BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-302

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TWO DOSE LEVELS OF BCX7353 AS AN ORAL TREATMENT FOR THE PREVENTION OF ATTACKS IN SUBJECTS WITH HEREDITARY ANGIOEDEMA

Version 4.0 (United States): 10 February 2020

IND No. 135,058

EudraCT No. 2017-003966-29

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CONFIDENTIAL

Protocol Number:	BCX7353-302
Study Title:	A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema
IND Number:	135,058
EudraCT No.	2017-003966-29
Investigational Product:	BCX7353
Indication Studied:	Hereditary angioedema
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA
Sponsor Medical Monitor:	Sylvia Dobo, MD Phone (24 hours): +1 919-859-7905 Email: mm@biocryst.com
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Principal Investigator:	Bruce Zuraw, MD Professor of Medicine US HAEA Endowed Chair Chief, Division of Rheumatology, Allergy & Immunology Director, US HAEA Angioedema Center UC San Diego +1 858-822-6597 bzuraw@ucsd.edu
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), International Council for Harmonisation guidelines and all locally applicable regulations. Essential study documents are currently archived in accordance with applicable regulations
Final Protocol Date:	Version 4.0 (United States): 10 February 2020 (United States)
Previous Version(s):	Version 3.0: 11 September 2019 Version 2.0: 11 October 2018 Version 1.0: 21 November 2017

1.1. Protocol Approval Signature Page

Protocol No: BCX7353-302

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

Date: Version 4.0 (United States): 10 February 2020

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

Melanie Cornpropst 13 Feb 2020

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

13 FEB 2020

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

12 FEB 2020

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

1.2. Clinical Study Protocol Agreement

Protocol No: BCX7353-302

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

Date: Version 4.0 (United States): 10 February 2020

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, International Council for Harmonisation guidelines for Good Clinical Practices, and all applicable regulatory requirements.

_____

Investigator's Signature Date

_____

Name (Print)

2. SYNOPSIS

Name of Sponsor/Company: BioCryst Pharmaceuticals, Inc.	
Name of Investigational Product: BCX7353	
Name of Active Ingredient: (*R*)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide	
Title of Study: A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema (Study BCX7353-302)	
Study centers: Multiple study centers in North America and Europe	
Principal Investigator: Bruce Zuraw, MD	
Enrollment period (months): Approximately 9 months	**Phase of development:** 3

Part 1 Primary Objective:

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

Part 1 Secondary Objectives:

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

Part 1 Primary Efficacy Endpoint:

- The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period

Part 1 Secondary Efficacy Endpoints:

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

Part 1 Exploratory Efficacy Endpoints:

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

Part 1 Safety Endpoints:

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

Part 1 Health Outcome Endpoints:

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

Part 2 Primary Objective:

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

Part 2 Secondary Objectives:

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

Part 2 Primary Endpoints:

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

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

Part 2 Secondary Endpoints:

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

Part 3 Primary Objective:

- To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 48- to up to 144-week administration period in subjects with HAE

Part 3 Secondary Objectives:

- To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 48- to up to 144-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 48- to up to 144-week administration period
- To evaluate subject satisfaction with BCX7353 over a 48- to up to 144-week administration period

Part 3 Primary Endpoints:

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

Part 3 Secondary Endpoints:

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

Methodology:

This is a randomized, placebo-controlled, double-blind, parallel-group, 3-part study. Part 1 is designed to test the hypothesis that the HAE attack rate during 24 weeks of prophylactic BCX7353 treatment at 2 dosage levels will be less than that observed during 24 weeks of placebo. The primary efficacy endpoint will be assessed after the last subject completes Part 1 (through Week 24). Part 2 is designed to primarily evaluate the long-term safety of BCX7353 at 2 dosage levels. Part 3 is open-label and designed to primarily evaluate the long-term safety of BCX7353. Parts 1, 2, and 3 will be conducted in sequence, with Parts 2 and 3 conducted as continuous roll-overs from Parts 1 and 2, respectively. All subjects will receive BCX7353 in Parts 2 and 3, including those randomized to receive placebo in Part 1. Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation.

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

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

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

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

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

Beginning at screening and through the Week 48 visit, details of acute attacks of angioedema will be recorded in an electronic diary (e-diary). Attacks will be treated in accordance with the subject's normal standard of care. Treatment medications for angioedema attacks will not be provided by the Sponsor.

Within approximately 2 business days of the end of each attack that occurs beginning at the screening visit through the Week 48 visit, subjects will be contacted by the Investigator (or appropriately trained designee) to discuss the clinical characteristics of the attack, any questions the Investigator has on the entered data, or to gain additional attack details not included in the e-diary that the Investigator deems

important to clinically evaluate the event, as applicable. This information, in conjunction with the e-diary record, will be used by the Investigator to verify or reject the event recorded in the diary as an HAE attack. All Investigator-confirmed attacks of HAE must include symptoms of swelling; prodromal symptoms in the absence of swelling are not considered HAE attacks, regardless of treatment. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling.

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

Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, electrocardiograms (ECGs), and physical examinations.

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

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

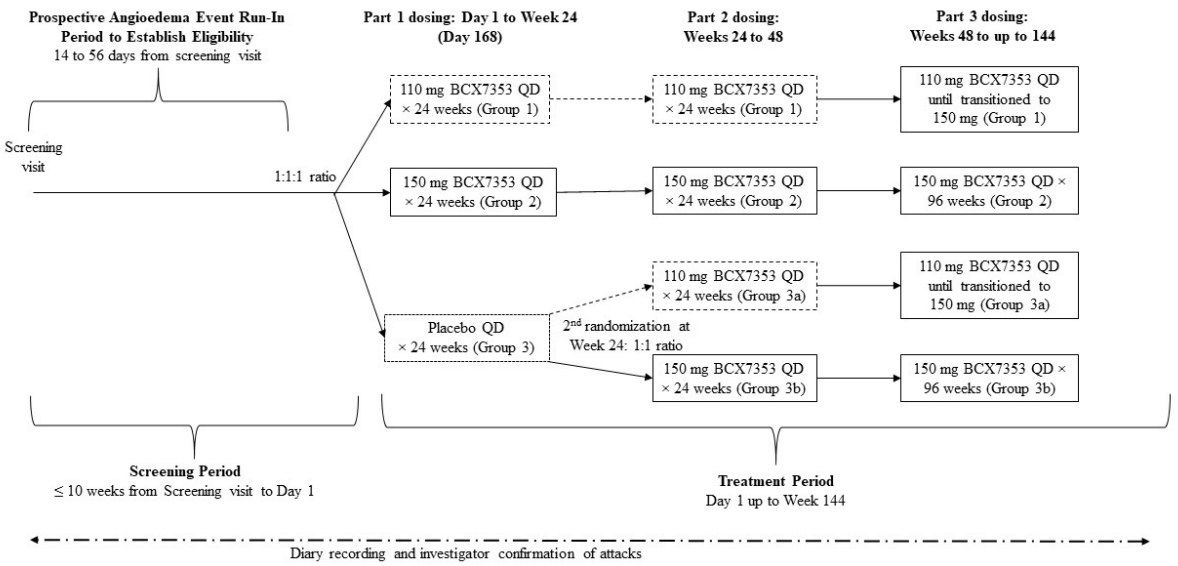
Part 2 of the study will start with the administration of the study drug dispensed at the Week 24 visit. Subjects in Groups 1 and 2 will continue to receive the same BCX7353 dose to which they were randomized in Part 1 of the study in a blinded manner. Subjects randomized to Group 3 (placebo) will undergo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

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

Part 3 (up to 96-week evaluation of safety of open-label BCX7353)

Part 3 of the study will start with the administration of the study drug dispensed at the Week 48 visit. Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation.

Study visits during Part 3 will occur during Weeks 60, 72, 84, 96 and approximately every 12 weeks thereafter, for a study duration of up to 144 weeks (approximately 3 years), or until another mechanism is available to provide drug to the subject (eg, market access) or the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Telephone contact will occur at Weeks 52, 56, 64, 68, 76, 80, 88, and 92. A final study follow-up visit will be scheduled approximately 3 weeks following the last administration of study drug. Investigator confirmation of attacks will not be required in Part 3. All attacks recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in the effectiveness analyses. These rules, which will be constructed in concert with HAE-treating physicians, will be outlined in the Statistical Analysis Plan.



Number of subjects (planned):

Approximately 96 subjects will be enrolled in this study (n = 32/group), which includes any adolescent subjects enrolled in the substudy.

A blinded interim analysis is planned to estimate the standard deviation from the pooled treatment groups after 50% of the subjects complete Part 1 of the study (through 24 weeks). The sample size may be re-estimated based on the variability from the pooled data.

The final sample size will be the maximum of either the original planned sample size (32 per group) or the re-estimated sample size. No statistical adjustment for the final analysis is planned.

Main criteria for inclusion:

1. Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy).
2. 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.
3. Subject weight of ≥ 40 kg.
4. A clinical diagnosis of hereditary angioedema 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 in the screening period with the results below the LLN reference range.

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

5. Access to and ability to use one or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH). Cinryze used for acute treatment of HAE attacks is an acceptable medication for this purpose.
6. Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.
7. The subject must have at least 2 HAE attacks which meet all the requirements below during the run-in period of a maximum of 56 days from the screening visit.
   - The attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
   - The attacks must have either been treated, required medical attention or be documented to cause functional impairment based on subject entry in the diary. Functional impairment is defined as the subject not being able to perform their daily activities without restriction (ie, subject records that they are at least slightly restricted in their daily activities during their HAE attack).
   - The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling.
   - The attacks are otherwise confirmed by the Investigator to be HAE attacks.

   Subjects who have recorded 2 such attacks may be randomized to receive study drug beginning on or after Day 28 of the run-in period; subjects who have recorded at least 3 such attacks may be randomized beginning on or after Day 14 of the run-in period. Under no circumstances should the run-in attack requirement for eligibility be disclosed to study subjects.
8. Female and male subjects must agree to the contraception requirements and must meet the inclusion criteria regarding contraception, and contraception of female partners (as applicable), as outlined in Section 8.2.1.

   Note: Contraception is no longer required for male subjects and their female partners under Protocol Version 3.0.
9. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate adequate compliance with all study procedures required from the screening visit through randomization, including diary recording of HAE attacks beginning at the Screening visit.

Main criteria for exclusion:

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject by participating in the study.
2. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.

3. Anticipated use of short-term prophylaxis of angioedema attacks for a pre-planned procedure during the screening or study periods (Parts 1 and 2 only).
4. Concurrent diagnosis of any other type of recurrent angioedema.
5. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a corrected QT interval using Fridericia's method (QTcF) > 470 msec for women, a QTcF > 450 msec for men, 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. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
7. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
8. History of or current implanted defibrillator or pacemaker.
9. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the Investigator, is clinically significant and relevant for this study. A calculated creatinine clearance of ≤ 30 mL/min or aspartate aminotransferase or alanine aminotransferase value ≥ 3 × the upper limit of the normal reference range value obtained during screening is exclusionary.
10. Prior enrollment in a BCX7353 study.
11. Suspected C1-INH resistance in the opinion of the Investigator or Sponsor.
12. History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcohol intake > 3 drinks/day).
13. Positive serology for human immunodeficiency virus or current infection with hepatitis B virus or hepatitis C virus.
14. Pregnant, planning to become pregnant during the study, or nursing.
15. Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
16. History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
17. Use of androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to the Screening visit or initiation during the study.
18. Use of C1-INH for prophylaxis of HAE attacks within the 14 days prior to the Screening visit or initiation during the study. Use of a C1-INH therapy for treatment of attacks is not excluded at any time, nor is C1-INH for preprocedure prophylaxis for an unplanned/unforeseen procedure.
19. Use of concomitant medications that are metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.

20. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study.
21. 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.
22. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
23. Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study (Parts 1 and 2 only).
24. Current participation in any other investigational drug study or received another investigational drug within 30 days of the Screening visit.
25. An immediate family relationship to either Sponsor employees, the Investigator, or employees of the study site named on the delegation log.
26. Held in an institution by a government or judicial order.

Investigational product, dosage and mode of administration:

BCX7353 capsules, to be administered orally.

Parts 1 and 2

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

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

Subjects randomized to Treatment Group 1 or 2 will receive the same dose in both Parts 1 and 2.

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

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

Subjects in Treatment Group 3 will receive a total duration of 24 weeks of active BCX7353 treatment during Part 2.

Part 3

BCX7353 capsules contain 110 and 150 mg of the active ingredient (free base equivalents). Based on the results of the current study's Part 1 analysis, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation. Subjects will then receive a single 150 mg capsule of BCX7353 in an open-label manner. Subjects will take a single capsule orally once daily at approximately the same time each day, with whichever meal is typically the largest of the day.

Subjects randomized to Treatment Groups 1 and 2 will receive a total of up to 144 weeks of active BCX7353 treatment and subjects randomized to Treatment Group 3 will receive a total of up to 120 weeks of active BCX7353 treatment, or until another mechanism is available to provide drug to the subject or the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first.

Reference therapy, dosage and mode of administration: Placebo-to-match BCX7353 capsules. Subjects randomized to Treatment Group 3 will take 2 capsules of placebo orally QD for 24 weeks during Part 1 with their largest meal of the day.
Duration of treatment: Subjects will take capsules of BCX7353 or placebo orally for 24 weeks in Part 1 and capsules of BCX7353 in Parts 2 and 3 orally for 120 weeks (24 weeks in Part 2 and up to 96 weeks in Part 3), for a total duration of study drug treatment of up to 144 weeks.

Criteria for evaluation:

Efficacy:

Number of HAE attacks and related details (timing, duration of symptoms, anatomical location, treatment used and emergency room visits and hospitalizations (through Week 96), number of days with HAE symptoms, number of subjects who are attack-free, assessment of attack severity, and discontinuations due to lack of efficacy (through Week 48).

Safety:

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

Health Outcomes:

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

Pharmacodynamics:

Kallikrein inhibition.

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

Pharmacokinetics (PK):
A blood sample for BCX7353 concentration will be drawn. Population PK of BCX7353 will be evaluated on a meta-study basis.

Statistical methods:

The primary study hypothesis is that the rate of HAE attacks during 24 weeks of prophylactic BCX7353 (at either 150 or 110 mg QD) will be superior to placebo. The primary efficacy endpoint is the monthly investigator-confirmed HAE attack rate in the entire treatment period (Day 1 [post-dose] to Day 168) in the intent-to-treat population, which includes all randomized subjects.

Each BCX7353 dose will be compared to placebo in the primary analysis. The primary analysis of treatment-effect will be performed using a Poisson regression model. The stratification variable (baseline monthly attack rate) will be included as a covariate and the logarithm of duration on treatment will be included as an offset variable. The estimated treatment differences in attack rate ratio (BCX7353 over placebo rate ratio) and their associated 95% confidence intervals will be provided. Monthly will be defined as 4 weeks.

Assuming a normalized placebo attack rate of 1 unit and a common standard deviation of 0.55 units for BCX7353 and placebo attack rates, a sample size of 32 subjects will have 94% power to detect a $\geq$ 50% attack rate reduction (a treatment difference of 0.5 units) between BCX7353 and placebo, based on a 2-sided test at significance level of 0.05. To account for multiplicity, the Hochberg step-up procedure will be used to adjust for the 2 active doses vs. placebo comparisons.

Safety assessments, data from HAE attack diaries and QoL questionnaires will be summarized and listed. PD data will be summarized in tables and figures.

The totality of data will be analyzed at the end of the study.

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LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1. Abbreviations and Specialist Terms

Abbreviation	Explanation
ABW	absolute body weight
ACR	spot urine microalbumin to creatinine ratio
AE	adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BK	bradykinin
BMI	body mass index
C1-INH	C1 esterase inhibitor
C3	complement 3
C4	complement 4
CBC	complete blood count
CK	creatine kinase
CK-MB	creatine kinase MB isoenzyme
CL_{CR}	creatinine clearance
C_{max}	maximum plasma concentration of the drug
CRF	case report form
CRA	clinical research associate
CSR	clinical study report
CYP	cytochrome P450
D_LCO	diffusion capacity of carbon monoxide
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
e-diary	electronic diary
EOSI	event of special interest
EQ-5D-5L	EuroQoL 5-dimensional, 5-level questionnaire
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltranspeptidase
GI	gastrointestinal
HAE	hereditary angioedema

Abbreviation	Explanation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HK	high-molecular weight kininogen
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	independent ethics committee
IMP	investigational medicinal product (study drug)
INR	international normalized ratio
IRB	institutional review board
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous
IXRS	interactive (web or voice) response system
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model of repeated measures
NGAL	neutrophil gelatinase-associated lipocalin
NHP	nonhuman primate
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
P-gp	p-glycoprotein efflux pump
PK	pharmacokinetic
PKK	Prekallikrein
PLD	phospholipidosis
PP	per protocol
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
QD	once daily
QoL	quality of life
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
RR	interval between successive heart beats using the R-wave peaks

Abbreviation	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TdP	torsade des pointes
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TpTe	Tpeak to Tend subinterval measurement
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
US	United States
WPAI	Work productivity and activity impairment questionnaire

5. INTRODUCTION

5.1. Background

Hereditary angioedema (HAE) with C1-esterase inhibitor (C1-INH) deficiency is an autosomal dominant disorder characterized by recurrent episodes of swelling of the skin, pharynx, larynx, gastrointestinal (GI) tract, genitals, and extremities (Longhurst and Cicardi 2012). The frequency of attacks varies between subjects, from rarely in some patients to every few days in others. Angioedema attacks may or may not be precipitated by a stimulus (such as stress, trauma, or estrogen) and are typically rapid in onset, with symptoms subsiding gradually over the following 3 to 5 days (Zuraw and Christiansen 2011). Oropharyngeal swelling can be life-threatening (Bork, Hardt et al. 2012), while attacks in other sites, including limbs, genitalia, face and intestines, can be painful, disabling, and disfiguring, and have a significant impact on functionality and quality of life (QoL) (Lumry, Castaldo et al. 2010). Although mortality risk from asphyxiation is much higher in undiagnosed patients with HAE, deaths still occur in diagnosed patients with access to care at centers of excellence (Bork, Hardt et al. 2012).

Extensive evidence from animal models and clinical studies supports the role of bradykinin (BK) as the principal mediator of the signs and symptoms that characterize attacks of HAE (Han, MacFarlane et al. 2002, Kaplan 2010, Zuraw and Christiansen 2011). Plasma kallikrein is a serine protease integral to the contact activation pathway (Saxena, Thompson et al. 2011). Kallikrein circulates in plasma as a zymogen, prekallikrein (PKK), bound to one of its main substrates, high-molecular-weight kininogen (HK). During contact activation, PKK is cleaved by activated factor XII, forming the active protease kallikrein. Kallikrein in turn cleaves HK, producing BK (Kaplan and Ghebrehiwet 2010). The activation of the bradykinin B2 receptor by BK ultimately results in vasodilatation, increased vascular permeability, and smooth muscle contraction, all of which lead to the tissue swelling that characterizes HAE (Kaplan 2010).

BCX7353 is a potent, synthetic small molecule inhibitor of plasma kallikrein. In contrast to parenterally administered options commercially available for prophylaxis against HAE attacks, inhibition of kallikrein with an orally bioavailable small molecule such as BCX7353 offers the advantage of oral administration.

5.2. Nonclinical Findings for BCX7353

The principal results of nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies of BCX7353 are described briefly below; additional details can be found in the BCX7353 Investigator's Brochure (IB).

