emergent GI Abdominal-related Events Serious Adverse Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.34.1	Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-related Events by System Organ Class and Preferred Term	Safety
14.3.1.34.2	Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-related Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety

Title		Population
14.3.1.34.3	Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-related Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.35.1	Drug-Related Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-related Events by System Organ Class and Preferred Term	Safety
14.3.1.35.2	Drug-Related Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-related Events by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.35.3	Drug-Related Treatment-Emergent Grade 3 or Grade 4 GI Abdominal-related Events by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.36.1	Treatment-Emergent GI Abdominal-related Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term	Safety
14.3.1.36.2	Treatment-Emergent GI Abdominal-related Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.36.3	Treatment-Emergent GI Abdominal-related Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.1.37.1	Treatment-Emergent GI Abdominal-related Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety
14.3.1.37.2	Treatment-Emergent GI Abdominal-related Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term by Time Since Discontinuation of Androgen Use	Safety
14.3.1.37.3	Treatment-Emergent GI Abdominal-related Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term by Duration of Prior Androgen Use	Safety
14.3.2.38.1	Treatment-Emergent GI Abdominal-related Events Requiring the Use of Concomitant Medications	Safety
14.3.2.38.2	Treatment-Emergent GI Abdominal-related Events Requiring the Use of Concomitant Medications by Time Since Discontinuation of Androgen Use	Safety
14.3.2.38.3	Treatment-Emergent GI Abdominal-related Events Requiring the Use of Concomitant Medications by Duration of Prior Androgen Use	Safety

Title		Population
14.3.1.39.1	Time to Development of GI Abdominal-related Events (KM Estimates)	Safety
14.3.1.39.2	Time to Development of GI Abdominal-related Events (KM Estimates) by Time Since Discontinuation of Androgen Use	Safety
14.3.1.39.3	Time to Development of GI Abdominal-related Events (KM Estimates) by Duration of Prior Androgen Use	Safety
14.3.1.41.1	Duration of GI Abdominal-related Adverse Events	Safety
14.3.1.41.2	Duration of GI Abdominal-related Adverse Events by Time Since Discontinuation of Androgen Use	Safety
14.3.1.41.3	Duration of GI Abdominal-related Adverse Events by Duration of Prior Androgen Use	Safety
14.3.1.44.1	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms	Safety
14.3.1.44.2	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms by Time Since Discontinuation of Androgen Use	Safety
14.3.1.44.3	Summary of GI Abdominal-Related Adverse Events and Unconfirmed HAE Attacks with Abdominal-Only Symptoms by Duration of Prior Androgen Use	Safety
14.3.1.45.1	Summary of Treatment-Emergent Adverse Event Rate Per 100 person-years of Exposure (PYE)	Safety
14.3.1.45.2	Summary of Treatment-Emergent Adverse Event Rate Per100 person-years of Exposure (PYE) by Time Since Discontinuation of Androgen Use	Safety
14.3.1.45.3	Summary of Treatment-Emergent Adverse Event Rate Per 100 person-years of Exposure (PYE) by Duration of Prior Androgen Use	Safety
14.3.1.46.1	Summary of Drug-Related Treatment-Emergent Adverse Event Rate Per 100 person-years of Exposure (PYE)	Safety
14.3.1.46.2	Summary of Drug-Related Treatment-Emergent Adverse Event Rate Per 100 person-years of Exposure (PYE) by Time Since Discontinuation of Androgen Use	Safety
14.3.1.46.3	Summary of Drug-Related Treatment-Emergent Adverse Event Rate Per 100 person-years of Exposure (PYE) by Duration of Prior Androgen Use	Safety
14.3.1.47.1	Summary of Treatment-Emergent Serious Adverse Event Rate Per 100 person-years of Exposure (PYE)	Safety

