BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-301

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 6.0: 07 August 2020

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Substitution of Text after the Approval of BCX7353

Once BCX7353 (berotralstat) receives marketing authorization in Japan, this study will continue as a post-marketing study until such time as BCX7353 is commercially available at each site. The sponsor of the study will be changed from BioCryst Pharmaceuticals, Inc. (BioCryst) to the marketing authorization holder in Japan, OrphanPacific, Inc. However, the clinical conduct of the study will continue to be overseen by BioCryst. The study will be conducted in compliance with Japan post-marketing regulations; only approved formulations and dosing regimens of BCX7353 will be provided in the study. The text used in this protocol will be substituted as follows:

Items	**Substitution**	
	Before Marketing Authorization	**After Marketing Authorization**
All text in the protocol	**Text describing investigational clinical study**	**Text describing post-marketing clinical study**

Protocol Number:	BCX7353-301 (APeX-J)
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
Investigational Product:	BCX7353
Indication Studied:	Hereditary angioedema
Sponsor:	Prior to BCX7353 marketing authorization in Japan: BioCryst Pharmaceuticals, Inc. (BioCryst) 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA After BCX7353 marketing authorization in Japan: OrphanPacific, Inc. 1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan BioCryst will continue to oversee the clinical conduct of the post-marketing study.
Japan Medical Monitor:	BioCryst Medical Monitoring team Phone: +81-3-6811-2332 Email: mmj@biocryst.com
BioCryst Medical Monitor:	Sylvia Dobo, MD Phone (24 hours): +1 919-859-7905 Email: mmj@biocryst.com
BioCryst Clinical Study Manager:	Lacy Reese Office: + 1 919-226-5877 Email: lreese@biocryst.com
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(s):	Version 1.0: 19 July 2018 Version 2.0: 26 September 2018 Version 3.0: 11 October 2018 (matches Pharmaceuticals and Medical Devices Agency [PMDA]-accepted Version 1.1 dated 01 October 2018) Version 4.0: 15 October 2018 Version 5.0: 29 August 2019 Version 6.0: 07 Aug 2020

1.1. Protocol Approval Signature Page

Protocol No: BCX7353-301 (APeX-J)

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 6.0: 07 August 2020

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

William P. Sheinde 11 AUG 2020

for Melanie Cornpropst, PharmD, PhD CM/SHP Date
Vice President, Clinical Development
BioCryst Pharmaceuticals, Inc.

11 AUG 2020

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

Elliott Berger 11 AUG 2020

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

OrphanPacific, Inc.

Reviewed and Approved by:

Y. Yonemoto 13 AUG 2020

Yoshiyuki Yonemoto Date
Director, Department of Clinical Development
OrphanPacific, Inc.

1.2. Clinical Study Protocol Agreement

Protocol No: BCX7353-301 (APeX-J)

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 6.0: 07 August 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 Practice, and all applicable regulatory requirements.

_____

Investigator's Signature Date

_____

Name (Print)

2. SYNOPSIS

Name of Sponsor/Company:

BioCryst Pharmaceuticals, Inc. (BioCryst)

After BCX7353 marketing authorization in Japan:

OrphanPacific, Inc.

BioCryst will continue to oversee the clinical conduct of the post-marketing study.

Name of Investigational Product:

BCX7353 (berotralstat)

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 BCX7353-301)

Study centers: Approximately 15 centers in Japan

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

Part 1 Primary Objective:

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

Part 1 Secondary Objectives:

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

Part 1 Primary Efficacy Endpoint:

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

Part 1 Secondary Efficacy Endpoints:

- Change from baseline in Angioedema Quality of Life questionnaire (AE-QoL) at Week 24 (total score)
- Number and proportion of days with angioedema symptoms through 24 weeks

- Rate of expert-confirmed angioedema events during dosing in the effective treatment period (beginning on Day 8 through 24 weeks)

Part 1 Exploratory Efficacy Endpoints:

- Number and proportion of subjects with no angioedema events over 24 weeks
- Use of medications to treat angioedema events over 24 weeks
- The proportion of responders to study drug, separately defined as at least a 50%, 70%, or 90% relative reduction in the rate of expert-confirmed angioedema events during treatment compared with the baseline expert-confirmed angioedema event rate

Part 1 Safety Endpoints:

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

Part 1 Health Outcome Endpoints:

- EuroQoL 5-dimensional, 5-level questionnaire (EQ-5D-5L) scores
- Treatment Satisfaction Questionnaire for Medication (TSQM) scores
- Work Productivity and Activity Impairment Questionnaire (WPAI) scores

Part 2 Primary Objective:

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

Part 2 Secondary Objectives:

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

Part 2 Primary Endpoints:

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE

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

Part 2 Secondary Endpoints:

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

Part 3 Primary Objective:

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

Part 3 Secondary Objectives:

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

Part 3 Primary Endpoints:

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

Part 3 Secondary Endpoints:

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

Methodology:

This is a randomized, placebo-controlled, double-blind, parallel-group, 3-part study. Part 1 is designed to test the hypothesis that the angioedema event rate during 24 weeks of prophylactic BCX7353 treatment at 2 dosage levels will be less than that observed during 24 weeks of placebo. An angioedema event is defined as an attack, symptoms, or swelling due to a subject's underlying hereditary angioedema disease. The primary efficacy endpoint will be assessed after the last subject completes Part 1 (through Week 24). Part 2 is designed to primarily evaluate the long-term safety of BCX7353 at 2 dosage levels. Part 3 is open-label and designed to primarily evaluate the long-term safety of BCX7353. Parts 1, 2, and 3 will be conducted in sequence. All subjects will receive BCX7353 in Parts 2 and 3, including those randomized to receive placebo in Part 1.

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

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

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

Group 1: BCX7353 110 mg QD administered orally for 24 weeks

Group 2: BCX7353 150 mg QD administered orally for 24 weeks

Group 3: Placebo QD administered orally for 24 weeks

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

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

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

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

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

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

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

Part 2 (evaluation of safety of blinded BCX7353)

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

Study visits during Part 2 will occur during Weeks 26, 28, 32, 36, 48, and 52, with telephone contact at Weeks 40 and 44. Subjects will continue to document all angioedema events (attack, symptoms, or swelling due to HAE) that occur while on study drug, as well as compliance with the study drug, in their e-diary and will have regular visits to assess safety and tolerability; investigator confirmation of angioedema events will continue to be required for Part 2. Interim safety analyses will be conducted while Parts 2 and 3 are ongoing to support regulatory filings.

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

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

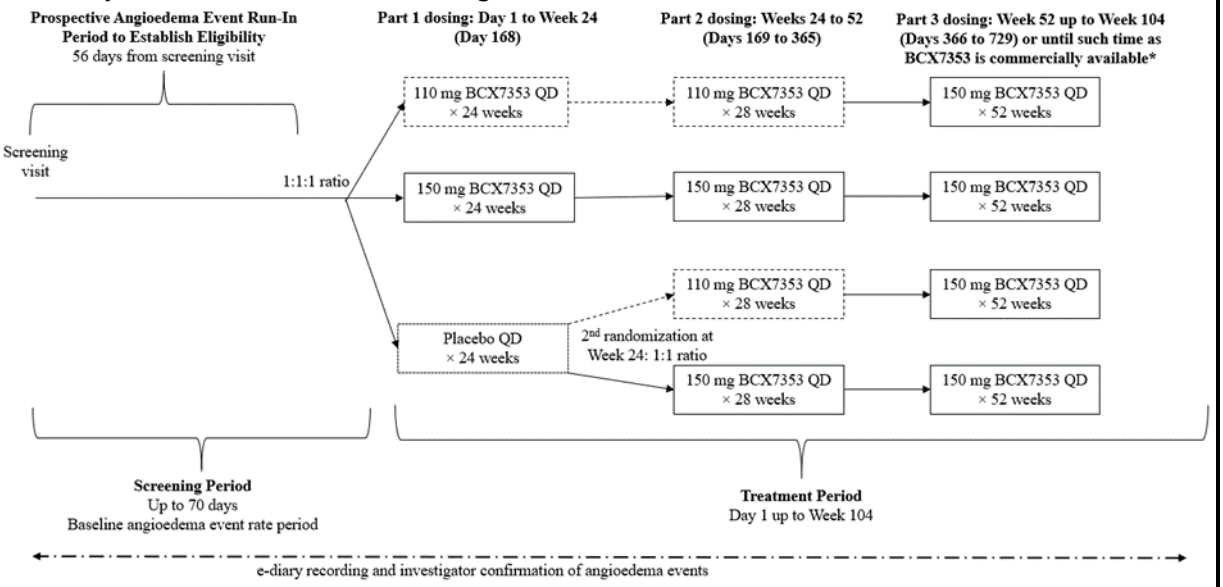
Study visits during Part 3 will occur during Week 60 and approximately every 12 weeks thereafter, for a total study duration of up to 104 weeks, until another mechanism is available to provide drug to the subject (eg, market access), or until the sponsor discontinues development of the product for the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