Safety pharmacology studies of BCX7353 indicated multiple cardiac ion channel effects, including the human ether-a-go-go related gene K^+ channel and the Na^+ and Ca^{2+} channels. However, studies in non-human primates (NHP) showed quantitatively small drug-related prolongation of the QT interval. There were no concerns for phototoxicity or genotoxicity.

Embryo-fetal developmental toxicity studies in the rat and rabbit showed no evidence of direct fetal toxicity of BCX7353, and no effects were seen in male and female rats in fertility studies.

Chronic-dosing toxicology studies were conducted in the NHP (39 weeks) and rat (26 weeks). BCX7353 was well tolerated in both rats and monkeys at doses up 30 and 20 mg/kg/day, respectively, and these dose levels were the no observed adverse effect levels (NOAELs). In

NHP, at the NOAEL dose of 30 mg/kg/day, mean maximal plasma concentration of the drug (C_{max}) and area under the concentration vs. time curve (AUC) from time 0 to 24 hours (AUC_{0-24}) on Day 270 (sexes combined) were 277 ng/mL and 3950 ng.h/mL, respectively. In the rat, at the NOAEL dose level of 20 mg/kg/day, C_{max} was 686 ng/mL, and AUC_{0-24} was 9710 ng.h/mL, on Day 182.

In the chronic toxicology study in rats the target organ was the liver. Minimal to mild bile duct hyperplasia and foamy/pigmented macrophages were observed at 20 mg/kg/day. Vacuolated epithelium of hepatic bile ducts was noted with minimal severity. A pathology peer-review of liver findings in the 26-week study concluded that the microscopic changes, including bile duct hyperplasia, were non-adverse.

In monkeys, the primary target organs were the liver and kidney. In one study that evaluated doses up to 20 mg/kg/day, the only effect noted was a mild increase in alanine aminotransferase (ALT), which partially resolved during the study despite continued dosing. In a subsequent study that evaluated doses of 30, 55, and 80 mg/kg/day, adverse findings in the liver and kidney were noted at 55 and 80 mg/kg/day. Increased liver weights and panlobular hepatocellular hypertrophy were observed together with increased ALT and aspartate aminotransferase (AST); and increased kidney weights, renal tubular epithelial cell degeneration, and renal tubular hyperplasia were also observed. Each of these effects were reversible during a 13-week drug-free recovery period.

In monkeys, pigmented and foamy macrophages were present in all regions of the small intestine, in mesenteric lymph nodes and in liver Kupffer cells at doses ≥ 30 mg/kg/day in females, and at doses ≥ 55 mg/kg/day in males. Dose-dependent increases in the urinary concentrations of the experimental biomarker for phospholipidosis (PLD), di-docosahexaenoyl (22:6)- Bis(mono) acylglycerol phosphate (BMP), were observed in both rats and monkeys. Electron microscopy evaluation of liver from rats in the 13-week toxicity studies demonstrated myelinosomes within the cytoplasm of Kupffer cells. These effects are consistent with PLD, a phenomenon noted in nonclinical toxicity studies with several approved drugs. PLD is considered an adaptive response to the presence of a drug, rather than a toxic manifestation.

In monkeys, spleen and thymus weights were increased at 55 and 80 mg/kg/day. The increased spleen weight correlated with lymphoid hyperplasia; there was no microscopic correlate for the increased thymus weights.

5.3. Clinical Findings for BCX7353

A clinical program, including a comprehensive clinical pharmacology program of Phase 1 studies and 2 Phase 2 clinical studies (BCX7353-203 [CSR available; results summarized herein] and BCX7353-204 [ongoing]) relevant to the current study have been conducted. One Phase 3 study (BCX7353-301) remains ongoing in Japan.

The principal results of clinical pharmacology, PK, and clinical safety and efficacy studies of BCX7353 are described in the BCX7353 IB.

5.3.1. Summary of Ongoing Study BCX7353-302

The primary objective of the current study (BCX7353-302) was to determine the efficacy of prophylactic BCX7353 150 and 110 mg administered orally once daily (QD) for 24 weeks (Part 1) compared to placebo in subjects with HAE. Parts 2 and 3 are ongoing.

In Part 2, all subjects receive active treatment with BCX7353 from Weeks 25 through 48, and Protocol Version 4.0, Part 3 extends treatment with BCX7353 up to 144 (United States only) or 240 (Europe and Canada) weeks. Results for Part 1 are summarized herein.

Overall, a total of 160 subjects were screened, 121 subjects were randomized (stratified by baseline attack rate, < 2 vs. ≥ 2 per 28 days), and 120 randomized subjects (99%) were treated. Of these, 108 subjects completed 24 weeks of study drug dosing in Part 1: 37 of 40 BCX7353 150 mg subjects (93%), 37 of 41 BCX7353 110 mg subjects (90%), and 34 of 39 placebo subjects (87%).

The mean baseline rate was 2.98 attacks per month. The majority of subjects (70%) had $\geq$ 2 attacks per month at baseline, and the attack frequency was generally well distributed across the 3 treatment groups.

The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period. This study achieved its primary endpoint for both dose levels, with the 150 and 110 mg doses reducing HAE attacks by 44% ($p < 0.001$) and 30% ($p = 0.024$), respectively, vs. placebo. The attack rate per 28 days over the 24-week Part 1 dosing period was 1.31 for BCX7353 subjects on 150 mg QD, 1.65 for BCX7353 subjects on 110 mg QD, and 2.35 for placebo subjects. These results were supported by sensitivity analyses and were consistent in subgroup analyses. Effects of BCX7353 in reducing attack rate were evident in the first 4 weeks and stable over the entire 24-week duration of Part 1.

Secondary endpoints (change from baseline in the angioedema quality of life questionnaire [AE-QoL], number and proportion of days with angioedema symptoms, and rate of investigator-confirmed HAE attacks during the effective dosing period [beginning on Day 8 through Week 24]) were analyzed using hierarchical testing. Results for the first secondary endpoint, AE-QoL, were not statistically significant vs. placebo for either treatment group; therefore, inferential statistical testing was not performed on the descending secondary efficacy endpoints. For placebo, subjects experienced least square means (LSM) of 19.7% of days with symptoms compared with 11.9% for BCX7353 150 mg (nominal $p = 0.006$) and 13.4% for 110 mg (nominal $p = 0.025$). The rate of investigator-confirmed HAE attacks during the effective dosing period was reduced by 46.5% for 150 mg BCX7353 (nominal $p < 0.001$) and by 30.4% for 110 mg (nominal $p = 0.026$).

BCX7353 significantly reduced the use of standard of care acute attack medication per 28 days vs. placebo by 53.6% (nominal $p < 0.001$) for 150 mg and 46.3% (nominal $p < 0.001$) for 110 mg. In responder analyses, 58%, 50%, and 23% of subjects receiving 150 mg BCX7353 had a $\geq 50\%$, $\geq 70\%$ or $\geq 90\%$ reduction in their HAE attack rates compared to baseline vs. 25%, 15%, and 8% of placebo subjects, nominal $p = 0.005$, nominal $p = 0.002$, and nominal $p = 0.073$, respectively.

Administration of BCX7353 at doses of 150 and 110 mg QD for 24 weeks was generally safe and well tolerated.

Overall 81.7% of subjects experienced a treatment-emergent adverse event (TEAE) on study: 85.0% of 150 mg subjects, 82.9% of 110 mg subjects, and 76.9% of placebo subjects; 39.5% of BCX7353-treated subjects and 33.3% of placebo subjects experienced a drug-related TEAE. Five subjects discontinued study drug due to TEAEs: 1 (2.5%) on 150 mg, 3 (7.3%) on 110 mg, and 1 (2.6%) on placebo. No subjects on 150 mg, 1 subject on 110 mg (2.4%), and 3 subjects on placebo (7.7%) experienced serious adverse events (SAEs) on study; none of these events were drug related. All drug-related TEAEs were mild to moderate on placebo and in the 150 mg group, and the majority of TEAEs in the 110 mg group were mild to moderate; 3/41 (7.3%) 110 mg subjects experienced Grade 3 drug-related TEAEs. Few subjects had treatment-emergent Grade 3 or 4 laboratory abnormalities. One subject on 150 mg BCX7353 who had previously been exposed to androgens had Grade 4 ALT elevation and Grade 3 AST elevation without symptoms, which resolved after discontinuing study drug.

The most common TEAEs across all arms were nasopharyngitis, nausea, and vomiting. Overall, 50.0% and 41.5% of BCX7353 150 and 110 mg subjects, respectively, had GI abdominal-associated TEAEs vs. 35.9% of placebo subjects. There were no drug-related rashes (events of special interest [EOSI]).

Orally administered BCX7353 was a generally safe, well tolerated, and effective treatment for the prevention of HAE attacks in Part 1 of this study, with greater efficacy at the 150 mg dose compared to the 110 mg dose, and no increase in safety or tolerability risk.

5.3.2. Summary of Study BCX7353-203

The results of the Phase 2 trial, Study BCX7353-203, were published in the *New England Journal of Medicine* (Aygoren-Pursun, Bygum et al. 2018). In summary, this Phase 2 sequential dose de-escalating, randomized, placebo-controlled study evaluated 4 dose levels of BCX7353 administered QD for 28 days: 350, 250, 125, and 62.5 mg (salt nomenclature [SN]). As reported in the publication:

> "The APeX-1 trial showed that BCX7353 at doses of 125 mg or more administered orally once daily resulted in markedly lower rates of angioedema attacks than placebo. An apparent U-shaped dose response was observed in the primary end point, with the highest treatment effect observed at the 125-mg dose: the attack rate was 73.8% lower than with placebo, and 43% of patients were attack-free."
>
> The data suggest that the efficacy of the BCX7353 doses of 250 mg and 350 mg was probably masked by GI adverse events [AEs] that may have been misattributed as early symptoms of abdominal angioedema attacks. Only the 125-mg dose group had a lower rate of abdominal attacks than the placebo group, whereas all groups that received BCX7353 at doses of 125 mg or more had lower rates of peripheral attacks than the placebo group (difference, 68% to 82%). GI AEs were more common at the doses of 250 mg and 350 mg than at lower doses, and a small number of liver abnormalities were observed at the highest doses in patients with extensive previous use of androgens. The side-effect profile in this trial was consistent with a trial involving healthy volunteers, in which GI AEs were more commonly reported in higher BCX7353 dose groups (Cornpropst, Dobo et al. 2016). The effectiveness of BCX7353 was further supported by secondary efficacy end points involving a post hoc hierarchical analysis, with substantial improvements observed in patients' QoL at the 125-mg dose level, although post hoc

P-values should be interpreted with some caution. The mean improvement (change from baseline) in the AE-QoL total score was > 4 times the minimal clinically important difference [MCID] of 6 points (Weller, Magerl et al. 2016)."

5.3.3. Data Monitoring Committee Review of Ongoing Studies BCX7353-302, BCX7353-301, and BCX7353-204

Data from Studies BCX7353-204, BCX7353-301, and the current study, BCX7353-302, are reviewed by the BCX7353 data monitoring committee (DMC) at protocol-specified intervals.

The latest data review as of the time of the protocol amendment, 30 July 2019, by the BCX7353 DMC included 120 dosed subjects on Study BCX7353-302, 226 dosed subjects on Study BCX7353-204, and 19 dosed subjects on Study BCX7353-301 with 315 subjects receiving study treatment for > 84 days (> 12 weeks).

The recommendation of the DMC was that all studies proceed per protocol.

5.4. Rationale for Study

Currently, the only prophylactic treatments approved for prevention of angioedema attacks in HAE are oral androgens, parenteral C1-INH therapies, and a monoclonal antibody inhibitor of plasma kallikrein. While patient experience has improved with the expansion of approved therapies for HAE, an orphan disease, a 2013 survey of 245 United States (US) physicians that treat HAE indicated that their perception is that only 40% of their patients are fully satisfied with current HAE treatments (Riedl, Banerji et al. 2013). Regular IV infusions of C1-INH for prophylactic use in HAE may lead to an increase in complications over time, such as thrombosis, infection, pain and limited venous access (Shire ViroPharma Inc. 2018). The currently approved formulation of subcutaneous (SC) C1-INH for prophylaxis of HAE attacks requires 13 steps to prepare the drug for administration and approximately 8 to 10 mL of drug to be administered twice weekly based on an adult weight range of 67 to 83 kg. This medication also requires slow administration into the SC space over a length of time considered comfortable for the patient (CSL Behring LLC 2017). Lanadelumab-flyo, a monoclonal antibody and plasma kallikrein inhibitor, was recently approved in the US for prophylaxis to prevent attacks of HAE (Shire 2018). It is administered via SC injection and patients or caregivers must be trained by a healthcare professional prior to use. Hypersensitivity is a risk associated with lanadelumab-flyo, and in clinical trials, 52% of patients who took the drug experienced injection site reactions (primarily pain, erythema, and bruising at the injection site). Even patients with HAE with no contraindications to androgens and who tolerate prophylactic androgens face long-term risks with continued treatment. Therefore, there remains a significant medical need to provide additional HAE treatment options that are efficacious, convenient, and well-tolerated.

BCX7353 is an oral kallikrein inhibitor in development for prevention of angioedema attacks in patients with HAE Type I and II. BCX7353 has activity against plasma kallikrein at low nM concentrations (Section 5.2) that are attainable and sustained in humans following oral administration. In both Part 1 of the current study and the proof-of-concept 28-day study BCX7353-203 (APeX-1), the rate of angioedema attacks in subjects randomized to BCX7353 was statistically significantly lower than in placebo subjects and BCX7353 was generally safe and well-tolerated. These data support further clinical development of BCX7353 as a potential future option for prophylaxis of HAE attacks.

5.4.1. Rationale for Study Design

This study is designed to evaluate the efficacy of 2 doses of BCX7353 compared to placebo in preventing attacks in subjects with Type I and II HAE, as measured by the rate of Investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period in Part 1. The current study expands upon the scope of Study BCX7353-203 by evaluating the safety and efficacy of BCX7353 over a longer duration (24 weeks in Part 1) relative to placebo in a greater number of subjects per dose (approximately 32 subjects will be enrolled in each dose group). Moreover, in the current study, the efficacy of BCX7353 will be evaluated in an HAE population potentially characterized by a wider range of attack frequency (minimum of 2 attacks in 8 weeks are required for entry). The current study will be conducted as a parallel cohort assessment of active doses vs. placebo. A parallel cohort design, in contrast to a crossover study design, reduces the number of important statistical assumptions and eliminates the concern of any carryover effects from one treatment period to another. However, greater than anticipated variance in attack rates in 1 or more groups may invalidate the power calculation and sample size chosen at the outset of the study. For this reason, a blinded sample size re-estimation is included in accordance with the FDA Guidance Adaptive Design Clinical Trials for Drugs and Biologics (DHHS 2010).

Subjects randomized to Treatment Groups 1 and 2 in Part 1 will continue to be administered their same dose of BCX7353 in Part 2 of the study. Subjects randomized to Treatment Group 3 will be randomized to receive an active dose in Part 2. In Part 3, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit in an open-label manner, regardless of their initial treatment allocation. Subjects randomized to Treatment Groups 1 and 2 will have a total duration of active treatment of up to 144 weeks, and subjects randomized to Treatment Group 3 will receive a total of up to 120 weeks of active BCX7353 treatment.

Conduct of Part 2, the blinded extension on active drug, in part satisfies regulatory authorities' requirement to obtain safety data over an extended treatment duration given that the BCX7353 will be ultimately administered as a chronic therapy. The doses of BCX7353 will remain blinded during Part 2 because subjects will reach the Week 24 visit based on enrollment date, precluding unblinding until at least Part 1 analysis is complete.

Conduct of Part 3, an unblinded extension on active drug, provides additional safety and effectiveness data over an extended treatment duration.

5.4.2. Rationale for BCX7353 Doses and Regimen

The BCX7353 dosage regimens selected for evaluation in this study are 110 and 150 mg BCX7353 administered QD (equivalent to 125 mg and 150 mg QD [SN]).

In Study BCX7353-203, the HAE attack rate was significantly lower vs. placebo in subjects who received daily doses of 125, 250, or 350 mg BCX7353 (SN) and the drug was well-tolerated. The plasma drug levels achieved at each dose were generally predictable and had an acceptable level of inter-subject variability.

Two doses (110 mg QD and 150 mg QD) were studied in the Part 1 (24-week) analysis of the current study BCX7353-302 and in versions of BCX7353-204 (Versions 1-5). In Part 1 of Study BCX7353-302, the rate of angioedema attacks in subjects randomized to BCX7353 was statistically significantly lower than in placebo subjects, with the 150 and 110 mg doses reducing

HAE attacks by 44% ($p < 0.001$) and 30% ($p = 0.024$), respectively, vs. placebo. Orally administered BCX7353 was a generally safe, well-tolerated, and effective treatment for the prevention of HAE attacks in Part 1 of the current study, with greater efficacy at the 150 mg dose compared to the 110 mg dose, and no increase in safety or tolerability risk.

Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation.

5.4.3. Study Population Rationale

The current study is limited to adults and adolescents (≥ 12 years of age) of both sexes with HAE Types I and II. Children < 12 years of age are excluded from participation in BCX7353 clinical trials until the benefit-risk profile in adults and adolescents has been better characterized. Population PK modeling of PK data generated to date indicate that weight is a covariate on the bioavailability of BCX7353. Simulations of exposures by weight at clinically relevant doses indicated that a weight of < 40 kg is associated with exposures considered significantly higher (ie, > 20%) than that generated from an adult of 70 kg at doses to be studied in this protocol. Therefore, participation in the trial will be restricted to subjects who weigh at least 40 kg. At a weight of 40 kg, simulated exposure was well within the efficacious exposures identified in Study BCX7353-203 that were well-tolerated; therefore, it is anticipated that exposure in adolescent subjects will not exceed safe and tolerable exposures in adults.

Based on past and ongoing studies conducted in HAE patients, it is anticipated that female subjects will comprise at least 50% of the subject population in this study. HAE affects both males and females, although the disease has a greater burden on females, with an increased frequency and severity of HAE attacks in women (Bork, Meng et al. 2006, Lumry, Castaldo et al. 2010). Estrogen appears to worsen the disease, as evidenced by an increased number of attacks reported following onset of puberty and when estrogen-containing therapy is initiated (Bouillet, Longhurst et al. 2008, Caballero, Farkas et al. 2012). Due to the gender distribution of HAE and the influence of hormones on the frequency of attacks, it is considered important to include both male and female subjects in this clinical study to gain an assessment of potential safety and population PK differences.

Although there is no evidence of embryo-fetal developmental toxicity with BCX7353 in reproductive toxicology studies (Section 5.2), appropriate precautions are still warranted with respect to administering BCX7353 to women of reproductive age, in accordance with International Council for Harmonisation (ICH) guidelines. Women of childbearing potential may be enrolled in this study provided they meet the contraceptive requirements and have a negative pregnancy test (Section 8.2.1).

Pregnant women will be excluded from participation in the current study. Additionally, any female subject who becomes pregnant on study will be required to immediately discontinue study drug and will be followed through the end of the pregnancy (see Section 12.1.6).

5.4.4. Rationale for Control Group and Prohibition of Current Prophylactic Medications

In the current study, all participants must have access to effective, approved treatments for attacks of angioedema as part of their routine medical care. Each subject will continue to use their prescribed acute medication to treat any attacks, under the medical management plan advised by their physician, throughout the study. This is consistent with guidance documents that strongly support the position that all subjects with C1-INH deficiency should have access to medications for treating attacks (Cicardi, Bork et al. 2012, Zuraw, Banerji et al. 2013).