Title		Population
14.3.1.47.2	Summary of Treatment-Emergent Serious Adverse Event Rate Per 100 person-years of Exposure (PYE) by Time Since Discontinuation of Androgen Use	Safety
14.3.1.47.3	Summary of Treatment-Emergent Serious Adverse Event Rate Per 100 person-years of Exposure (PYE) by Duration of Prior Androgen Use	Safety
14.3.1.48	Summary of Treatment-Emergent Adverse Events for Subjects Entering on Prophylactic Medications for HAE	Safety
14.3.5.1.1	Summary of Observed and Change from Baseline in Laboratory Data: Clinical Chemistry	Safety
14.3.5.1.2	Summary of Observed and Change from Baseline in Laboratory Data: Clinical Chemistry by Time Since Discontinuation of Androgen Use	Safety
14.3.5.1.3	Summary of Observed and Change from Baseline in Laboratory Data: Clinical Chemistry by Duration of Prior Androgen Use	Safety
14.3.5.2	Summary of Observed and Change from Baseline in Laboratory Data: Hematology and Coagulation	Safety
14.3.5.3	Summary of Observed and Change from Baseline in Laboratory Data: Continuous Urinalysis Parameters	Safety
14.3.5.4	Summary of Observed Laboratory Data: Categorical Urinalysis Parameters	Safety
14.3.5.5	Summary of Observed and Change from Baseline in Laboratory Data: Additional Tests	Safety
14.3.5.6	Summary of Observed and Change from Baseline in Laboratory Data: Complement Factors	Safety
14.3.5.7.1	Shift from Baseline to Worst Postbaseline Assessment: Clinical Chemistry	Safety
14.3.5.7.2	Shift from Baseline to Worst Postbaseline Assessment: Clinical Chemistry by Time Since Discontinuation of Androgen Use	Safety
14.3.5.7.3	Shift from Baseline to Worst Postbaseline Assessment: Clinical Chemistry by Duration of Prior Androgen Use	Safety
14.3.5.8	Shift from Baseline to Worst Postbaseline Assessment: Hematology and Coagulation	Safety
14.3.5.9	Shift from Baseline to Worst Postbaseline Assessment: Urinalysis	Safety
14.3.5.10.1	Summary of Treatment-Emergent Graded Laboratory Abnormalities	Safety

Title		Population
14.3.5.10.2	Summary of Treatment-Emergent Graded Laboratory Abnormalities by Time Since Discontinuation of Androgen Use	Safety
14.3.5.10.3	Summary of Treatment-Emergent Graded Laboratory Abnormalities by Duration of Prior Androgen Use	Safety
14.3.5.11.1	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities	Safety
14.3.5.11.2	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities by Time Since Discontinuation of Androgen Use	Safety
14.3.5.11.3	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities by Duration of Prior Androgen Use	Safety
14.3.5.12.1	Summary of Treatment-Emergent Laboratory Toxicity Grade Increase from Baseline	Safety
14.3.5.12.2	Summary of Treatment-Emergent Laboratory Toxicity Grade Increase from Baseline by Time Since Discontinuation of Androgen Use	Safety
14.3.5.12.3	Summary of Treatment-Emergent Laboratory Toxicity Grade Increase from Baseline by Duration of Prior Androgen Use	Safety
14.3.5.13.1	Summary of Fold × ULN for Liver Function Tests	Safety
14.3.5.13.2	Summary of Fold × ULN for Liver Function Tests by Time Since Discontinuation of Androgen Use	Safety
14.3.5.13.3	Summary of Fold × ULN for Liver Function Tests by Duration of Prior Androgen Use	Safety
14.3.5.14.1	Summary of Fold Change from Baseline for Liver Function Tests	Safety
14.3.5.14.2	Summary of Fold Change from Baseline for Liver Function Tests by Time Since Discontinuation of Androgen Use	Safety
14.3.5.14.3	Summary of Fold Change from Baseline for Liver Function Tests by Duration of Prior Androgen Use	Safety
14.3.5.15.1	Summary of Elevations in Post-Baseline Liver Function Tests	Safety
14.3.5.15.2	Summary of Elevations in Post-Baseline Liver Function Tests by Time Since Discontinuation of Androgen Use	Safety
14.3.5.15.3	Summary of Elevations in Post-Baseline Liver Function Tests by Duration of Prior Androgen Use	Safety
14.3.5.18.1	Time to First Occurrence of Grade 3 or 4 ALT (KM Estimates)	Safety