While there are approved therapies in the US and European Union (EU) for prophylaxis against HAE attacks, including C1-INH, consensus recommendations do not exist for either prophylactic treatment as a standard of care or a definition of indications for prophylaxis. A guideline published on the management of HAE by the US HAE Association Medical Advisory board suggests that decisions on when to use prophylaxis should be individualized (Zuraw, Banerji et al. 2013):

> *'The decision about when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient. Decisions regarding which patients should be considered for long-term prophylaxis should take into account attack frequency, attack severity, comorbid conditions, access to emergent treatment, and patient experience and preference.'*

Therefore, a subject randomized to placebo in the current study who has access to effective attack medications is considered to be treated in-line with current guidelines. Nevertheless, these guidelines acknowledge that the medical management of HAE in some subjects is best suited by use of an approved prophylactic medication in addition to an acute attack medication. Therefore, patients who need prophylaxis to manage their HAE will not be considered appropriate for this study.

To safeguard against enrolling subjects who need prophylaxis, subjects must meet an inclusion criterion assessing whether they are medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study. The informed consent and assent for this study will inform subjects on available prophylactic therapies and will note that they cannot discontinue prophylaxis for the sole purpose of screening for the trial; there must be medical and personal choice reasons to do so. If a subject has voluntarily discontinued prophylactic therapy outside of the specified window (see below) in advance of the Screening visit for medical or personal choice reasons, then they may be screened for study eligibility.

Use of androgens, or tranexamic acid for prophylaxis of HAE attacks are not allowed within 28 days of the screening visit; C1-INH prophylaxis is not permitted within 14 days of the screening visit. Use of lanadelumab-flyo is also prohibited. Initiation of any of these prophylactic medications is not allowed during the study.

The stipulated timeframe in advance of screening is intended to allow stabilization of attack rate after discontinuing prophylactic therapies before prospective collection of attacks required for eligibility and for the baseline attack rate for the study, which begins at screening. However, it should be noted that subjects may receive approved C1-INH therapies for acute treatment of angioedema attacks at any time.

5.4.5. BCX7353 Benefit-Risk Analysis

Given that BCX7353 is a small molecule kallikrein inhibitor with safety data available from completed Phase 1 and 2 studies, and Part 1 (24 weeks) of this randomized, double-blind, placebo-controlled, Phase 3 study, there is an acceptably low risk of severe or serious adverse reactions. Potential risks and findings from nonclinical and clinical studies of BCX7353 are discussed in Section 6 of the IB (Summary of Data and Guidance for the Investigators).

5.4.6. Benefits of Trial Participation

Study subjects will receive regular medical care for the duration of the study. Subjects may experience a reduction in the number of attacks if they are randomized to a BCX7353 treatment. The development of BCX7353 is expected to be of benefit to the wider community/patients with HAE.

5.4.7. Overall Benefit-Risk Assessment

The risks from daily oral administration of BCX7353 seen to date in both nonclinical and clinical studies were primarily mild, monitorable, and reversible. Based on the utility of other kallikrein inhibitors such as C1-INH and the pharmacology of BCX7353, and Phase 3 data from Part 1 of the current Study BCX7353-302, there is an expectation of benefit to the individual subject. The information obtained from this study will support the development of BCX7353 for HAE, a serious, debilitating, and potentially life-threatening disease. The overall benefit-risk balance is therefore considered to be acceptable.

6. TRIAL OBJECTIVES

6.1. Objectives

6.1.1. Part 1 Primary Objective

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

6.1.2. Part 1 Secondary Objectives

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

6.1.3. Part 2 Primary Objective

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

6.1.4. Part 2 Secondary Objectives

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

6.1.5. Part 3 Primary Objective

- To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 48- to up to 144-week administration period in subjects with HAE

6.1.6. Part 3 Secondary Objectives

- To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 48- to up to 144-week administration period
- To evaluate QoL and HAE disease activity of BCX7353 over a 48- to up to 144-week administration period
- To evaluate subject satisfaction with BCX7353 over a 48- to up to 144-week administration period

7. OVERALL STUDY DESIGN AND PLAN

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 3-part study. Part 1 is designed to test the hypothesis that the HAE attack rate during 24 weeks of prophylactic BCX7353 will be less than that observed during 24 weeks of placebo. The primary efficacy endpoint will be assessed after the last subject completes Part 1 (through Week 24). Part 2 is designed to primarily evaluate the long-term safety of BCX7353 at 2 dosage levels. Part 3 is open-label and designed to primarily evaluate the long-term safety of BCX7353. Parts 1, 2, and 3 will be conducted in sequence, with Parts 2 and 3 conducted as continuous roll-overs from Parts 1 and 2, respectively. All subjects will receive BCX7353 in Parts 2 and 3, including those randomized to receive placebo in Part 1. Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation.

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

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

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

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

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

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

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

Qualifying attacks during the run-in are characterized as follows:

- The attacks must occur during the run-in period, which is a minimum of 14 consecutive days and a maximum of 56 consecutive days, starting on the day of the screening visit.
- The attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
- The attacks must have either been treated, required medical attention or be documented to cause functional impairment, based on the subject's entry in the diary. Functional impairment is defined as the subject not being able to perform their daily activities without restriction (ie, subject records that they are at least slightly restricted in their daily activities during their HAE attack).
- The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling.
- The attacks are otherwise confirmed by the Investigator to be HAE attacks.

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

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

The main study will be comprised of adult subjects (aged ≥ 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. Main study and substudy subjects will be randomized via a separate

randomization scheme; however, study-mandated procedures will be identical, and the analyses will include all subjects who participate in the study.

A blinded interim analysis may be performed to estimate the standard deviation (SD) from the pooled treatment groups after 50% of the subjects complete 24 weeks. The sample size may be re-estimated based on the variability from the pooled data. The final sample size will be the maximum of either the original planned sample size (32 per group) or the re-estimated sample size. No statistical adjustment for the final analysis is planned.

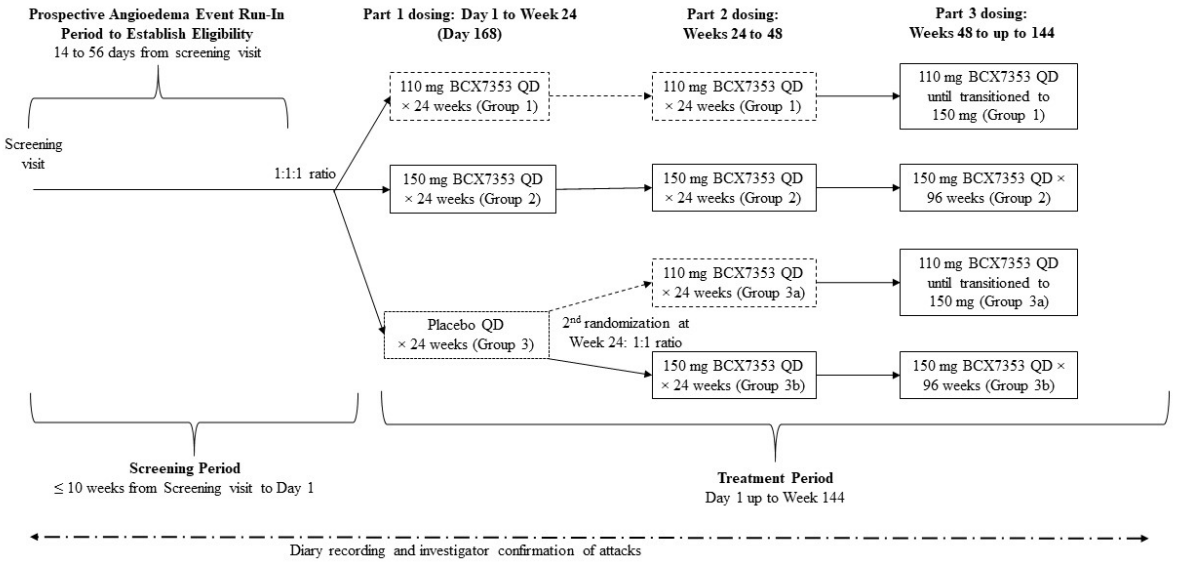
Study visits in Part 1 will occur at screening, baseline and Weeks 2, 4, 8, 12, 18, and 24. The primary efficacy analysis will occur after the last subject completes their Week 24 visit and will include all data through Week 24. Subject treatment will remain blinded to the subject, site, and Sponsor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

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

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

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

Figure 1. Study Schema



Abbreviations: QD = once daily.

Part 3 (up to 96-week evaluation of safety of open-label BCX7353)

Part 3 of the study will start with the administration of the study drug dispensed at the Week 48 visit. Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation.

Study visits in Part 3 will occur during Weeks 60, 72, 84, 96 approximately every 12 weeks thereafter, for a study duration of up to 144 weeks (approximately 3 years), or until another mechanism is available to provide drug to the subject (eg, market access) or the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first.

There will be telephone contact at Weeks 52, 56, 64, 68, 76, 80, 88, and 92.

Subjects will continue to document all angioedema attacks that occur in their diary throughout Part 3 and will have regular visits to assess safety and tolerability. Investigator confirmation of attacks will not be required for Part 3. All attacks recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in effectiveness analyses. These rules, which will be constructed in concert with HAE-treating physicians, will be outlined in the Statistical Analysis Plan (SAP). Additional related details of long-term experience on study will be summarized.

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

7.1. Endpoints

7.1.1. Part 1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is as follows:

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

7.1.2. Part 1 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

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

7.1.3. Part 1 Exploratory Efficacy Endpoints

- Number and proportion of subjects with no attacks over 24 weeks

- Use of HAE attack medications over 24 weeks
- The proportion of responders to study drug, defined as at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks during treatment compared with the baseline attack rate

7.1.4. Part 1 Safety Endpoints

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

7.1.5. Part 1 Health Outcome Endpoints

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

7.1.6. Part 2 Primary Endpoints

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

7.1.7. Part 2 Secondary Endpoints

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

- Durability in TSQM scores
- Durability in WPAI scores

7.1.8. Part 3 Primary Endpoints

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

7.1.9. Part 3 Secondary Endpoints

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

Approximately 96 subjects are planned to be enrolled in the study, which includes any adolescent patients enrolled in the substudy; additional subjects may be required after the potential sample size re-estimation based on the pooled, blinded SD of the weekly attack rate following 50% of subjects completing 24 weeks.

8.2. Subject Selection

8.2.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy).
2. Able to provide written, informed consent. Subjects who are aged 12 to 17 years of age at 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.
3. Subject weight of ≥ 40 kg.
4. A clinical diagnosis of HAE Type I or Type II, defined as having a 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 in the screening period with the results below the LLN reference range.

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

   If a subject has a normal C4 at the screening visit and it is desired to utilize a family history of C1-INH deficiency to establish an HAE diagnosis for eligibility, the Investigator should document this as a source file note based on either the Investigator's personal knowledge (ie, if a relative of the screening subject is also a patient of the same Investigator/practice) or interaction with medical staff of the treatment facility where the relative receives HAE care, who confirms the diagnosis. No historical laboratory documentation on the relative should be collected in the source documents.

   If a subject has a normal C4 at the screening visit and has C4 subsequently retested during an attack, C4 must be less than the LLN to establish an HAE diagnosis for eligibility. Normal C4 drawn during an attack excludes the subject from study participation.

   For patients with a normal C4 at the screening visit, historical SERPING analysis will not be permitted to establish eligibility. Mutations known to be associated with HAE or those that are likely associated with HAE (ie an unidentified mutation in the active binding site of C1-INH) will be accepted.
5. Access to and ability to use one or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH). Cinryze used for acute treatment of HAE attacks is an acceptable medication for this purpose.
6. Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.

7. The subject must have at least 2 HAE attacks which meet all of the requirements below during the run-in period of a maximum of 56 days from the Screening visit:
    - The attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
    - The attacks must have either been treated, required medical attention or be documented to cause functional impairment based on subject entry in the diary. Functional impairment is defined as the subject being unable to perform their daily activities without restriction (ie, subject records that they are at least slightly restricted in their daily activities during their HAE attack).
    - The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling.
    - The attacks are confirmed by the Investigator to be HAE attacks. Subjects will be contacted within 2 business days of the attack to discuss the attack, any queries on the entered data in the e-diary, as applicable.

      Subjects who have recorded 2 such attacks may be randomized to study drug beginning on or after Day 28 of the run-in period; subjects who have recorded at least 3 such attacks may be randomized to study drug beginning on or after Day 14 of the run-in period. Under no circumstances should the run-in attack requirement for eligibility be disclosed to study subjects.
8. Female subjects must meet at least 1 of the following requirements:
    a. Be a woman of childbearing potential (defined as a nonmenopausal adult or adolescent female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) who agrees to use at least an acceptable effective contraceptive method during the study and for a duration of 30 days after last dose of study drug. One or more of the following methods are acceptable:
        - Surgical sterilization (ie, bilateral tubal occlusion or vasectomy of male partner).
        - Placement of an intrauterine device (IUD) or intrauterine system (IUS) (implanted any time prior to or during screening).
        - Progesterone-only (implantable or injectable only) or oral (norethindrone-based only) hormonal contraception associated with inhibition of ovulation initiated at least 7 days prior to the screening visit. Note: Desogestrel is not permitted during this study.
        - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
        - Male or female condom with or without spermicide.
        - Use of an occlusive cap (diaphragm, or cervical/vault caps) with spermicide (foam/gel/film/cream/suppository).

      Female subjects who report being postmenopausal for ≤ 2 years and have a follicle-stimulating hormone (FSH) ≤ 40 mIU/mL must agree to use at least an

acceptable effective contraceptive method and (as proposed above) during study and for 30 days after the last dose of study drug.

Female subjects of childbearing potential who declare themselves as either sexually abstinent or exclusively having female sexual partners do not need to use an acceptable method of contraception. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."

b. Be a woman of nonchildbearing potential (defined as postmenopausal for > 2 years or having an FSH > 40 mIU/mL if postmenopausal ≤ 2 years or have had a hysterectomy, bilateral oophorectomy, or documented ovarian failure.

9. Male subjects must comply with the following requirements through the end of the study:

a. Subjects with female partners of childbearing potential (defined as postmenopausal ≤ 2 years or a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) must agree to utilize at least 1 acceptably effective contraceptive method. At least 1 or more of the following methods are acceptable:

- Surgical sterilization (ie, vasectomy or bilateral tubal occlusion of a female partner)
- Placement of an IUD or IUS
- Any form of hormonal contraception (oral, implantable, injectable, intravaginal, or transdermal)
- Use of a condom with or without spermicidal foam/gel/film/cream/suppository
- Partner's use of an occlusive cap (diaphragm, or cervical/vault caps) with spermicidal (foam/gel/film/cream/suppository)

Male subjects who declare themselves as sexually abstinent are acceptable for the purposes of this study. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."

Note: Contraception is no longer required for male subjects and their female partners under Protocol Version 3.0.

10. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate adequate compliance with all study procedures required from the screening visit through randomization, including diary recording of HAE attacks beginning at the screening visit.

8.2.2. Exclusion Criteria

Subjects must meet none of the numbered exclusion criteria below to be eligible for participation in this study. Medications prohibited for use during the study are addressed in Section 9.7.1.

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject by participating in the study.

2. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
3. Anticipated use of short-term prophylaxis of angioedema attacks for a pre-planned procedure during the screening or study periods (Parts 1 and 2 only).
4. Concurrent diagnosis of any other type of recurrent angioedema.
5. Clinically significant abnormal electrocardiogram (ECG) at the screening visit. This includes, but is not limited to, a QT interval corrected by Fridericia's formula (QTcF) > 470 msec for women, a QTcF > 450 msec for men, 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. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
7. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
8. History of or current implanted defibrillator or pacemaker.
9. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the Investigator, is clinically significant and relevant for this study. A calculated creatinine clearance (CL_{CR}) of ≤ 30 mL/min or AST or ALT value ≥ 3 × the upper limit of the normal (ULN) reference range value obtained during screening is exclusionary.
10. Prior enrollment in a BCX7353 study.
11. Suspected C1-INH resistance in the opinion of the Investigator or Sponsor.
12. History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 drinks/day).
13. Positive serology for human immunodeficiency virus (HIV) or current infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
14. Pregnant, planning to become pregnant during the study, or nursing.
15. Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
16. History of severe hypersensitivity to multiple medicinal products, or severe hypersensitivity/anaphylaxis with unclear etiology.
17. Use of androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to the screening visit or initiation during the study.

    Prophylaxis is defined as administration of a medication in the absence of symptoms of an HAE attack.

18. Use of C1-INH for prophylaxis of HAE attacks within the 14 days prior to the screening visit or initiation during the study. Use of a C1-INH therapy for treatment of attacks is not excluded at any time, nor is C1-INH for preprocedure prophylaxis for an unplanned/unforeseen procedure.

    Prophylaxis is defined as administration of a medication in the absence of symptoms of an HAE attack.

19. Use of concomitant medications that are metabolized by cytochrome P450 (CYP) 2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study (see Section 9.7.1).
20. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study (see Section 9.7.1).
21. Use of a medication that is transported by p-glycoprotein efflux pump (P-gp) and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study (see Section 9.7.1).
22. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
23. Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study (Parts 1 and 2 only). Established use (initiation ≥ 56 days prior to screening) during the study is permitted.
24. Current participation in any other investigational drug study or received another investigational drug within 30 days of the Screening visit.
25. An immediate family relationship to either Sponsor employees, the Investigator or employees of the study site named on the delegation log.
26. Held in an institution by a government or judicial order.

8.3. Subject Withdrawal from the Study and from Study Drug

8.3.1. Subject Withdrawal from the Study

Participation in the study is strictly voluntary; a subject may withdraw consent to contribute additional study information at any point. A subject who withdraws consent will be requested to attend an early termination visit to complete all end-of-study evaluations. Although a subject may withdraw from the study at any time without specifying a reason for withdrawal, if known, the reason for withdrawal will be recorded in the subject's medical records (source documents) and also in the CRF. If the reason for subject withdrawal is not known, the subject must be contacted to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 12. If at any point in the study the clinic is unable to contact the subject after appropriate attempts have been made, the subject will be considered lost to follow-up.

Once subjects have withdrawn from the study, the Sponsor will no longer provide treatment through the study. Following withdrawal from the study, a subject will be able to receive further

treatment as recommended by their treating physician and according to the accepted standard of care.

8.3.2. Subject Discontinuation from Study Drug

A subject will be permanently discontinued from study drug for any of the following reasons, which will be recorded in the source documents and CRF.

- Emergence of any laboratory abnormality or AE that in the judgment of the Investigator compromises the ability of the subject to continue study-specific procedures or it is considered not to be in the subject's best interest due to an altered risk/benefit profile.
- Recurrence of treatment-emergent AST or ALT elevation > 5 × ULN (confirmed) if BCX7353 is restarted after meeting hold criteria as outlined in Section 12.2.2.
- Treatment-emergent ALT or AST > 3 × ULN combined with either laboratory abnormalities indicative of significant hepatic toxicity (ie, meeting Hy's law, total bilirubin > 2 × ULN OR with an international normalized ratio [INR] > 1.5 or with symptomatology of acute hepatitis [ie, severe fatigue, nausea, vomiting, right upper quadrant pain and tenderness, fever, rash, and/or eosinophilia (> 5%)]).
- Subsequent determination that inclusion/exclusion criteria were not met
- Intercurrent illness or emergence of a new illness/medical condition that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.
- Subject noncompliance with study drug or to the protocol.
- The subject has a QTcF > 500 msec (confirmed on repeat ECG testing).
- The subject has a QTcF increase of more than 60 msec (confirmed by repeat ECG) from the mean QTcF value obtained from triplicate ECGs obtained at the Baseline visit and a simultaneous absolute QTcF > 450 msec (males) or > 470 msec (females).
- Subjects with a study drug related Grade 3 or 4 rash as described by the Division of Microbiology and Infectious Diseases (DMID) criteria "Skin-mucocutaneous" will be discontinued from study drug and treated according to best medical practice. All subjects with a suspected drug rash should undergo specific rash evaluation as described in Section 12.2.1. A Grade 3 rash is defined as vesiculation or moist desquamation or ulceration and a Grade 4 rash is defined as exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson syndrome or necrosis requiring surgery. Subjects with a Grade 1 or 2 study-drug related rash may be continued on BCX7353 if the Investigator, subject and Sponsor deem it appropriate. The protocol for continuing BCX7353 in the presence of a rash is described in Section 12.2.1.

Subjects who discontinue from study drug in Parts 1 or 2 will be requested to complete all regularly scheduled visits and procedures outlined in Table 2 or Table 3, respectively, through the end of the study part (ie, Part 1 or 2) in which they were being treated. Subjects who discontinue in Part 1 will be requested to complete all regularly scheduled visits and procedures

through Week 24. Subjects who discontinue in Part 2 will be requested to complete all regularly scheduled visits and procedures through Week 48. Subjects who discontinue in Part 3 will have an Early Termination visit 3 weeks after their last dose of study drug. All subjects who discontinue from all parts should be treated in accordance with local clinical practice for HAE.

If a subject who discontinues from study drug subsequently withdraws consent to continue study visits as previously outlined, please see Section 8.3.1.

Subjects are not eligible for treatment in Parts 2 or 3 if they discontinue study drug in Parts 1 or 2, respectively, due to any of the above cited reasons.

8.4. End of Study Definition

The end of study will be defined as when the last subject completes the last protocol-scheduled visit.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug and Study Drug Product

BCX7353 is an oral small molecule inhibitor of plasma kallikrein. All subjects will receive BCX7353 (150 or 110 mg) or matching placebo (Part 1 only) capsules for oral administration once daily for 24 to up to 144 weeks. Study drug in this study consists of BCX7353 and placebo capsules.

The investigational active pharmaceutical ingredient (API) is BCX7353, which is supplied as 55 or 75 mg capsules in Parts 1 and 2 and 110 or 150 mg capsules in Part 3. The capsules are comprised of the API (BCX7353) blended with the excipients pregelatinized starch, polyplasdone XL, colloidal silicon dioxide, and magnesium stearate in a gelatin capsule.

The matching placebo will also be provided as capsules to match the BCX7353. The matching placebo will contain microcrystalline cellulose.

In Parts 1 and 2, subjects will be instructed to take 2 capsules of study drug together daily. In Part 3, subjects will take a single capsule of study drug daily.

Additional details for the chemical and physical characteristics of BCX7353 may be found in the IB.

9.2. Description of Study Drug Packaging, Labeling, and Storage

The study drug will be packaged in bottles. Subjects will be dispensed a sufficient number of bottles and capsules to cover the dosing period until the next study visit.

Each container of study drug will be labeled with the information required per local law and may include: Sponsor name, study protocol number, description of the contents, a statement regarding the investigational (clinical trial) use of the study drug, expiry date, and kit number.

Study drug must be stored between 15°C and 25°C (room temperature).

Details on the study drug packaging, labeling, shipment, storage and dispensing will be provided in the investigational medicinal product (IMP) manual.

9.3. Randomization and Study Drug Blinding

9.3.1. Blinding

This is a double-blind study throughout both Parts 1 and 2. As such, study drug assignment will be blinded to the Investigator, study staff, study subjects, and clinical research organization staff. Part 3 will be open-label. No blinding will be used.

During Part 1, Sponsor employee(s) will also be blinded to the treatment allocation of individual subjects, with the exception of Sponsor staff responsible for managing clinical supplies. Employees who are not blinded to drug assignment will have no access to any other subject-level information for the duration of the study. Sponsor employees interacting with sites will remain blinded for Part 2 of the study, however, unblinding of these staff may occur out of necessity during document preparation for regulatory filings of the study.

The bioanalytical laboratory performing BCX7353 plasma concentration analysis will be given a copy of the randomization scheme.

Information on unblinding in the event of an SAE is provided in Section 12.1.9.

9.3.2. Randomization

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

9.3.2.1. Part 1 Randomization

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

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

Randomization will proceed in accordance with a computer-generated randomization schedule prepared by a nonstudy statistician. There will be a separate randomization schedule for main study and substudy subjects (adult and adolescent subjects, respectively).

Sites will randomize eligible subjects in the IXRS, preferably after all baseline assessments to reconfirm eligibility have been completed.

If required by site procedures (ie, dispensing of randomized study drug must occur through a pharmacy), the subject may be randomized on the business day prior to the planned baseline visit. The Sponsor may require review of screening data prior to randomizing a subject (eg, concomitant medications); any requirements will be provided to the site separately.

Enrollment into treatment groups will be stratified by the baseline HAE attack rate ($\geq$ 2 attacks/month vs. < 2 attacks/month). The baseline attack rate must be provided during randomization and is calculated by:

> (The number of HAE attacks meeting the criteria of an HAE attack below from the Screening visit through the time of randomization × 28) divided by the number of days

during the timeframe from the Screening visit through randomization, rounded up to 2 decimal places

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

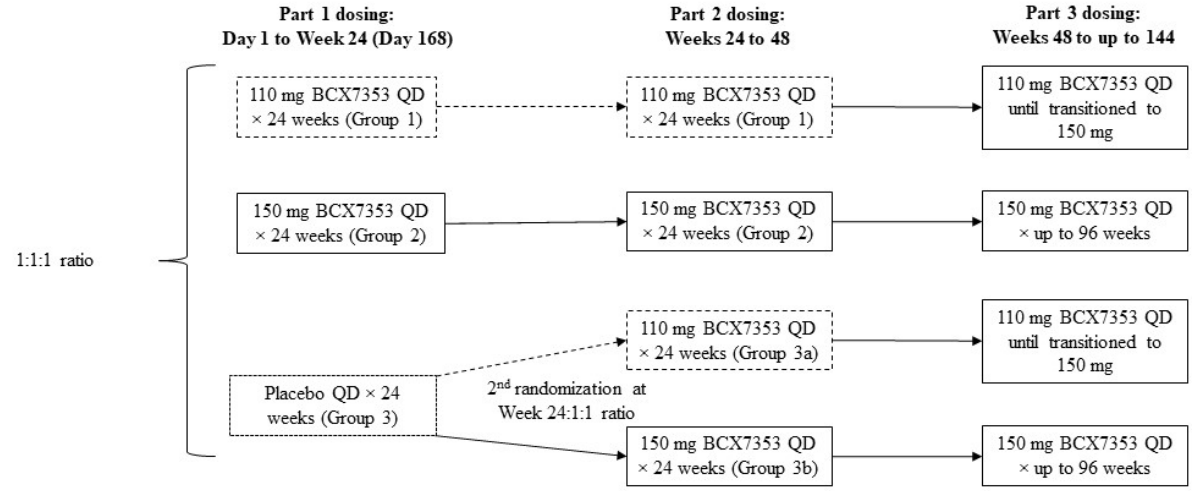
- The attacks must be unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
- The attacks must have either been treated, required medical attention or be documented to cause functional impairment based on subject entry in the diary. Functional impairment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

9.3.2.2. Part 2 Randomization

Sites will randomize subjects in the IXRS at the Week 24 visit for Part 2 study drug. Subjects who received active BCX7353 in Part 1 of the study (Treatment Groups 1 and 2) will continue to receive the same dosing regimen in Part 2. Randomization for subjects randomized to placebo in Part 1 (Treatment Group 3) will proceed in accordance with a computer-generated randomization schedule prepared by a nonstudy statistician. These subjects will be randomized in a 1:1 ratio to receive a 110 or 150 mg dose (see Figure 2). Sites will assign drug/randomize subjects in the IXRS at the Week 24 visit for Part 2 study drug. Sites using a centralized pharmacy may assign/drug randomize the subject the day prior to the Week 24 visit.

Based on the results of the current study's Part 1 analysis of better efficacy and no increase in safety risk at the 150 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial treatment allocation. Subjects will receive 150 mg of BCX7353 in an open-label manner.

Figure 2. Study Randomization



Abbreviations: QD = once daily.

9.4. Study Drug Administration and Treatment Compliance

Subjects will be instructed to take BCX7353 capsules orally QD at approximately the same time each day through up to 144 weeks as follows:

- Treatment Group 1 (110 mg QD):
  - Parts 1 and 2: two 55 mg capsules of BCX7353 QD × 48 weeks
  - Part 3: one 110 mg capsule of BCX7353 QD until the subject can be transitioned to the 150 mg dose
- Treatment Group 2 (150 mg QD):
  - Parts 1 and 2: two 75 mg capsules of BCX7353 QD × 48 weeks
  - Part 3: one 150 mg capsule of BCX7353 QD × up to 96 weeks
- Treatment Group 3a:
  - Parts 1 and 2 (placebo in Part 1, 110 mg in Part 2): two capsules of placebo QD × 24 weeks (Days 1 to 168) followed by two 55 mg capsules of BCX7353 QD × 24 weeks (Days 169 to 337)
  - Part 3: one 110 mg capsule of BCX7353 QD until the subject can be transitioned to the 150 mg dose.
- Treatment Group 3b:
  - Parts 1 and 2 (placebo in Part 1, 150 mg in Part 2): two capsules of placebo QD × 24 weeks (Days 1 to 168) followed by two 75 mg capsules of BCX7353 QD × 24 weeks (Days 169 to 337)
  - Part 3: one 150 mg capsule of BCX7353 QD × up to 96 weeks

Subjects will be instructed to take study drug at approximately the same time each day, with whichever meal is typically the largest meal of the day, or up to 30 minutes after consuming that meal. It is recommended that the study drug be administered with food to help minimize GI effects. If GI-related symptoms are noted as an AE, the site should query the subject and record whether the drug is being taken as instructed (ie, with a meal).

Day 1 for the purposes of analysis in Part 1 is defined as the day that subjects take their first dose of study drug. If the first study drug administration is different than the day of the baseline visit, subsequent visits will be calculated from the day of first dose (Day 1), rather than the day of the baseline visit. Clinic administration of study drug during study visits is not required. Subjects will take study drug in Part 1 beginning on Day 1 and will complete Part 1 dosing on Study Day 168 (the day before the Week 24 visit). Subjects will take Part 2 active study drug no sooner than the conclusion of the Week 24 visit on Study Day 169, after all other study procedures have been completed. Subjects will take Part 3 unblinded active study drug no sooner than the conclusion of the Week 48 visit.

Subjects will be instructed to maintain approximately the same daily dosing interval between study drug doses. If a subject forgets to take the study drug at the correct time, the dose may be taken later in the day; however, no more than 1 dose of BCX7353 should be taken on any calendar day. The subject should resume their regular dosing schedule on the next day. Dosing may not be split across a day.

Subjects will be instructed to record in their diary the time of day study drug was taken, and the number of capsules of study drug taken.

With the exception of the Week 2 and 26 visits, subjects will be instructed to bring all drug kits (including both unused and used bottles) and diaries with them for each study visit. Accountability and adherence will be reviewed at these visits.

During the conduct of the study, responsibility for kit supply and resupply may be transferred to a specialty pharmacy selected by the Sponsor and subjects may receive study drug directly from the specialty pharmacy. Detailed instructions will be provided at the time of implementation.

If a specialty pharmacy is used, specialty pharmacy staff may contact subjects directly to better understand the subject experience with study drug during the subject's participation in the study.

9.5. Study Drug Dose Modification

Dose reductions are not permitted. Study drug interruptions are discussed in Section 12.1.8. Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation, or, for those initially on 110 mg, their satisfaction with this dose level.

9.6. Study Drug (Investigational Medicinal Product) Accountability

Accountability of study drug dispensed and returned (as applicable) will be performed at Day 1 and at each study visit with the exception of the Week 2 visit and Week 26 visit. Returned study

drug bottles and/or kits must be retained and reviewed during monitoring visits by the clinical research associate (CRA) (Section 14.2).

The Investigator/pharmacist must maintain accurate records of the disposition of all study drugs received from the Sponsor, issued to the subject (including date), and any drug accidentally destroyed. At the end of the study, information describing study drug supplies (eg, kit numbers) and disposition of supplies for each subject must be provided, signed by the Investigator or designee, and collected by the CRA. If any errors or irregularities in any shipment of study medication to the site are discovered at any time, the Sponsor (and or designee) must be contacted immediately.

At the end of the study or at other times as agreed by all involved parties, all study drug not dispensed or administered will either be collected under the supervision of the CRA and returned to the Sponsor or destroyed on site as dictated by the appropriate Standard Operating Procedure at the participating institution.

9.7. Concomitant Medications

All subjects in the study must refrain from taking prohibited concomitant medications as outlined in Section 9.7.1.

Any regularly administered concomitant medication not listed as prohibited must be anticipated to be continued through the study and be of a stable dose and regimen up to Week 96.

Details of all prior medications (taken within 30 days of screening; prior contraceptive medications taken within 60 days of screening) and all current concomitant medication use (including herbal supplements) through the follow-up/early termination visit, including all medications administered for the treatment of AEs, will be recorded in the source documentation/CRFs.

9.7.1. Prohibited Medications

C1-INH for prophylaxis of HAE attacks is prohibited within the 14 days prior to the Screening visit or initiation during the study. However, use of a C1-INH therapy for treatment of attacks is not excluded at any time, nor is C1-INH for unplanned/unanticipated preprocedure prophylaxis.

Use of lanadelumab-flyo for prophylaxis of HAE attacks is prohibited during the study.

In addition, the following medications are excluded during the study (Section 8.2.2):

- Angiotensin-converting enzyme inhibitors within 7 days of the baseline visit or planned initiation during the study (potential for exacerbation of HAE).
- Another investigational drug within 30 days of the Screening visit or initiation during the study.
- Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study (Parts 1 and 2 only, potential for increasing HAE attack rate).
- Use of a medication that is transported by P-gp and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study. For the

purposes of this protocol, these are limited to: aliskiren, digoxin, posaconazole, and talinolol.

- Use of a concomitant medication that is metabolized by CYP2D6, CYP2C9, CYP2C19, or CYP3A4 and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study. For the purposes of this protocol, these are limited to: warfarin, phenytoin, s-mephenytoin, thioridazine, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus and desogestrel. Note: Topical or ophthalmic tacrolimus or sirolimus is allowed.
- Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study. For the purposes of this protocol, these are limited to: donepezil, thioridazine, haloperidol, methadone, procainamide and amitriptyline.
- Androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to the Screening visit or initiation during the study. Androgens must not be used at all during the study. Note: Use of testosterone replacement therapy is allowed.

10. STUDY CONDUCT

10.1. Overview

This is a randomized, double-blind, placebo-controlled study. A subject's participation in this study is expected to be up to 157 weeks (inclusive of the screening and follow-up periods), or until another mechanism is available to provide drug to the subject, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first.

Each eligible subject who consents to participate in the study will receive either 24 weeks (168 days) of BCX7353 (110 or 150 mg) or placebo in Part 1. Based on the results of the current study's Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects will be transitioned to the 150 mg dose of BCX7353 on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation. All subjects will undergo a screening period (including a prospective HAE attack run-in period between 14 and 56 days) of up to 10 weeks and a 3-week follow-up period. During the 144-week dosing period, all subjects will be required to attend at least 28 visits: Day 1 (Baseline), Week 2 (Day 15; liver enzymes only), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 18 (Day 127), Week 24 (Day 169), Week 26 (Day 183, liver enzymes only), Week 28 (Day 197), Week 32 (Day 225), Week 36 (Day 253), Week 48 (Day 337), Week 60 (Day 421), Week 72 (Day 505), Week 84 (Day 589), Week 96 (Day 673), Week 108 (Day 757), Week 120 (Day 841), Week 132 (Day 925), and Week 144 (Day 1009). A follow-up visit off of study drug will also be scheduled during Week 147.

10.2. Schedule of Assessments

The schedule of assessments for this study is presented in Table 2, Table 3, and Table 4 (for Parts 1, 2, and 3, respectively; study procedures are described in Section 11).

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

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

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

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

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

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

[c] The Week 2 visit will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, ALP); urine and additional tubes of blood may be required to accommodate possible reflex testing for abnormal GGT, AST or ALT (see Table 5). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

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

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

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

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

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

[h] Table 5 lists parameters to be assessed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[b] The Week 26 visit will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, ALP); urine and additional tubes of blood may be required to accommodate possible reflex testing for abnormal GGT, AST or ALT (see Table 5). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

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

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

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

[f] Table 5 lists parameters to be assessed.

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

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

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

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

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

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

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

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

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

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

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

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

Assessment	**Part 3 Open-Label, Active Study Drug Administration[a]**					**Follow-up/ Early Termination Visit** Week 147 + 1 week
	Week 60 Day 421 ± 6 days	Week 72 Day 505 ± 6 days	Week 84 Day 589 ± 6 days	Week 96 Day 673 ± 6 days	Visits every 12 weeks until Week 144 ± 6 days[o]	
In-clinic evaluations	X	X	X	X	X	X
Telephone contact[b]						
Subject weight[q]	X	X	X	X	X	X
Physical examination[c]	X	X	X	X	X	X
Urine pregnancy test	X	X[d]	X[d]	X	X	X
Vital signs[e]	X	X	X	X	X	X
Safety laboratory evaluations[f]	X	X	X	X	X	X
Troponin I and Troponin T	X	X	X	X	X	X
NGAL	X	X	X	X	X	X
CK-MB	X	X	X	X	X	X
Urinalysis[f]	X	X	X	X	X	X
12-lead ECG[g]	X	X	X	X	X	X
EQ-5D-5L[h,i]	X	X	X	X	X	
AE-QoL, TSQM, WPAI, long-term experience survey[i,p]	X	X	X	X	X	
Concomitant medications	←	—	—	—	—	→
AEs	←	—	—	—	—	→
Diary instruction/review[j]	X	X	X	X	X	X
Diary daily completion[k]	←	—	—	—	→	
Study drug dosing[l]	←	—	—	—	→	
Study drug accountability/ dispensing	X	X	X	X	X	X
Plasma for PK analysis[n]						X[m]
Plasma for kallikrein inhibition[n]						X[m]

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

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

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

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

[d] At clinic visits, sites in Europe will dispense urinary pregnancy tests to subjects who are women of childbearing potential. These will be performed by the subject at home at monthly intervals between study visits.

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

[f] Table 5 lists parameters to be assessed.

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

[h] Two EQ-5D-5L assessments will be administered at Weeks 60, 72, 84, and 96. The subject will fill out the first EQ-5D-5L to describe their current health state today as instructed per the instrument. The subject will also fill out a second EQ-5D-5L based on a recollection of their health state during an average attack that they experienced since the last study visit. If the subject has not had an attack since their last study visit, the subject is not required to fill out the second, attack-related EQ-5D-5L. After Week 96, the EQ-5D-5L will be administered every 24 weeks (Weeks 120 and 144) and at end-of-study visit.

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

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

[k] Any time the diary is in the subject's possession after Week 48 the subject will enter HAE attacks and relevant details at least once per day. No dosing information will be collected in in subject diaries in Part 3.