	Title	Population
14.3.5.18.2	Time to First Occurrence of Grade 3 or 4 ALT (KM Estimates) by Time Since Discontinuation of Androgen Use	Safety
14.3.5.18.3	Time to First Occurrence of Grade 3 or 4 ALT (KM Estimates) by Duration of Prior Androgen Use	Safety
14.3.5.20.1	Time to First Occurrence of Grade 3 or 4 AST (KM Estimates)	Safety
14.3.5.20.2	Time to First Occurrence of Grade 3 or 4 AST (KM Estimates) by Time Since Discontinuation of Androgen Use	Safety
14.3.5.20.3	Time to First Occurrence of Grade 3 or 4 AST (KM Estimates) by Duration of Prior Androgen Use	Safety
14.3.5.22.1	Time to First Occurrence of Grade 3 or 4 Total Bilirubin (KM Estimates)	Safety
14.3.5.22.2	Time to First Occurrence of Grade 3 or 4 Total Bilirubin (KM Estimates) by Time Since Discontinuation of Androgen Use	Safety
14.3.5.22.3	Time to First Occurrence of Grade 3 or 4 Total Bilirubin (KM Estimates) by Duration of Prior Androgen Use	Safety
14.3.5.25.1	Summary of Rate of Elevations in Post-Baseline Liver Function Tests Per 100 person-years of Exposure (PYE)	Safety
14.3.5.25.2	Summary of Rate of Elevations in Post-Baseline Liver Function Tests Per 100 person-years of Exposure (PYE) by Time Since Discontinuation of Androgen Use	Safety
14.3.5.25.3	Summary of Rate of Elevations in Post-Baseline Liver Function Tests Per 100 person-years of Exposure (PYE) by Duration of Prior Androgen Use	Safety
14.3.6.1	Summary of Observed and Change from Baseline in Vital Signs	Safety
14.3.7.1	Summary of Observed and Change from Baseline in Electrocardiograms	Safety
14.3.7.3	Summary of ECG Findings	Safety
14.3.7.4	Summary of Observed and Change from Baseline QTcF Categorical Findings	Safety
PK/PD Section		
Figures		
14.6.2.2	Scatterplot of %KKI by BCX7353 Plasma Concentration/4	PK/PD

Title		Population
Tables		
14.5.1.1	Summary of Plasma BCX7353 Concentration (ng/mL)	Safety
14.5.2.1	Plasma BCX7353 Concentration (ng/mL) Trough Samples above Kallikrein Inhibition EC_{50}	Safety
14.6.1.1	Summary of Plasma Kallikrein Inhibition (%)	PD
14.6.2.1	Plasma Kallikrein Inhibition Trough Samples above 50% and 80%	PD

Listings

Title		Population
16.2.1.1	Informed Consent and Screen Failures	All Subjects
16.2.1.2	Subject Allocation, Site, and Country	Safety
16.2.1.3	Prior BioCryst Studies	Safety
16.2.1.4	Listing of Planned and Actual Treatment Assignments for Subjects with Incorrect Treatment	Safety
16.2.1.5	Subject Disposition	Safety
16.2.1.6	Analysis Populations	Safety
16.2.2.1	Inclusion/Exclusion Criteria Not Met	Safety
16.2.2.2	Protocol Deviations	Safety
16.2.4.1.1	Demography	All Subjects
16.2.4.1.2	Demography – Contraception	All Subjects
16.2.4.1.3	Confirmation of Clinical Diagnosis of HAE	All Subjects
16.2.4.2.1	Medical History Not Recorded in Prior BioCryst Studies	Safety
16.2.4.2.2	HAE Medical History	Safety
16.2.4.2.3	HAE Medication History – Past and Current On-Demand HAE Treatment	Safety
16.2.4.2.4	HAE Medication History – Past Prophylactic HAE Treatment	Safety
16.2.4.3.1	Medications Taken within 30 Days of Screening and Discontinued Prior to Study Drug Initiation	Safety
16.2.4.3.2	Concomitant Medication Use	Safety
16.2.4.3.3	Use of Concomitant Medications for HAE	Safety
16.2.4.3.4	Prior Androgen Use for HAE	Safety
16.2.4.3.5	HAE Medication–Current Prophylactic HAE Treatment	Safety
16.2.5.1	Drug Accountability	Safety