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

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

[n] PK and PD blood samples will be drawn on all subjects with no particular relationship to the timing of study drug dosing. The Investigator (or designee) must ensure that the time of the last dose prior to PK and PD draw is recorded in the CRF. Blood sample for PK is not required at the follow-up visit; blood sample is only required at an early termination visit occurring before Week 48.

[o] Up to 144 weeks or until another mechanism is available to provide drug to the subject, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first.

[p] After Week 96, the TSQM and WPAI will be administered every 24 weeks (Weeks 120 and 144). Beginning at Week 96, the subject long-term experience survey will be administered every 24 weeks (96, 120, and 144).

[q] Adolescent subjects will also have height measured at Weeks 96 and 144.

10.3. Study Visits

10.3.1. Screening Visit

Written informed consent and assent (as applicable) must be obtained from each subject before initiation of any screening assessments or procedures. Each subject will receive a copy of the signed and dated study-specific informed consent form (ICF). Prospective subjects who have signed an ICF who are interested in participation in the study will then undergo assessments at a screening visit to determine eligibility. Signing of the ICF may occur prior to the screening visit, which is defined as the visit where site-conducted screening procedures, including e-diary dispensing, are performed.

The Investigator (or designee) will conduct the following assessments at the screening visit, including:

- Signing of informed consent form (if not done prior to the visit) and assent (as applicable)
- Review of inclusion and exclusion criteria
- Medical and medication history (including HAE medical and medication history)
- Complete physical examination
- 12-lead ECG
- Height/weight/body mass index (BMI) estimation
- Vital signs (blood pressure, pulse rate, temperature, and respiratory rate)
- Serum pregnancy test for female subjects of child-bearing potential
- Blood collection for clinical chemistry, hematology, coagulation, HBV/HIV/HCV serology, C1-INH function, C4 level, and FSH (for women who declare that they have been post-menopausal ≤ 2 years). Blood may also be drawn for possible SERPING-1 gene analysis (see Section 11.2.10)
- Urine collection for urinalysis, drugs of abuse screen and possible reflex testing for abnormal gamma-glutamyltranspeptidase (GGT), AST, or ALT
- Recording of AEs and concomitant medications
- HAE attack e-diary provision and instruction

All subjects will receive an e-diary at the screening visit to establish eligibility during the run-in period (ie, a minimum of 14 days to a maximum of 56 days from the date of the screening visit) and also to provide a baseline attack rate to properly stratify the subject during Part 1 randomization. The subject will record daily attacks in the e-diary beginning at the screening visit.

In the case of time limitations for conduct of the screening visit, a site is permitted to perform screening assessments over more than one screening visit; however, the e-diary should be dispensed on the first screening visit day, initiating the run-in period.

Rescheduling of the screening visit should be considered if the subject reports a dose of C1-INH has been taken for an attack within approximately 3 days of the planned visit as C1-INH functional level is more likely to come back normal or to not meet Inclusion Criterion #4.

10.3.2. Period Between Screening and Baseline

Procedures to be performed by the site and/or clinical trial participants between screening and baseline are outlined in Table 2 and described in Section 11. Subject attendance at the clinic is not required to complete these procedures, unless additional blood sampling to confirm HAE diagnosis is warranted.

A subject's eligibility based upon the number of HAE attacks will be determined during the run-in period; the baseline attack rate of the subject will also be calculated during the period from the Screening visit through randomization for the purposes of properly stratifying the subject during randomization.

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

In order for the subject to qualify for the study, the subject must have at least 2 HAE attacks during the run-in period which meet all of the following requirements below:

- The attacks are unique, which is defined as an attack that does not begin within 48 hours of the end of a previous attack.
- The attacks must have either been treated, required medical attention or be documented to cause functional impairment based on subject entry in the diary. Functional impairment is defined as the subject being unable to perform their daily activities without restriction (ie, subject records that they are at least slightly restricted in their daily activities during their HAE attack).
- The attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling.
- The attacks are otherwise confirmed by the Investigator to be HAE attacks.

Once a subject records 2 such attacks, they may be randomized to study drug beginning on or after Day 28 of the run-in period; subjects having at least 3 such attacks may be randomized to study drug beginning on or after Day 14 of the run-in period. The maximum run-in period duration is 56 days.

Under no circumstances should the run-in attack requirement for eligibility be disclosed to study subjects.

The Investigator (or designee) must call and talk to the subject at least weekly in between the screening and baseline visits; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the Investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of attack details (if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an attack as the Investigator must call and confirm or reject the attack.

If a subject has a normal C4 level (as is the case in a small percentage of subjects with HAE) drawn at the screening visit, the site may take another sample for C4 level assessment, during an attack. A normal C4 level, when drawn during an attack, excludes the subject from study participation.

If a subject has a normal C4 at the screening visit and it is desired to utilize a family history of C1-INH deficiency to establish an HAE diagnosis for eligibility, the Investigator should document this as a source file note based on either the Investigator's personal knowledge (ie, if a relative of the screening subject is also a patient of the same Investigator/practice) or interaction with medical staff of the treatment facility where the relative receives HAE care, who confirms the diagnosis. No historical laboratory documentation on the relative should be collected in the source documents.

A SERPING-1 mutation known, or likely, to be associated with HAE Type I or II is acceptable to confirm the diagnosis of HAE.

For a C1-INH functional level that is between 50% and the LLN (74%), the site may draw another C1-INH functional level or, if desired, have a SERPING-1 gene mutational analysis performed by the central laboratory. A C1-INH functional level < 50% or a SERPING-1 mutation known, or likely, to be associated with HAE Type I or II, as assessed by the central laboratory, is acceptable to confirm the diagnosis of HAE.

Blood for possible SERPING-1 gene sequencing may be drawn at the Screening visit but analyzed in the period between the screening and baseline visits only if required for eligibility (normal C4 at screening or a C1-INH level between 50% and the LLN [74%]).

Subjects who are deemed ineligible for the study will return their e-diary to the study site.

Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, will be approved or denied on a case-by-case basis by the Sponsor Medical Monitor. Retesting of specific assessments within the screening period without entirely rescreening a subject may be permitted. Additionally, the Investigator must gain Sponsor approval to enroll subjects who are not randomized within 10 weeks of the screening visit; this may require screening labs to be redrawn. Subjects will not be permitted to rescreen if they did not meet the HAE attack requirements during the run-in period.

A screening failure CRF page will be completed for those subjects who do not proceed with study dosing, recording the reason for screen failure.

AEs and concomitant medications will be recorded if reported during this period.

10.3.3. Part 1

10.3.3.1. Baseline Visit (Day 1)

Subjects who meet all study eligibility criteria, and who agree to participate will be asked to return for a scheduled Day 1 visit, to be held 70 days or less from the screening visit.

Before any study drug is administered the following assessments will be completed:

- Administration of EQ-5D-5L, AE-QoL, TSQM, and WPAI questionnaires. Where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions.
- Review of inclusion and exclusion criteria, medical and medication history (including HAE medical and medication history) and prohibited medications
- Subject weight
- Vital signs (blood pressure, temperature, respiratory rate, and pulse rate)
- 12-lead ECG (in triplicate)
- Complete physical examination
- Blood collection for clinical chemistry, hematology, and coagulation, C1-INH antigenic level, complement 3 (C3), Troponin I and Troponin T, NGAL, HLA typing, and CK-MB
- PK and PD plasma samples
- Optional blood collection for exploratory pharmacogenomics testing (provided a separate informed consent/assent has been obtained; sample can be drawn at any visit)
- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT and urine pregnancy test for female subjects of childbearing potential. A negative urine pregnancy result must be recorded for the subject to be dosed.
- Review of concomitant medications and AEs
- e-Diary instruction and review
- Randomization, study drug accountability and dispensing. It is preferred that randomization occur after all Baseline assessments have been completed.

After completion of the above bulleted items, the first dose of study drug may be administered in the clinic (see Section 9.3.2) or administered at home on the day of the visit. Day 1 of the study is defined as the day in which subjects take the first dose of study drug.

During the Part 1 dosing period, Investigators will contact subjects to confirm all HAE attacks recorded in the e-diary within approximately 2 business days of the end of the attack. Moreover, any noncompliance will warrant contact with the subject.

The Investigator (or designee) must call and talk to the subject at least weekly; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the Investigator (or designee) will assess the subject's overall

wellbeing, discuss compliance (if applicable), proper recording of attack details (if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an attack as the Investigator must call and confirm or reject the attack.

10.3.3.2. Week 2 Visit

The Week 2 visit will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, alkaline phosphatase [ALP]); urine and additional tubes of blood may be required to accommodate reflex testing for abnormal GGT, AST, or ALT (see Table 5). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

During Part 1, Investigators will contact subjects to confirm all HAE attacks recorded in the e-diary within approximately 2 business days of the end of the attack. Moreover, any noncompliance will warrant contact with the subject.

10.3.3.3. Week 4, 8, 12, and 18 Visits

Subjects will return to the clinic during Week 4 (Day 29 ± 2 days), Week 8 (Day 57 ± 2 days), Week 12 (Day 85 ± 2 days), and Week 18 (Day 127 ± 2 days).

Subjects do not need to withhold any doses on clinic days or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing.

The following assessments will be performed:

- Administration of EQ-5D-5L (1 or 2 questionnaires), AE-QoL, TSQM, and WPAI questionnaires. Where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions.
- Subject weight
- Vital signs (blood pressure and pulse rate)
- 12-lead ECG (single assessments)
- Abbreviated physical examination (targeted to new signs and symptoms)
- Blood collection for clinical chemistry, hematology, and coagulation, Troponin I and Troponin T, NGAL, and CK-MB
- PK and PD plasma samples
- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT and urine pregnancy test for female subjects of childbearing potential
- Review of concomitant medications and AEs
- Review of HAE attack and dosing diary completion and study drug compliance
- Study drug accountability and dispensing

During the Part 1 dosing period, Investigators will contact subjects to confirm all HAE attacks recorded in the e-diary within approximately 2 business days of the end of the attack. Moreover, any noncompliance will warrant contact with the subject.

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

At the Week 12 and 18 visits, sites in Europe will dispense urinary pregnancy tests to subjects who are women of childbearing potential. These will be completed by the subject at home at Weeks 16 and 22.

At the Week 18 visit and during phone calls prior to Week 24, subjects will be instructed to take their last dose of study drug on Day 168, the day prior to the Week 24 visit.

10.3.3.4. Week 24 Visit

The Week 24 visit will be conducted on Day 169, the day after the last dose of study drug in Part 1. Before any study drug for Part 2 is administered the following assessments will be completed:

- Administration of EQ-5D-5L (1 or 2 questionnaires), AE-QoL, TSQM, and WPAI questionnaires. Where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions.
- Subject weight
- Vital signs (blood pressure, temperature, respiratory rate, and pulse rate)
- 12-lead ECG (in triplicate)
- Complete physical examination
- Blood collection for clinical chemistry, hematology, and coagulation, Troponin I and Troponin T, NGAL, and CK-MB
- PK and PD plasma samples
- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT and urine pregnancy test for female subjects of child-bearing potential. A negative urine pregnancy result must be recorded for the subject to be dosed.
- Review of concomitant medications and AEs
- Part 1 study drug collection/accountability
- e-diary instruction and review

After completion of the above bulleted items, subjects may be randomized at the conclusion of the visit. Part 2 study drug may then be dispensed and accountability performed. The first dose of study drug in Part 2 may be administered (if timing coincides with typical dosing time, see Section 9.3.2). Study drug in Part 2, if not taken during the visit, should be taken the day of the visit at home.

During the Part 2 dosing period, Investigators will contact subjects to confirm all HAE attacks recorded in the e-diary within approximately 2 business days of the end of the attack. Moreover, any noncompliance will warrant contact with the subject.

10.3.4. Part 2

10.3.4.1. Week 26 Visit

The Week 26 visit (± 2 days) 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, AST, or ALT (see Table 5). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

During the Part 2 dosing period, Investigators will contact subjects to confirm all HAE attacks recorded in the e-diary within approximately 2 business days of the end of the attack. Moreover, any noncompliance will warrant contact with the subject.

10.3.4.2. Week 28, 32, 36, and 48 Visits

Subjects will return to the clinic during Week 28 (Day 197 ± 2 days), Week 32 (Day 225 ± 2 days), Week 36 (Day 253 ± 2 days), and Week 48 (Day 337 + 7 days).

The Week 48 visit will be conducted on Day 337 (+ 7 days). Subjects do not need to withhold any doses for the Week 28, 32, or 36 visits or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing.

The following assessments will be performed:

- Administration of EQ-5D-5L (1 or 2 questionnaires), AE-QoL, TSQM, and WPAI questionnaires. Where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions.
- Subject weight
- Vital signs (blood pressure and pulse rate)
- 12-lead ECG (single assessments)
- Abbreviated physical examination (targeted to new signs and symptoms)
- Blood collection for clinical chemistry, hematology, and coagulation, Troponin I and Troponin T, NGAL, and CK-MB
- PK and PD plasma samples
- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT and urine pregnancy test for female subjects of child-bearing potential
- Review of concomitant medications and AEs
- Review of HAE attack and dosing diary completion and study drug compliance
- Study drug accountability and dispensing

During the Part 2 dosing period, Investigators will contact subjects to confirm all HAE attacks recorded in the e-Diary within approximately 2 business days of the end of the attack. Moreover, any noncompliance will warrant contact with the subject.

At the Week 36 and 48 visits, sites in Europe will dispense urinary pregnancy tests to subjects who are women of childbearing potential. These will be performed by the subject at home at Weeks 40, 44, 52, and 56.

10.3.4.3. Week 40 and 44 Phone calls

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

10.3.5. Part 3

10.3.5.1. Week 60, 72, 84, and 96, 108, 120, 132, and 144 Visits

Subjects will return to the clinic for additional study visits for up to 144 weeks, until another mechanism is available to provide drug to the subject, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Study visits are planned to occur at Week 60 (Day 421 ± 6 days), Week 72 (Day 505 ± 6 days), Week 84 (Day 589 ± 6 days), Week 96 (Day 673 ± 6 days), Week 108 (Day 757 ± 6 days), Week 120 (Day 841 ± 6 days), Week 132 (Day 925 ± 6 days), and Week 144 (Day 1009 ± 6 days)..

Subjects do not need to withhold any doses on clinic days or take a dose in the clinic, unless the clinic visit occurs during the subject's normal time of dosing.

The following assessments will be performed:

- Administration of EQ-5D-5L (1 or 2 questionnaires), AE-QoL, TSQM, and WPAI questionnaires. Long-term experience on study will be assessed every 24 weeks beginning at Week 96 via brief questionnaire. After Week 96, EQ-5D-5L, TSQM and WPAI will be administered every 24 weeks (Weeks 120 and 144) and at end-of-study visit. Where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions.
- Subject weight (adolescent subjects will also have height measured at Weeks 96 and 144)
- Vital signs (blood pressure and pulse rate)
- 12-lead ECG (single assessments)
- Abbreviated physical examination (targeted to new signs and symptoms)
- Blood collection for clinical chemistry, hematology, and coagulation, Troponin I and Troponin T, NGAL, and CK-MB

- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT and urine pregnancy test for female subjects of childbearing potential
- Review of concomitant medications and AEs
- Review of HAE attack diary completion and study drug compliance
- Study drug accountability and dispensing (collection only at Week 144)

During the Part 3 dosing period, investigator confirmation of HAE attacks recorded in the diary is not required. The diary should be reviewed with the subject at all study visits. Any noncompliance will warrant contact with the subject.

At all clinic visits, sites in Europe will dispense urinary pregnancy tests to subjects who are women of childbearing potential. These will be performed by the subject at home at monthly intervals between study visits.

10.3.5.2. Week 52, 56, 64, 68, 76, 80, 88, and 92 Phone Calls

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

10.3.6. Follow-up/Early Termination Visit

Following completion of study drug on Week 144 or earlier, all subjects will return to the clinic 3 weeks post-last dose (+ 1 week) for their follow-up assessments.

The following assessments will be performed for study completers at the follow-up visit held approximately 3 weeks following the last dose of study drug. These assessments will also be conducted at an early termination visit for those withdrawing consent during any study part (see Section 8.3.1):

- Subject weight
- Targeted physical examination
- Vital signs (blood pressure and pulse rate)
- 12-lead ECG
- Blood collection for clinical chemistry, hematology, coagulation, Troponin I and Troponin T, NGAL, and CK-MB
- Urine collection for urinalysis, possible reflex testing for abnormal GGT and urine pregnancy test for female subjects of childbearing potential
- Review of concomitant medications and AEs
- Review and collection of diary
- Blood for plasma PD and PK (early termination visit prior to Week 48 only)

If an AE is ongoing at the last follow-up visit, additional clinic visit(s) or telephone contact(s) may be warranted (see Section 12.1.2).

11. ASSESSMENTS

The schedule of procedures and assessments to be conducted throughout the study are outlined in Table 2 ,Table 3, and Table 4 (for Parts 1, 2, and 3, respectively) with details on the conduct of the procedures/ assessments provided below.

11.1. Chronology of Assessments

The following chronology of events should be adhered to during the scheduled visits, as applicable:

- QoL/health outcome questionnaires: obtain prior to all clinic procedures
- ECGs: obtain prior to vital signs and blood specimen collection
- Vital signs: obtain prior to blood specimen collection
- Randomization and study drug dispensing/dosing: end of the visit

11.2. Investigator-Completed Assessments

Demographic information, including year of birth, sex, race, and ethnicity will be captured for each subject participating in the study at the screening visit. Medical and medication history will be captured at the screening visit and updated at baseline. Subject participation in a prior BCX7353 study will be captured (eg, study, previous subject number).

Contraceptive methods enabling eligibility will be captured in source documentation at the screening visit. Contraceptive methods and/or lifestyle should be reviewed throughout the study to ensure they remain appropriate for the subject.

11.2.1. HAE Medical and Medication History

An HAE medical history questionnaire provided by the Sponsor will be completed at screening. All questions should be completed by the Investigator (or designee) from historical source documentation when available, with subject input as necessary to complete the remaining questions. The completed HAE Medical History Questionnaire will be considered a source document and must be entered in the CRF in full to enable randomization (see Section 9.3.2).

11.2.2. Physical Examination

A full physical examination will be conducted at Screening, Baseline, and at Week 24. All other physical examinations will be abbreviated (ie, targeted or symptom-directed) to include, at a minimum, evaluation of any new signs or symptoms.

Genitourinary and breast examinations may be omitted when not required by normal site practice.

11.2.3. Weight/Body Mass Index

For determination of height and weight, subjects should be clothed with shoes removed.

BMI should be calculated using the following formula:

$$BMI = \text{weight (kg)}/\text{height (m)}^2$$

BMI and height are only to be captured at the screening visit. Adolescents will also have height captured at Weeks 48, 96, and 144.

11.2.4. 12-lead Electrocardiograms

A standard bedside or routine 12-lead ECG machine that calculates heart rate and measures the PR, QRS, QT, RR, and QTc (QTcF) intervals will be utilized. Prior to obtaining an ECG, subjects should rest quietly in a supine position for at least 10 minutes.

Qualified site personnel should review the ECGs and automated findings in real-time for gross abnormalities and interval measurements of concern (absolute readings and for postbaseline ECGs, a change from baseline). For all ECGs, the clinical interpretation of the ECG and calculated QTcF (including adjudication of any automated measurements or diagnoses) should be recorded directly on a hard copy of the ECGs. Copies of the ECGs may be requested by the Sponsor. All subject identifiers will be masked prior to provision to the Sponsor.

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

An ECG should be repeated for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec.

11.2.5. Vital Signs

Blood pressure (systolic and diastolic) and pulse rate should be taken after the subject has rested in the supine position for at least 5 minutes. Blood pressure measurements must be obtained with an appropriate cuff size and with the subject's arm supported at the level of the heart. It is acceptable to obtain a pulse rate from the blood pressure or ECG machine. Temperature and respiratory rate will be captured at Screening, Baseline, and Week 24 only.

11.2.6. Clinical Laboratory Evaluations

Blood and urine samples will be obtained per the schedule of events. Individual laboratory tests to be performed are provided in Table 5.

All laboratory samples will be collected using kit supplies provided by the central laboratory, which will also analyze all samples, the possible exception of Week 2 and Week 26 liver function assessments which may be drawn and resulted locally. If results are obtained from both central and local laboratories for the same assessments at a single study time point, only the central laboratory results will be used for study purposes. Additionally, urine pregnancy tests will be provided by the central lab but will be analyzed at the clinical site. A laboratory reference manual will be provided to the site detailing kit contents, reordering instructions, subject fasting requirements (if any), sample collection, handling, storage, and shipment.

Results from the laboratory values should be reviewed as received by the Investigator. Evidence of this review should be provided in the source records and may include printing of the laboratory reports with a signature attesting to a review. For out-of-range laboratory findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings in the opinion of the Investigator should be recorded as an AE and handled as described in Section 12.1.

Table 5. Clinical Laboratory Evaluations

Chemistry

- Albumin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Bilirubin (total and direct)
- Blood glucose
- Blood urea nitrogen (BUN)
- Electrolytes (calcium, sodium, potassium, chloride, bicarbonate [CO2], phosphorus)
- Lipid panel (total cholesterol, triglycerides)
- Creatine kinase
- Creatinine and calculated CL_{CR}
- Gamma-glutamyl transferase (GGT)
- Lactate dehydrogenase (LDH)
- Total serum protein
- Uric acid
- *If amylase is > 2 × ULN, reflex to* lipase

Urinalysis

- Specific gravity
- Blood
- Bilirubin
- Glucose
- Leukocytes
- Ketones
- Nitrites
- pH
- Protein
- Urobilinogen
- Microalbumin to creatinine ratio
- Reflex Microscopy if dipstick is abnormal

Hematology

- Hemoglobin
- Hematocrit
- Erythrocytes
- Mean corpuscular haemoglobin (MCH)
- Mean corpuscular haemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils)
- Platelets

Coagulation

- Prothrombin time (PT) and international normalized ratio (INR)
- Activated partial thromboplastin time (aPTT)

Pregnancy Test

Serum (screening) and urine (other scheduled visits) βHCG for women of childbearing potential only

Drug screen

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Opiates
- Methamphetamine
- Ecstasy

Additional Tests

- FSH for women postmenopausal ≤ 2 years
- Hepatitis B surface antigen, hepatitis C antibody, HIV antibody; if HCV antibody positive, reflex to HCV RNA testing
- Troponin I
- Troponin T
- Neutrophil gelatinase-associated lipocalin (NGAL)
- CK-MB
- C3
- HLA typing
- Sample for possible exploratory pharmacogenomic analysis (optional)
- C1-INH level and function
- C1-INH antigenic level
- C4
- *If GGT, AST or ALT is ≥ 3 × ULN, reflex to* carbohydrate deficient transferrin (CDT)
- *If GGT, AST or ALT is ≥ 3 × ULN, reflex to* urinary ethyl glucuronide

CL_{CR} will be calculated using the Cockcroft-Gault formula and actual body weight (ABW):

$$CL_{cr}\ (mL/min) = \frac{(140 - \text{age in years}) \times ABW\ (kg)}{72 \times \text{serum creatinine (in mg/dL)}}\ (\times 0.85 \text{ for females})$$

11.2.7. Screening for Human Immunodeficiency Virus, Hepatitis B, and Hepatitis C Serology

Blood samples will be collected at screening for serologic testing for evidence of HIV, chronic hepatitis B, and chronic hepatitis C infection.

11.2.8. HLA Typing

All subjects will have a blood sample drawn at Baseline (or any other time point on study if not obtained at Baseline) for HLA typing. Samples will be sent to a central laboratory for analysis. The results will not be communicated back to the Investigator or subjects because the results are not intended for diagnostic or prognostic purposes and will be used in a research related fashion only. Relationships between safety assessment findings and HLA typing results may be examined on a meta-study basis

11.2.9. Pregnancy Testing

FSH will be measured at screening in women declaring themselves postmenopausal ≤ 2 years to establish childbearing status. At screening, a serum pregnancy test should also be drawn in the event a woman subject postmenopausal ≤ 2 years is found to be of childbearing potential.

For women and adolescents of childbearing potential, a serum pregnancy test will be administered at screening. Urinary pregnancy tests will be assessed at all subsequent visits. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test.

Urine pregnancy tests will be provided by the central laboratory but will be resulted locally.

Women of childbearing potential who enroll at sites in Europe will be dispensed urinary pregnancy tests as noted in the Schedule of Assessments to be completed at home at Weeks 16, 22, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92 and then monthly between clinic visits. Sites will confirm negative test results by telephone and record in source documents.

11.2.10. HAE Diagnostic Confirmation

C1-INH functional level and C4 are to be drawn at the screening visit; it is recommended that samples not be drawn within 3 days of C1-INH administration (eg, use for treatment of an HAE attack).

If a subject has a normal C4 level (as is the case in a small percentage of subjects with HAE) drawn at the screening visit, the site may draw another C4 level during an attack. A normal C4 level drawn during an attack excludes the subject from study participation.

Alternatively, the site may also utilize SERPING-1 gene mutational analysis or a family history of C1-INH deficiency in the case of a normal C4 level. To utilize a family history of C1-INH deficiency to establish an HAE diagnosis for eligibility, the Investigator should document this as a source file note based on either the Investigator's personal knowledge (ie, if a relative of the

screening subject is also a patient of the same Investigator/practice) or interaction with medical staff of the treatment facility where the relative receives HAE care, who confirms the diagnosis. No historical laboratory documentation on the relative should be collected in the source documents. A SERPING-1 mutation known or likely to be associated with HAE Type I or II assessed during the screening period is acceptable to confirm the diagnosis of HAE.

For subjects with a normal C4 at the screening visit, historical SERPING analysis will not be permitted to establish eligibility.

For a C1-INH functional level that is between 50% and the LLN (74%), the site may draw another C1-INH functional level sample or, if desired, have SERPING-1 gene mutational analysis performed. A C1-INH functional level < 50% or a SERPING-1 mutation known or likely to be associated with HAE Type 1 or 2 is acceptable to confirm the diagnosis of HAE.

Blood for possible SERPING-1 gene sequencing may be drawn at the Screening visit or during the period between screening and baseline but analyzed only if required (normal C4 at screening or a C1-INH functional level between 50% and the LLN [74%]).

11.2.11. Other Laboratory Assessments

Troponin I, Troponin T, NGAL, and CK-MB will be measured in this study at Baseline, at on-treatment visits (except for Weeks 2 and 26) and at follow-up.

C3 level will be taken at Baseline and subsequently only if required for study drug-related rash (see Section 11.2.14)

A C1-INH antigenic level will be measured at Baseline.

11.2.12. Pharmacokinetics and Pharmacodynamics

All plasma samples for determination of BCX7353 will be analyzed using a validated liquid chromatography-mass spectroscopy assay. The analysis of PK samples obtained from subjects randomized to placebo will be limited. The bioanalytical lab performing the analysis may be given the randomization scheme prior to unblinding to avoid analysis of subjects who received placebo.

Blood samples for PK and kallikrein inhibition will be drawn on all subjects at baseline and subsequent visits through Week 48 (except Weeks 2 and 26).

Actual date and time of sample collection will be recorded in the CRF. Sites will ensure that the time of the previous dose prior to the blood draw is recorded in the diary (may also be captured in the CRF).

Instructions for collection, processing, storage, and shipment of PK samples will be provided to the clinical site in a separate document.

11.2.13. Pharmacogenomic Testing

All subjects who are willing to participate and sign a separate informed consent will have a blood sample drawn at Baseline (or any other time point on study if not obtained at Baseline) for possible exploratory pharmacogenomics testing. Testing may be undertaken in one or more locus/loci if desired by the Sponsor to examine whether allelic variations account for efficacy or

safety findings. Samples will be sent to a central laboratory for analysis and results will not be returned to sites.

Pharmacogenomic samples will be pseudo-anonymous and will be identified by a code number. Neither the subject's name nor initials will be used on any forms or blood samples. Subjects may withdraw their consent for participation in the optional pharmacogenomic portion of the study after the sample has been collected by notifying the Investigator. If the sample has not yet been analyzed, it will be destroyed. If the sample has been analyzed, the information that has been collected will be retained.

Pharmacogenomic samples will be stored for up to 7 years after the last subject completes the study.

Possible SERPING genetic analysis is discussed in Section 11.2.10.

11.2.14. Rash Assessment

Because of the potential for a study drug-related rash, all sites are required to have the ability to obtain high resolution photographs and obtain an appropriate skin biopsy.

These can be performed by experienced site physicians or a dermatologist on retainer for this study. All subjects should be instructed to call the site for any new skin rash. Photos may be sent by the subject to the Investigator to help determine the need for urgent medical assessment at the site.

Subjects should be medically evaluated within 24 to 36 hours of awareness of any diffuse maculopapular rash that could be drug-related. Rashes that resolve within 24 to 36 hours and therefore cannot be medically evaluated will not result in a protocol deviation. In the event the site is notified of a rash by a subject on the weekend, the medical evaluation and Sponsor notification can be performed on the next working day. The site must inform the Sponsor medical monitor via the EOSI form of all BCX7353-related maculopapular rashes (Section 12.1.5.1). If the rash is assessed as not maculopapular (eg, urticarial) or not related to BCX7353 (ie, has a clear alternative etiology), then the rash should be reported as an AE not an EOSI, treated per Investigator judgement, and no further special assessment is required.

The following assessments must be completed for all subjects with a diffuse maculopapular rash assessed as related to BCX7353 as soon as logistically possible:

- Full dermatological exam to include the scope of the rash (location), vital signs, and mucosal examination. The notes documenting the examination should include detailed description of the rash; presence or absence of desquamation; presence or absence of blistering and if present, its extent; presence or absence of mucosal involvement and if present, its extent; and any other associated abnormal physical findings.
- High resolution photographs taken to provide both detail regarding the rash and details regarding the extent of the rash. Cameras must be able to provide clear images taken in close proximity to the skin. The picture should include a ruler (centimeter) for scale. Every attempt to protect subject anonymity should be made.

- All detailed clinical information regarding the rash, examination, treatment and interpretation of the event needs to be reported on an SAE/EOSI report form as per Section 12.1.5.1.
- Blood taken for clinical chemistry, hematology including differential, and C3 level. Table 5 outlines the clinical chemistry and hematology analytes to be assessed. If the Investigator wishes more rapid results, a second set of blood tubes may be sent to the local lab for faster processing.
- Vital signs including temperature
- Urine sent to local laboratory for urine eosinophils (if evaluation is available locally).
- Subjects should be requested to undergo a standard dermatologic punch biopsy for H&E staining and immunofixation. The biopsy should be of fresh lesion both for diagnostic and scientific purposes, after obtaining specific informed consent. This type of biopsy requires only antisepsis and local anesthesia, without the need for sutures. The biopsy results will significantly help to clarify the underlying pathophysiology of the rash and more fully inform the risk/benefit assessment and ultimate therapeutic course. If the study site cannot perform a biopsy or any of the above mandatory assessments (ie, photographs), then subjects should be referred to a physician who can perform the assessments/biopsy (ie, a dermatologist). If a non-study physician performs any of the assessments or biopsy, a full written consultation report should be obtained expeditiously and include clinical examination findings and clinical diagnostic assessment. Biopsies should be at least 3 mm minimum diameter. Instructions for preparation of the samples and details regarding histopathological assessment will be according to local practice. Note: If the rash is no longer present by the time of medical evaluation, biopsy is not required.

  If a subject with drug-related treatment-emergent maculopapular rash does not agree to undergo skin punch biopsy, study drug dosing may be continued, but with weekly visits until the rash has resolved.
- Subjects will also be required to donate a blood sample for peripheral blood mononuclear cells (PBMCs) for analysis of possible drug-specific immune responses and possible drug-responsive T-cells. This sample should be obtained preferably 1 to 3 months but as late as 5 years after occurrence of the rash. Information on PBMC collection, processing, and shipment will be communicated to sites prior to sample collection. All additional detailed clinical information regarding the rash, examination, treatment and interpretation of the event needs to be reported on the SAE/EOSI report form as per Section 12.1.5.1.

11.2.15. Adverse Events

AEs will be assessed and recorded from the time that the ICF is signed through the last follow-up visit or until the AE is resolved or the subject is in a clinically stable condition with regards to the AE. Full details on recording and reporting AEs are provided in Section 12.1.2.

11.3. Patient-Reported Outcomes

The AE-QoL, TSQM, and WPAI will each be administered once at Baseline (predose) and at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 48, 60, 72, 84, and 96. After Week 96, the TSQM and WPAI will be administered every 24 weeks (Weeks 120 and 144).

The EQ-5D-5L will be administered once at Baseline and at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 48, 60, 72, 84, and 96. After Week 96, the EQ-5D-5L will be administered every 24 weeks (Weeks 120 and 144). Subjects will fill out this questionnaire as instructed, describing their current health state today. During the on-treatment visits (post-baseline), subjects will fill out a second EQ-5D-5L questionnaire if they have had an attack since the previous visit. The subject will be instructed to fill out this second questionnaire based on a recollection of their health state during an average attack that they experienced since the previous visit.

Subjects will also be queried about their long-term experience on study beginning at Week 96 via brief long-term experience survey.

Each questionnaire will be translated into the local language as required. For all subject-completed forms, clinic staff should ensure the subject reads the instructions and completes the questionnaires in full prior to filing in the source documentation.

Where possible, the questionnaires should be completed by the subject prior to other assessments for that visit to prevent influencing subject perceptions.

11.4. HAE Attack and Dosing Diary and Attack Confirmation

11.4.1. Screening and Parts 1 and 2

11.4.1.1. HAE Attack and Dosing Diary

The Sponsor will supply e-diaries to sites. Study-specific manuals will be prepared for both site staff and subjects for use of the e-diary for this study.

While a subject has an e-diary in their possession, the subject will fill out the HAE attack e-diary daily, recalling whether or not symptoms of an HAE attack were experienced in the previous 24 hours. Subjects will fill out the e-diary daily regardless of the presence of HAE symptoms. If the subject does report an attack, additional details about the attack will be entered into the e-diary including start and stop time of the attack, attack symptoms, anatomical location of swelling (if applicable), severity, treatment(s) administered and times of administration, and whether additional medical care was sought for the attack. During study drug administration, subjects will also record the times of day study drug was taken daily in the e-diary.

All subjects will fill out an HAE e-diary during the run-in period of a minimum of 14 days to a maximum of 56 consecutive days from the Screening visit to enable the qualifying attack rate to be established. Subjects will continue to fill out their e-diary after the run-in period in advance of the baseline visit, as applicable. Subjects will continue to fill out the e-diary daily during the treatment and follow-up periods.

Site staff will set up the e-diary when a subject is initially provided an e-diary at the Screening visit and then as needed during the study (eg, to turn off entry into the dosing diary when not receiving study drug). Subjects should be instructed to bring their e-diary with them to each

study visit, up to and including Week 48, except Weeks 2 and 26. Once a subject completes or discontinues the study, the site should ensure that e-diaries are returned.

Given that real-time access to e-diary entries for subjects is available via website access, the Investigator (or designee) will proactively assess compliance, beginning during the screening period. Further training on completing the e-diary should be provided if e-diary completion compliance is < 90% at any point that during the study. A phone call may be necessary if compliance issues are noted in between clinic visits. Scheduled phone calls during the screening period and through Part 1 of the study to Week 24 are required to assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of attack details (if applicable), or any usability issues with the e-diary.

Study staff are not permitted to make any entries into the diary.

In the event that a subject's e-diary becomes nonfunctional or is otherwise not available for data recording, a paper diary may be utilized for short-term HAE attack and dose recording until the subject receives a replacement e-diary. Other scenarios for which the use of the paper diary and/or the shipment of a replacement e-diary may be permitted, following consultation with the Sponsor. During the period of paper diary use, it will be necessary for the subject to contact the Investigator after each attack that occurs.

Subjects who discontinue study drug should continue to record the occurrence of HAE attacks in their diary until the follow-up visit.

11.4.1.2. Investigator Confirmation of Attacks

Sites will have real-time access to e-diary entries for their subjects, including all attack details recorded, and will receive a notification for each attack that is recorded.

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

During the run-in period, HAE attacks used to establish eligibility must meet the following stipulations, in addition to the Investigator confirmation:

- The attacks must occur during the run-in period which is a minimum of 14 consecutive days and a maximum of 56 consecutive days, starting on the day of the Screening visit. Subjects who record 2 eligible attacks may be randomized to study drug beginning on or after Day 28 of the run-in period; subjects having at least 3 such attacks may be randomized to study drug beginning on or after Day 14 of the run-in period.

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

During the remainder of the screening period (after eligibility has been established during the run-in period but prior to randomization), HAE attacks must meet the following stipulations to be counted in the baseline attack rate calculation necessary for stratification, in addition to the Investigator confirmation:

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

After randomization through the end of Part 2, Investigators will use their judgment to confirm or reject a reported event as an HAE attack; however, all attacks must include symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions which are indicative of internal swelling.

11.4.1.3. Scheduled Telephone Contact

The Investigator (or designee) must call and talk to the subject at least weekly in between the Screening and Baseline visits and on-treatment through Week 24 and once during Weeks 40 and 44. Alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the Investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of attack details (if applicable), or any usability issues with the e-diary. The phone call may be omitted if the subject records an attack as the Investigator must call and confirm or reject the attack.

11.4.2. Part 3

11.4.2.1. HAE Attack Diary

The Sponsor will supply diaries to sites.

While a subject has a diary in their possession, the subject will fill out the HAE attack diary daily, recalling whether or not symptoms of an HAE attack were experienced in the previous 24 hours. Subjects will fill out the diary regardless of the presence of HAE symptoms. If the subject does report an attack, additional details about the attack will be entered into the diary including start and stop time of the attack, attack symptoms, anatomical location of swelling (if applicable), severity, treatment(s) administered and times of administration, and whether additional medical care was sought for the attack (through Week 96 only).

Subjects should be instructed to bring their diary with them to each study visit, up to and including Week 144. Once a subject completes or discontinues the study, the site should ensure that diaries are collected.

Study staff are not permitted to make any entries into the diary and are not permitted to change entries.

Subjects who discontinue study drug should continue to record the occurrence of HAE attacks in their diary until the follow-up visit.

11.4.2.2. Scheduled Telephone Contact

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

12. ADVERSE EVENT MANAGEMENT AND REPORTING

12.1. Adverse Events

AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period.

12.1.1. Definitions

12.1.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject. No causal relationship with the study drug or with the clinical study itself is implied. An AE may be an unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (eg, requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be AEs. If the diagnostic procedure prompts no additional treatment, visits, or monitoring, it may not meet the definition of an AE.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 12.1.2), including medical triggers resulting in an HAE attack. Emotional stress will not be considered an AE unless it results in a medical diagnosis or requires medical treatment.