Title		Population
16.2.5.2	Dosing Diary	Safety
16.2.5.3	100 Person-Years of Exposure (PYE)	Safety
16.2.6.1.1	HAE Attack Diary	Safety
16.2.6.1.2	HAE Attack Diary Detail	Safety
16.2.6.1.3	HAE Attack Level Summary – Subject-Reported Attacks	Safety
16.2.6.1.4	HAE Attack Level Summary – Adjusted Attacks	Safety
16.2.6.1.5	Attack Rate	Safety
16.2.6.1.6	Subjects who Are Adjusted Attack-Free During Entire Dosing Period	Safety
16.2.6.1.7	Days with Angioedema Symptoms from Adjusted Attacks	Safety
16.2.6.1.8	Efficacy Endpoint Profile	Safety
16.2.6.1.9	Subject-Level Additional Derived Endpoint Profile	Safety
16.2.6.2.1	AE-QoL: Individual Question Responses and Days Missed	Safety
16.2.6.2.2	AE-QoL: Domain Scores	Safety
16.2.6.3.1	TSQM Global Satisfaction Individual Question Scores	Safety
16.2.6.3.2	TSQM Effect, Side Effect, Convenience and Global Satisfaction Scores	Safety
16.2.7.1	Adverse Events	Safety
16.2.7.2	Serious Adverse Events	Safety
16.2.7.3	Grade 3 or 4 Adverse Events	Safety
16.2.7.4	Adverse Events Leading to Discontinuation of Study Drug	Safety
16.2.7.5	Adverse Events Leading to Interruption of Study Drug	Safety
16.2.7.6	Fatal Serious Adverse Events	Safety
16.2.7.7	Adverse Events of Special Interest: Investigator-Identified Rash	Safety
16.2.7.8	Gastrointestinal Abdominal-Related Adverse Events	Safety
16.2.7.9	Adverse Events for Subjects with Elevated LFTs	Safety
16.2.7.10	Listing of GI Abdominal-Related Events and Abdominal-Only Symptoms from Subject-reported HAE Attacks	Safety
16.2.7.11	Adverse Events for Subjects on Prophylactic HAE Medications	Safety
16.2.8.1	Clinical Chemistry	Safety
16.2.8.2	Hematology	Safety
16.2.8.3	Coagulation	Safety
16.2.8.4	Urinalysis	Safety
16.2.8.5	Other Laboratory Tests	Safety

Title		Population
16.2.8.6	Complement Factors C3, C4, and C1-INH	Safety
16.2.8.7	SERPING-1	Safety
16.2.8.8	Pregnancy Tests	Safety
16.2.8.9	Graded Laboratory Abnormalities	Safety
16.2.8.10	Grade 3 or 4 Laboratory Abnormalities	Safety
16.2.8.11	All Liver Function Test Results for Subjects Experiencing a Treatment-Emergent Grade 3 or 4 Liver Function Test	Safety
16.2.8.11.1	All Liver Function Test Results for Subjects Experiencing a Treatment-Emergent Grade 3 or 4 Liver Function Test, Subjects with Prior Androgen Use	Safety
16.2.8.12	Prior Androgen Use and Worst Post-Baseline ALT Elevation	Safety
16.2.8.13	Vital Signs	Safety
16.2.8.14	12-Lead Electrocardiogram	Safety
16.2.8.15	QTcF Values >450msec or QTcF Change from Baseline Values >30msec	Safety
16.2.8.16	Physical Exam	Safety
16.2.8.17	Pharmacokinetic Sample Collection	Safety
16.2.8.18	Plasma Kallikrein Inhibition (%)	PD

13.2. Data Display Specifications

Mock (shell) versions of data displays for tables and listings will be provided in separate documents.

13.3. 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
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

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

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

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

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

Code	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	SOC
10017885	Gastrooesophageal reflux disease	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10062879	Gastrooesophageal sphincter insufficiency	Gastrointestinal atonic and hypomotility disorders NEC	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10021333	Ileus paralytic	Non-mechanical ileus	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
10021335	Ileus spastic	Non-mechanical ileus	Gastrointestinal motility and defaecation conditions	Gastrointestinal disorders
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