- Findings from protocol-mandated interventions. This can include laboratory assessments performed in the course of the clinical trial. AEs should only be reported if the abnormalities are changes from baseline and are clinically significant as described above.
- Pre-existing medical conditions (other than the condition being studied) judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period. When recording such events on an AE/SAE eCRF page, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

An adverse reaction is defined in Article 2(n) of Directive 2001/20/EC as follows: all untoward and unintended responses to a study drug/IMP related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the study drug/IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

For the purposes of this protocol, HAE attacks and their associated symptoms will not be defined as AEs, even if the subject requires hospitalization. This information, as well as HAE attacks and associated symptoms are reported in the subject's diary and are a reflection of the disease under study. The events that may trigger an HAE attack, such as an infection or trauma, are considered AEs and should be reported as such.

Hospitalization scenarios do not require reporting as an SAE where there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform a routine control screening for a preexisting illness or to diagnose a suspected illness. In the case of the latter, the symptomatology should be reported as an AE and amended if a diagnosis is confirmed.
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed (eg, a joint replacement for which the subject was on a waiting list).
- Undergo medical observation due to HAE (eg, admission after routine dental procedure in a subject with HAE).
- Undergo medical observation without the occurrence of an AE due to standard of care in the region or hospital.

Surgical procedures should not be reported as AEs. The condition for which the surgery is required should be reported as the AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

AEs are designated as "nonserious" or "serious."

12.1.1.2. Serious Adverse Event

A SAE is an adverse event/reaction that results in any of the following outcomes:

- Death
- Is life-threatening (subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization (refer to Section 12.1.1.1 for details on hospitalization SAE criteria).
- Results in persistent or significant disability/incapacity (ie, there is a substantial disruption of a person's ability to carry out normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject's health or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. For this study, examples of such events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization.

In addition, the sponsor considers events of abortion (spontaneous or induced), fetal demise, and still birth as SAEs for reporting purposes.

Some hospitalization scenarios, as outlined in Section 12.1.1.1. do not require reporting as SAEs.

Overdose will be considered an SAE only if any of the seriousness criteria are met. Any clinical complication in association with the overdose should be reported as an AE or SAE (as applicable) along with the overdose (see Section 12.2.3). Details of signs or symptoms, clinical management and outcome should be reported, if available. Overdose without associated signs or symptoms should not be recorded as AEs but should be recorded as protocol deviations.

12.1.1.3. Adverse Events of Special Interest

For this protocol, nonserious treatment-emergent maculopapular rashes that are deemed related to BCX7353 will be considered EOSIs. This does not include other types of rashes such as urticaria or eczema. All treatment-emergent skin conditions should be reported as AEs but only maculopapular rashes deemed related to BCX7353 should be considered EOSIs.

An EOSI event in and of itself will not be considered serious unless it meets the seriousness criteria above. Events of maculopapular rash assessed as possibly, probably, or definitely related to BCX7353 regardless of severity must be reported to the Sponsor Medical Monitor as described in Section 12.1.5.1. Management of BCX7353 drug-related rash is provided in Section 12.2.1.

12.1.2. Method, Frequency, and Time Period for Detecting Adverse Events and Reporting Serious Adverse Events

Reports of all AEs and SAEs, regardless of Investigator attribution, are to be collected from the time of signing of the informed consent through to the last study visit (ie, through the posttreatment follow-up visit). All AEs and SAEs are to be reported on the AE CRF.

AEs should be documented on CRFs as Investigators become aware of them. AEs are to be followed until the event resolves. If an event is ongoing at the last follow-up visit, Grade 1 and 2 events do not need to be followed if the event is deemed unlikely to be related or not related to study drug (see Section 12.1.3 for AE grading). For all Grade 3 and 4 events or events deemed possibly related to use of study drug, the event should be followed until the AE is resolved or the subject is in a clinically stable condition with regards to the AE.

The Investigator shall report all SAEs immediately to the Sponsor by communicating with the Medical Monitor (phone or email) and by submission of an SAE report form via email, and entering the event onto the AE CRF within 24 hours of their knowledge of the event (see Section 12.1.5). The SAE report form is a detailed, written report on the SAE provided by the Sponsor or designee. The Investigator should follow all unresolved SAEs observed during the study until they are resolved, or are judged medically stable, or are otherwise medically explained.

The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. In such cases, the diagnosis should be documented as the AE and not the individual sign/symptom. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually. Once a diagnosis is made during evaluation or treatment, the Investigator will update the AE record with this diagnosis. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter to ensure that the Sponsor shall have the necessary information to continuously assess the benefit-risk profile of the study drug in a clinical trial.

12.1.3. Definition of Severity

All AEs will be assessed (graded) for severity and classified using the DMID criteria for grading AEs (Publish date November 2007, see Section 16.1). Any AEs not covered by the DMID criteria will be assessed and classified into 1 of 4 clearly defined categories as follows:

Mild:	(Grade 1): Transient or mild symptoms; no limitation in activity; no intervention required. The AE does not interfere with the participant's normal functioning level. It may be an annoyance.
Moderate:	(Grade 2): Symptom results in mild to moderate limitation in activity; no or minimal intervention required. The AE produces some impairment of functioning, but it is not hazardous to health. It is uncomfortable or an embarrassment.
Severe:	(Grade 3): Symptom results in significant limitation in activity; medical intervention may be required. The AE produces significant impairment of functioning or incapacitation.
Life-threatening:	(Grade 4): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required to prevent death, hospitalization; or hospice care probable.

Severity refers to the medical perspective of an event while seriousness reflects the outcome of the event (ie, hospitalization). Events of mild severity can lead to hospitalization and therefore be serious while severe events such as a headache may not meet seriousness criteria.

12.1.4. Definition of Relationship to Study Drug

The Investigator or medically qualified designee must review each AE and make the determination of relationship to study drug using the following guidelines:

Not Related:	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident, and no temporal relationship exists between the study drug and the event.
Unlikely:	The event does not follow a reasonable temporal sequence from drug administration and is readily explained by the subject's clinical state or by other modes of therapy administered to the subject.
Possibly Related:	There is some temporal relationship between the event and the administration of the study drug and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident.
Probably Related:	The event follows a reasonable temporal sequence from drug administration, abates upon discontinuation of the drug, and cannot be reasonably explained by the known characteristics of the subject's clinical state.
Definitely Related:	The event follows a reasonable temporal sequence from study drug administration, follows a known or suspected response pattern to the study drug, is confirmed by improvement upon stopping the study drug (dechallenge), and reappears upon repeated exposure (rechallenge, if rechallenge is medically appropriate).

12.1.5. Reporting Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

Any SAE must be reported by phone or email to the Sponsor Medical Monitor and in writing via email using the SAE report form within 24 hours of the Investigator's awareness of the SAE. In addition, all SAEs must be recorded on the AE CRF in real time. All additional follow-up evaluations of the SAE must be reported to BioCryst or its designee as soon as they are available. The SAE report forms should be sent to the following email addresses:

Phone (24 hours): +1-919-859-7905
Email: safety@biocryst.com
mm@biocryst.com

Immediate reporting should allow BioCryst to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the initial report should be submitted by the Investigator within a very short period of time and under no circumstances should this period exceed 24 hours following awareness of the SAE.

The follow-up report should allow BioCryst to determine whether the SAE requires a reassessment of the benefit-risk profile of the study drug in a clinical trial, if the relevant information was not already available and provided in the initial report.

US-based Investigators or designees at each site are responsible for submitting any investigational new drug safety report (initial and follow-up) (ie, suspected unexpected serious adverse reaction [SUSARs]) or other safety information (eg, revised IB) to the institutional review board (IRB) and for retaining a copy in their files, unless otherwise instructed.

European-based Investigators or designees at each site are responsible for retaining copies of all SUSAR reports (initial and follow-up) and other safety information (eg, revised IB) in their files.

BioCryst or its designee will submit all SUSAR reports (initial and follow-up) or other safety information (eg, revised IB) to the required authorities.

BioCryst shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all participating countries, including European Member States concerned and the US, and to the independent ethics committees (IECs), and in any case no later than 7 days after knowledge by BioCryst of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days, in accordance with all applicable local laws. All other SUSARs shall be reported to the competent authorities concerned and to the IECs concerned as soon as possible but within a maximum of 15 days of first knowledge by BioCryst. BioCryst or designee shall also inform all Investigators.

12.1.5.1. Reporting Events of Special Interest

All events of diffuse maculopapular rash assessed as related to study drug/IMP, regardless of severity must be reported by phone or email to the Sponsor Medical Monitor and in writing via email using the SAE/EOSI report form within 24 hours of the Investigator's assessment of the event. High resolution photographs must also be submitted as described in Section 11.2.14. In addition, the event must be recorded on the AE CRF in real time. All additional follow-up evaluations of the event must be reported to BioCryst or its designee as soon as they are available. The SAE/EOSI report form should be sent to the following email addresses:

Phone (24 hours): +1-919-859-7905
Email: safety@biocryst.com;
mm@biocryst.com

This method of reporting will allow BioCryst to obtain more information than can be captured in the eCRF for this event. The report form will allow a full clinical description and information regarding the evaluation that cannot be documented in the electronic data capture due to free text limitations to be shared with BioCryst. Therefore, the initial report and photographs should be submitted by the Investigator within a very short period of time and under no circumstances should this period exceed 24 hours following assessment of the event.

The follow-up report should contain information about the clinical course, medical evaluation, additional photographs (if relevant), biopsy (if done), and laboratory results.

12.1.6. Pregnancy

Any female subject who becomes pregnant during the study should have study drug discontinued immediately and must be followed through the end of the pregnancy. While pregnancy is not considered an AE, all cases of fetal drug exposure via the parent as a study participant (including partners of study participants) are to be reported immediately to BioCryst or its designee. Consent from a pregnant partner of a study participant will be obtained prior to reporting any details of the pregnancy. Information related to the pregnancy must be given on a "Pregnancy Confirmation and Outcome" form that will be provided by the Sponsor or its designee so that the pregnancy may be followed and an outcome determined. Any AEs or SAEs experienced by a pregnant subject are to be reported as directed above in Section 12.1.2 and Section 12.1.5. Any complications reported in a subject's pregnant partner should be reported on the Pregnancy Confirmation and Outcome form. All pregnancies must be followed to outcome which occurs when an infant is delivered (live or still born), there is fetal demise, or there is an abortion (spontaneous or induced). Abortion (spontaneous or induced), fetal demise, and still birth along with congenital abnormalities in the newborn, should be reported as separate SAEs.

12.1.7. Serious Breaches of Good Clinical Practice

It is the responsibility of the Sponsor to notify the licensing authority of any serious breach of Good Clinical Practice which is likely to effect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study. All serious breaches will be notified to the relevant competent authority within 7 days. The reporting to the Sponsor will be performed by the party who suspects the serious breach.

12.1.8. Treatment Interruptions

Treatment interruptions as a result of Investigator management of AEs potentially related to study drug are permissible. Resumption of study drug administration is also permissible upon resolution of the event, as assessed by the Investigator, with a plan for stringent monitoring of the subject for recurrence of the AE as appropriate. In addition, other extenuating circumstances may lead to treatment interruptions such as vomiting during an abdominal HAE attack or required fasting for medical procedures; in these cases, study drug should be resumed once the extenuating circumstance is resolved. Treatment interruptions following suspected drug-related rashes are discussed in Section 12.2.1.

The exception to treatment interruption and resumption is when study drug is stopped for a rash considered study drug related (possibly, probably, definitely related). If study drug is interrupted for > 10 days due to a related drug rash, study drug may not be restarted. However, interruption for ≤ 10 days will be allowed because the study drug's long half-life would allow sufficient plasma concentrations to remain for safe reintroduction of study drug.

The Sponsor Medical Monitor should be notified in the event of a treatment interruption due to an AE. Any treatment interruption will be recorded in the CRF and source documents, including the reason for the interruption.

12.1.9. Emergency Procedures

Access to study drug/IMP assignment will be available immediately through the IXRS system if the Investigator deems it necessary to break the study blind in the interest of a subject's medical

safety, in case of a medical emergency, to meet regulatory reporting obligations, or if warranted during scheduled safety reviews. Where medically appropriate, the Investigator will contact the Sponsor Medical Monitor to discuss the situation which has arisen and resulted in the need for unblinding of the subject. The Sponsor Medical Monitor will not be involved in the decision to unblind.

12.2. Toxicity Management

The Investigator (or qualified designee) will grade clinically significant events and laboratory abnormalities according to that detailed in Section 12.1.3. Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing and before any contemplated study drug discontinuation, unless such a delay is not consistent with good medical practice.

In the event that a new clinically significant safety signal emerges, a meeting of the DMC may be convened by the Sponsor to evaluate risk to subjects and recommend appropriate actions. Based on the data presented, a decision will be made as to whether to halt the study, to continue dosing, or to continue dosing with provisions introduced into the protocol via substantial amendment.

12.2.1. Rash

Special evaluation of diffuse maculopapular drug rash is required as per Section 11.2.14 and special reporting is described in Section 12.1.5.1.

Management of rash should be based on best medical practice and address the subject's presentation. If a subject experiences a Grade 3 or 4 rash suspected to be due to study drug/IMP, the subject should have study drug/IMP dosing stopped immediately as per Section 8.3.2. Grade 3 rashes would include rashes with vesiculation, moist desquamation, or ulceration; Grade 4 rashes would encompass rashes with mucous membrane involvement or significant exfoliation, erythema multiforme, suspected Stevens-Johnson syndrome, or necrosis requiring surgery.

12.2.1.1. Study Drug Administration for Grade 1 or 2 Rashes Considered Related to Study Drug

Investigators and subjects may elect to continue dosing if the subject experiences a Grade 1 or 2 rash that is deemed related to BCX7353 but the subject is considered to be deriving benefit. By DMID criteria, this reaction would be described as pruritus and/or erythema (Grade 1) or a diffuse maculo-papular rash and/or dry desquamation (Grade 2). In addition, subjects would have to be constitutionally well (no fever, no change in appetite, no malaise, etc), have no mucosal involvement, no vesicles and have no clinically significant lab abnormalities in relevant analytes such as liver enzymes and creatinine. Mild or moderate eosinophilia may be present but should not prevent continuation of study drug if all other criteria are met. Rash treatment should primarily address symptoms (ie, antihistamines, topical antipruritics, and/or topical corticosteroids). Oral corticosteroids should be avoided, as there is no evidence that oral corticosteroids benefit patients with bland drug-related cutaneous reactions. Subjects who remain on study drug should be followed closely until the rash resolves.

If the subject's rash does not improve, or worsens to include vesicles, wet desquamation, or ulceration (Grade 3), then BCX7353 should be immediately discontinued.

For those who experience a BCX7353-related rash and the intent is for the subject to remain on BCX7353, the Sponsor must also agree based upon the completed EOSI form and photographs of the rash, at a minimum. Additionally, to ensure subject safety and provide highly specialized expertise, a group of independent experts will be made available if requested by either the Investigator or the Sponsor to provide advice on the diagnosis, prognosis, and management of subjects with a rash. Subjects may continue on BCX7353 while awaiting advice or have study drug held in anticipation of the advice, with the plan to resume treatment.

To be eligible for continued treatment, subjects must not have missed > 10 consecutive doses in the time since the rash was noted. Results from any assessments described in Section 11.2.14, including the biopsy, if performed, will be sent to the Sponsor and expert group (if applicable) as they become available to better inform the suspected diagnosis, pathophysiology and prognosis of the rash.

12.2.2. Aminotransferase (ALT or AST) Elevation

All baseline or treatment-emergent ALT or AST elevations > 3 × ULN (ie, Grade 3 and above) should be confirmed within 72 hours with repeat assessment of ALT and AST as well as total bilirubin, ALP, prothrombin time/INR, and complete blood count (CBC) for eosinophil levels. If subjects are asymptomatic with no other pertinent laboratory abnormality, study drug may be continued under close observation with weekly assessment of transaminase levels, total bilirubin, and ALP. These may be done at a local laboratory as long as results are reported to the Investigator as soon as they are available and the investigative site contacts the subject to ascertain any symptoms. If ALT or AST continue to increase and the subject remains asymptomatic, study drug dosing must be held if:

- Either ALT or AST is > 5 × ULN for > 2 weeks
- The ALT or AST reaches > 8 × ULN

The subject should continue weekly assessment of ALT, AST, total bilirubin, ALP, prothrombin time/INR, and CBC for eosinophil levels until ALT and/or AST are < 3 × ULN.

Provided specific criteria are met, the Investigator and subject may elect to resume BCX7353 dosing. All of the following criteria must be met for dosing to resume.

- The subject is considered to have been deriving benefit from BCX7353 prior to holding study drug.
- Transaminases return to ≤ 2 × ULN for subjects whose baseline transaminase levels were above the ULN, and ≤ ULN for those whose baseline transaminase levels were ≤ ULN.
- Subjects have not initiated or restarted androgens during the period BCX7353 was held.
- The subject agrees to continue weekly monitoring of ALT, AST, total bilirubin, ALP, CBC (eosinophil levels) and prothrombin/INR until levels appear stable and transaminase levels remain < 3 × ULN for at least 1 month after restarting BCX7353 dosing.

If at any time, the criteria as outlined in Section 8.3.2 are met, the study drug must be permanently discontinued.

12.2.3. Overdose

To date there is no experience with overdose of oral BCX7353. Single doses of up to 1000 mg, 7 days of dosing up to 500 mg/day, and 14 days of dosing with 350 mg/day revealed no clinically significant safety concerns in healthy subjects. Safety data generated in Study BCX7353-203 with 28-day dosing of up to 350 mg/day revealed no clinically significant safety concerns in subjects with HAE. Subsequently, subjects enrolled in BCX7353-106 were exposed to BCX7353 450 mg QD for 14 days without any unanticipated AEs or increased AE severity.

In the event that study personnel become aware of an overdose of study drug/IMP (> 1 dose per calendar day) that is associated with an AE, both the overdose and the resultant event should be reported as AEs. Overdose without any symptoms (ie, AEs) does not need to be reported as an AE. If overdose occurs with or without associated AEs, subjects should undergo clinical and laboratory monitoring as appropriate for their clinical condition and, if indicated, should receive clinically-indicated supportive therapy. Overdose without associated signs or symptoms should not be recorded as an AE but should be recorded as a protocol deviation.

Additional information about overdose as an AE or SAE is discussed in Section 12.1.1.2.

12.3. Data Monitoring Committee

An independent DMC will review the safety data from this study in concert with the cumulative safety information generated across the BCX7353 clinical development program. The DMC will convene and review safety data in Part 1 once the first 20 subjects enrolled complete 8 weeks of dosing. Given that the previous duration of dosing in HAE subjects was 4 weeks and no critical safety issues were discovered, this will allow the DMC to evaluate a reasonable number of subjects who have completed approximately half the dosing period, allowing the DMC and Sponsor to intervene if any safety signals arise. Subsequently, the DMC will meet and review all safety data on all subjects whenever an additional 20 subjects complete 8 weeks of dosing. Refer to Section 5.3.3 for DMC reviews performed as of the date of this protocol version. The final Part 1 DMC meeting using this schedule will be held when the last enrolled subject completes 8 minimum of 8 weeks of data in addition to all previously available safety data in aggregate from both Parts 1 and 2). The final efficacy analysis at 24 weeks will also include a full safety analysis that will be shared with the DMC. Once all subjects have completed Part 1, the DMC will transition to meet every 12 weeks until approximately 200 subjects across BCX7353-204 and the current study (BCX7353-302) have completed 48 weeks of dosing with active study drug. Once a total of approximately 200 subjects have completed 48 weeks across the 2 studies, the DMC will be provided with data for review every 6 months until the last subject completes the study or the product is approved in the first country globally. A formal meeting of the DMC members will not be required; however, if the data review identifies any concern, the DMC members may elect to hold a formal meeting. In addition, the emergence of a new clinically significant safety signal may prompt an ad hoc DMC review. Where possible, scheduled DMC reviews and meetings for this protocol may be aligned with those of other protocol(s).

At any point, the DMC will be allowed to request various levels of unblinding to fully evaluate subject safety.

The DMC may also meet at any time should a safety issue arise that requires DMC input or a partial or full unblinded review. This will be based on routine blinded safety data monitoring by the Sponsor and notification of the DMC. A separate DMC charter maintained in the trial master file will describe membership, roles, timing of DMC review, and responsibilities of the DMC members.

13. STATISTICS

13.1. Hypotheses

The primary study hypothesis is that the treatment effect in reduction of HAE attacks during 24 weeks of prophylactic BCX7353 (at either 150 mg QD or 110 mg QD) will be superior to placebo.

For each BCX7353 dose, the hypotheses can be expressed as

$$\text{Null hypothesis } (H_0): R_A - R_p = 0$$

$$\text{Alternative hypothesis } (H_1): R_A - R_p < 0$$

Where the R_A is the investigator-confirmed HAE attack rate on BCX7353 and R_p is the HAE investigator-confirmed attack rate on placebo

The primary efficacy endpoint is the monthly Investigator-confirmed HAE attack rate in the entire treatment period (Day 1 [post-dose] to Day 168 in the intent-to-treat population, which includes all randomized subjects.

The primary comparisons of interest will be performed at the 5% level of significance. All hypothesis tests will be 2-sided. Each BCX7353 dose will be compared to placebo in the primary analysis.

To account for the multiplicity of two BCX7353 doses, the Hochberg's step-up testing procedure will be used to control the overall type I error.

The primary objective of the study will be fulfilled at Week 24. The Hochberg step-up procedure will be used to control multiplicity of the 2 BCX7353 comparisons to placebo, 1 comparison for each dose. The error rate is controlled at the 5% level. Success will be declared when either active dose is shown to be statistically significantly different from placebo. With the Hochberg procedure, the p-values for the two doses are ordered. If the maximum p-value is < 0.05, success for both doses will be declared. If the maximum p-value is ≥ 0.05, then the p-value for the other comparison must be < 0.025 to be able to declare success for that dose only.

13.2. Sample Size Considerations

The pooled SD of the attack rate during effective dosing period in Study BCX7353-203 was 0.55. The observed treatment difference between 125 mg and placebo was 0.66 attacks/week, representing a 71% reduction in attack rate from the placebo group. The difference between the combined 125 mg and 250 mg group vs. placebo was 0.53, representing a 57% reduction.

Assuming a normalized placebo attack rate of 1 unit and a common SD of 0.55 units for BCX7353 and placebo attack rates, a sample size of 32 subjects will have 94% power to detect a

50% attack rate reduction (a treatment difference of 0.5 units) between BCX7353 and placebo, based on a 2-sided test at significance level of 0.05.

13.3. Sample Size Re-estimation

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

The final sample size will be the maximum of either the initial sample size (32 per group) or the re-estimated sample size.

13.4. Stratification

Randomization of subjects will be stratified by the baseline period HAE attack rate ($\geq$ 2 attacks/month vs. < 2 attacks/month)

13.5. Statistical Methods

A detailed SAP will be developed to describe the methods of analyses and summaries, including all endpoints, time points, populations, missing data, etc. Deviations from the analyses outlined in the SAP will be described in the clinical study report.

13.5.1. Analysis Populations

The analysis populations are defined below.

13.5.1.1. Screen Failures

Subjects who give written informed consent but are not randomized to study treatment are noted as screen failures in the eCRF are considered screen failures.

13.5.1.2. Intent-to-Treat Population

The ITT population will include all subjects who are randomized. The ITT population will be used as the primary population for efficacy analyses. Subjects will be analyzed based on the treatment to which they were randomized.

13.5.1.3. Safety Population

The safety population will include all subjects who received at least 1 capsule of study drug. This population will be used for all analyses of accountability, demographics, BCX7353 drug concentrations, and safety. Subjects will be analyzed based on the actual treatment received.

13.5.1.4. Per Protocol Population

The Per Protocol (PP) population will include subjects in the safety population that complete Part 1. A decision will be made prior to database lock on which (if any) subjects are to be excluded from the PP population based upon major protocol deviations. In the per-protocol

analysis, subjects will be assessed based on the actual treatment received on study Day 1. The PP population may be used as a secondary population for efficacy analyses.

13.5.1.5. Completers Population

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

13.5.1.6. Pharmacodynamic Population

The PD population for plasma kallikrein inhibition will include all subjects for whom at least 1 pre- and postdose plasma kallikrein inhibition result can be estimated. This population will be used for all analyses of plasma kallikrein inhibition.

13.5.1.7. Pharmacokinetic/Pharmacodynamic Population

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

13.5.2. General Considerations for Data Analysis

In general, descriptive summaries will include n, mean, SD, median, minimum, and maximum for continuous variables and n and percent for categorical variables. Summaries will be presented by study visit.

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

13.5.3. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race and ethnicity, height, weight, BMI, and HAE history including medication history will be summarized by treatment group.

Subject disposition will be presented for all subjects. The number of subjects who complete the study and those who discontinue from the study will be provided. The reasons for early discontinuation also will be presented. A tabulation of the number of subjects exposed to study drug and duration of exposure will also be presented for each treatment group. Treatment adherence, dose interruptions, and reason for dose interruptions will be provided as summaries or listed as appropriate.

13.5.4. Analysis of Efficacy Variables

The primary efficacy analyses will be based on Part 1 of the study. The efficacy analyses will be based on the ITT population. The analyses of the PP population and completers population will be used to support the primary efficacy analyses.

Efficacy data will be summarized by treatment group and total subjects who received BCX7353. HAE attacks will generally be summarized over 2 treatment periods: the entire dosing period and the steady-state or effective dosing period. The entire dosing period (Day 1 through Day 168, inclusive) is the date of first dose to the last dose in Part 1 on Day 168 + 24 hours, or 24 hours after the last dose of the study drug, whichever is earlier.

The effective dosing period (Day 8 through Day 168, inclusive) is the date of first dose + 7 days to the last dose in Part 1 on Day 168 + 24 hours, or 24 hours after the last dose of the study drug, whichever is earlier.

13.5.4.1. Primary Efficacy Analysis

The primary efficacy endpoint is the rate of investigator-confirmed HAE attacks during dosing in the entire treatment period of Part 1.

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

The Poisson model assumes that the mean and variance are equal. When the variance in the data is larger than the mean, the model is said to be over-dispersed. The assumptions of the Poisson model will be examined by looking for over-dispersion by examining the ratio of the variance to the mean. If there is evidence of overdispersion, a negative binomial model will be used in place of the Poisson regression model.

The potential impact of missing data on the primary efficacy outcome will be explored. Sensitivity analyses will be conducted to support the primary analysis. This will include analyses based on subjects who completed study and on those in the PP population. Missing data analyses will include imputation or use of data collected post- discontinuation for subjects who discontinue study treatment prior to Part 2. Details of missing data imputation will be provided in the SAP.

13.5.4.2. Secondary and Exploratory Efficacy Analyses

Part 1 secondary efficacy endpoints include:

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

Part 1 exploratory efficacy endpoints include:

- Number and proportion of subjects with no attacks over 24 weeks

- Use of HAE attack medications over 24 weeks
- The proportion of responders to study drug, defined as at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks during treatment compared with the baseline attack rate

Treatment comparisons in the AE-QoL total score change from baseline will be analyzed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation and an unstructured covariance matrix. The estimated treatment difference for each BCX7353 dose–placebo at each visit will be displayed together with the 95% confidence interval and the associated p-value. Primary inferences will be drawn from treatment differences for the changes from baseline derived from the MMRM model at Week 24. The change from baseline in the AE-QoL domain scores (function, fatigue, nutrition, and fear/shame) will also be analyzed using a MMRM model.

The secondary and exploratory efficacy endpoints will be summarized and listed. The between-treatment comparisons will be performed using the similar Poisson regression model for the Investigator-confirmed HAE attacks during the effective treatment period. The between treatment comparison for the responder endpoints will be performed using Cochran-Mantel-Haenszel, Chi-square, or Fisher's exact test. Multiplicity adjustments for the secondary efficacy endpoints will be described in the SAP.

Additional related details of HAE attacks (eg, symptoms, anatomical location, hospitalizations, emergency room visits, and attack duration) will be summarized and listed. Details of these analyses will be provided in the SAP.

The efficacy endpoints for Parts 2 and 3 include:

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of HAE attack medications
- Discontinuations due to lack of efficacy (through Week 48 only)
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

The analyses of efficacy at the end of the study will be provided descriptively. For the placebo subjects switched to an active BCX7353 dose, the change from placebo to the active dosing period will be summarized. The details of the planned efficacy analyses for the entire study will be provided in the SAP.

13.5.5. Planned Analyses

A single, blinded interim analysis for the purposes of possible sample size re-estimation may be performed after 50% of the subjects complete 24 weeks (See Section 13.3).

The primary analysis is planned after the last subject completes Week 24 of the study.

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

13.5.6. Analysis of Safety Variables

The safety analyses will be analyzed separately for Part 1; Parts 1, 2, and 3 will be combined for a long-term safety assessment.

Safety endpoints that will be summarized include, at a minimum, the number and proportion of subjects 1) with a TEAE; 2) who discontinue BCX7353 due to a TEAE 3) who experience a TESAE; 4) who experience a treatment-emergent Grade 3 or 4 AE; and 5) who experience a treatment-emergent Grade 3 or 4 laboratory abnormality. In addition, the proportion of subjects with a treatment-emergent, treatment-related AE consistent with a drug rash will also be summarized.

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class (SOC). The occurrence of TEAEs will be summarized using MedDRA preferred terms, SOC, and severity. Separate summaries of TEAEs, TESAEs, AEs considered to be related to study drug, and AEs leading to study drug interruption or to discontinuation will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries of vital signs, weight, bedside ECG parameters, and clinical laboratory results will be presented. Laboratory abnormalities will be graded according to the DMID Adult Toxicity Table (Publish Date: Draft, November 2007; Appendix 16.1).

Any graded abnormality that occurs following the initiation of study drug and represents at least 1-grade increase from the baseline assessment is defined as treatment-emergent. The number and percentage of subjects who experience treatment-emergent graded toxicities will be summarized. Laboratory toxicity shifts from baseline to worst postbaseline assessments will be summarized.

Clinically significant abnormal morphological ECG findings will be summarized.

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

$$\Delta_{ik} = (\text{QTcF for subject at time point k} - \text{Baseline QTcF})$$

Where QTcF measurements will be the average of triplicate ECGs at baseline and single values at each time point.

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.

Physical examination findings will be listed.

Concomitant medications will be coded using the World Health Organization drug dictionary and summarized.

As applicable, safety data will be summarized by treatment group and total BCX7353. No tests of hypothesis are planned for safety data.

13.5.7. Health Outcome Analyses

Health Outcome endpoints are as follows:

- EQ-5D-5L scores
- TSQM scores
- WPAI scores

The between-treatment comparisons for, EQ-5D-5L, TSQM, and WPAI will be performed using a mixed-effect model, including terms of treatment, visit, treatment and visit interaction, and baseline score. Details will be provided in the SAP.

13.5.8. Pharmacokinetic Analyses

Plasma samples for determination of BCX7353 concentrations are planned to be collected at Baseline/Day 1, Weeks 4, 8, 12, 18, 24, 28, 32, 36, and 48 and early termination (if applicable). The resulting PK data will be pooled in a meta-analysis to facilitate population PK analyses.

13.5.9. Pharmacodynamic Analyses

Plasma kallikrein inhibition data will be expressed as percent inhibition compared to subject baseline activity. Ex vivo plasma kallikrein activity will be listed by subject, treatment, day, and time and summarized separately by treatment, day, and time. Descriptive statistics will be reported. Mean and individual plasma kallikrein inhibition vs. time profiles will be plotted by treatment group.

13.5.10. Pharmacokinetic/Pharmacodynamic Analyses

Exposure-response analyses of the relationships between plasma kallikrein inhibition, efficacy endpoints, and BCX7353 plasma concentrations may be explored using model-based techniques as applicable.

14. STUDY ADMINISTRATION

14.1. Regulatory and Ethical Considerations

14.1.1. Regulatory Authority Approvals

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH E6); FDA/European Medicines Agency regulatory requirements and other national laws as applicable; and in accordance with the ethical principles of the Declaration of Helsinki. In addition, the study will be conducted in compliance with all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

14.1.2. Institutional Review Board and Ethics Committee Approvals

Before initiation of the study at an investigational site, the protocol, the ICF, the subject information sheet (if applicable), and any other relevant study documentation will be submitted

to the appropriate IRB/IEC. Written approval of the study must be obtained before the study center can be initiated or the IMP can be released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained, in particular, for changes to the study, such as modification of the protocol, the ICF, the written information provided to subjects, and/or other procedures.

The IRB/IEC will be promptly provided any new information that may adversely affect the safety of the subjects or the conduct of the study. On completion of the study, the IRB/IEC will be provided with a report of the outcome of the study.

Written reports of clinical study status will be submitted to the IRB/IEC annually or more frequently if requested by the IRB/IEC. A final study notification will also be forwarded to the IRB/IEC after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations. The study will be considered completed once the last subject completes the last study visit. Copies of all contact with the IRB/IEC should be maintained in the study file. Copies of clinical study status reports (including termination) should be provided to BioCryst.

14.1.3. Subject Informed Consent: Adults

A signed ICF must be obtained from each subject prior to performing any study-related procedures. Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study. Subjects will not be screened or treated until the subject has signed an approved ICF written in a language in which the subject is fluent.

The ICF that is used must be approved both by BioCryst and by the reviewing IRB/IEC. The ICF should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policies.

The Investigator must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice future treatment. They will also be told that their records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available. Subjects must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's dated signature. The subject should receive a signed and dated copy of the ICF. The original signed ICF should be retained in the study files. The Investigator shall maintain a log of all subjects who sign the ICF and indicate if the subject was enrolled into the study or reason for nonenrollment.

14.1.4. Subject Informed Consent: Adolescents

Signed informed consent must be obtained from each parent/caregiver of adolescent subjects aged 12 to 17 who enroll in the study prior to performing any study-related procedures. Similarly, subject assent by subjects 12 to 17 years will be obtained from each adolescent prior to performing any study-related procedures. If the local requirements limit the age of assent, then

assent will be obtained based on those requirements. Each parent/caregiver and subject should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process should take place under conditions where the parent/caregiver has adequate time to consider the risks and benefits associated with his/her child's participation in the study. Subjects will not be screened or treated until the parent/caregiver and subject has signed an approved ICF and assent form written in a language in which the subject is fluent. The ICF and assent forms that are used must be approved both by BioCryst and by the reviewing IRB/IEC. The ICF and assent forms should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policy.

The Investigator must explain to potential subjects and their parent/caregiver the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Each parent/caregiver will be informed that they are free for their child not to participate in the trial and that they may withdraw consent for their child to participate at any time. They will be told that refusal for their child to participate in the study will not prejudice future treatment. They will also be told that their child's records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available.

Parents/caregivers and subjects must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent and assent should be appropriately recorded by means of the parent's/caregiver's dated signature. The parent/caregiver should receive a signed and dated copy of the ICF, and the assent. The original signed informed consent and assent should be retained in the study files. The Investigator shall maintain a log of all subjects for whom consent was signed and indicate if the subject was enrolled into the study or reason for non-enrollment.

14.1.5. Investigator Reporting Requirements

The Investigator will provide timely reports regarding safety to his/her IRB/IEC as required.

14.2. Study Monitoring

During trial conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow BioCryst representatives, monitors, or its designees direct access to source documents to perform this verification.

It is important that the Principal Investigator(s) and their relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.3. Quality Assurance

The Principal Investigator may be subject to visits by the IRB/IEC, and/or by a quality assurance group for audits performed by BioCryst, or its designee, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

14.4. Study Termination and Site Closure

Overall, the Sponsor may suspend enrollment into the study, suspend treatment of ongoing subjects, or terminate the study to ensure that subjects' safety and welfare are protected. The entire study, or individual sites, may be terminated for any of the following reasons:

- Changes in scientific knowledge that lead to a negative impact on the risk/benefit profile for subjects
- Request of BioCryst or competent public authorities/IRB/IEC
- If recruitment cannot be completed in specified time frame
- If the permit to manufacture or import IMP is revoked
- If the study drug becomes commercially available or another mechanism is available to provide drug to the subject

BioCryst reserves the right to discontinue the trial prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects immediately after notification. As directed by BioCryst, all study materials must be collected and all CRFs completed to the greatest extent possible.

An individual trial center that is determined to be unsuitable by Sponsor, competent public authorities or IRB/IEC may be terminated, without affecting the other trial sites.

Except for those situations outlined in Section 8.3, no other formal stopping rules for individual subjects, parts of the trial or the entire trial, will be defined. Individual subjects will be discontinued from the study following the emergence of any laboratory abnormality or AE that in the judgment of the Investigator compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest.

14.5. Records Retention

To enable evaluations and/or audits from regulatory authorities or BioCryst, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs, and medical/hospital records), all original signed ICFs, all original signed assents (where applicable), all CRFs, and detailed records of study drug accountability and treatment disposition. The records should be retained by the Investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to BioCryst. The Investigator must obtain BioCryst's written permission before disposing of any records and must notify BioCryst before transferring any records to another facility.

All correspondence related to records retention, destruction or transfer of study documents should be sent directly to BioCryst study personnel, copying the email archives@biocryst.com.

14.6. Confidentiality of Information and Data

BioCryst affirms the subject's right to protection against invasion of privacy and secure maintenance of the confidential nature of their personal data. Only a subject identification number and subject identifiers permitted by local regulation will identify subject data retrieved by BioCryst. However, in compliance with federal regulations, BioCryst requires the Investigator to permit BioCryst's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study, maintaining pseudo-anonymity.

All parties will abide by all applicable laws and regulations regarding subject privacy and confidentiality, including, the Health Insurance Portability and Accountability Act (HIPAA), where this rule is applicable and the requirements of the Data Protection Act in the EU, where applicable. A valid authorization and consent must meet the specifications of the applicable laws and regulations relating to such personal data and health information. It is the responsibility of the Investigator and institution to obtain such waiver/authorization in writing from the appropriate individual. HIPAA authorizations are required for US sites only.

14.7. Study Publication

All data generated from this study are the property of BioCryst and shall be held in strict confidence along with all information furnished by BioCryst. Except as provided through written agreement with BioCryst, independent analysis and/or publication of these data by the Investigator or any member of his/her staff is not permitted. Such consent will not be withheld unreasonably. BioCryst is in agreement with the principle of full disclosure of clinical trial results.

15. REFERENCES

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16. APPENDICES

16.1. DMID Adult Toxicity Table (DRAFT, Publish Date: November 2007)

Copies of the DMID Toxicity Table will be available to the medical staff throughout the project.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

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HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

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CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

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CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

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ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

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CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

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RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

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GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

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MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

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SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self