Subjects will continue to document all angioedema events (attack, symptoms, or swelling due to HAE) that occur while on study drug in their e-diary in Part 3. However, subjects will not be required to document compliance with the study drug. In addition, investigator confirmation of angioedema events will not be required in Part 3. All angioedema events recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in the effectiveness analyses. These rules will be outlined in the Statistical Analysis Plan.

Post-Marketing Study

Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 through Week 104 or until such time as BCX7353 is commercially available at his or her site, whichever occurs first, unless the subject discontinues his or her participation in the study. During this period, BCX7353 will be administered at the dose regimen that is approved in Japan. In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended with additional telephone contacts conducted at 4-week intervals (Weeks 108, 112, etc.) and clinic visits completed at 12-week intervals (Week 116, etc.) to allow each subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study. Once BCX7353 is commercially available at each site, an end-of-study (EOS) visit will be scheduled for each subject to complete his or her participation in the study and transition to commercial drug product. Subjects will not have to wait for their next scheduled clinic visit to complete the EOS visit. Subjects may not continue on study for more than 3 months after National Health Insurance price listing in Japan. Subjects who choose not to continue their participation in the study at any time will be asked to complete an early termination visit within 3 weeks (+ 1 week) after their last dose of BCX7353.

The study is summarized in the following schema:



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

* In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period may be extended to allow the subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study. After marketing authorization, BCX7353 will be administered at the dose regimen that is approved in Japan.

Number of subjects (planned):

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

Main criteria for inclusion:

1. Males and non-pregnant, non-lactating females ≥ 12 years of age.

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

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

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

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

   Under no circumstances should the run-in angioedema event requirement for eligibility be disclosed to study subjects.
7. Female subjects must agree to the contraception requirements and must meet the inclusion criteria regarding contraception, as outlined in Section 8.2.1.
8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate

adequate compliance with all study procedures required from the screening visit through randomization, including e-diary recording of angioedema events beginning at the screening visit.

Main criteria for exclusion:

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject by participating in the study.
2. Dementia, altered mental status, or any psychiatric condition or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
3. Anticipated use of short-term prophylaxis of angioedema events for a preplanned procedure during the screening or study periods.
4. Concurrent diagnosis of any other type of recurrent angioedema.
5. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a corrected QT interval using Fridericia's method (QTcF) > 470 msec for women, a QTcF > 450 msec for men, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
6. Any clinically significant history of angina, myocardial infarction, syncope, cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
7. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
8. History of or current implanted defibrillator or pacemaker.
9. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the investigator, is clinically significant and relevant for this study. A calculated creatinine clearance of ≤ 30 mL/min or aspartate aminotransferase or alanine aminotransferase value ≥ 3 × the upper limit of the normal reference range value obtained during screening is exclusionary.
10. Prior enrollment in a BCX7353 study.
11. Suspected C1-INH resistance in the opinion of the investigator or sponsor.
12. History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcohol intake > 3 drinks/day).
13. Positive serology for human immunodeficiency virus or current infection with hepatitis B virus or hepatitis C virus.
14. Pregnant or planning to become pregnant during the study.
15. Currently breastfeeding. Women who want to enter the study must agree to suspend breastfeeding at the screening visit. Women must wait at least 3 weeks after the last dose of BCX7353 to commence breastfeeding.

16. Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
17. History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
18. Use of androgens or tranexamic acid for prophylaxis of angioedema events within the 28 days prior to the screening visit or initiation during the study.
19. Use of C1-INH for prophylaxis of angioedema events within the 14 days prior to the screening visit or initiation during the study. Use of a C1-INH therapy for treatment of angioedema events is not excluded at any time, nor is C1-INH for preprocedural prophylaxis for an unplanned/unforeseen procedure.
20. Use of concomitant medications that are metabolized by cytochrome P450 (CYP) 2D6, CYP2C9, CYP2C19, and/or CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
21. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study.
22. Use of a medication that is transported by P-glycoprotein and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.
23. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
24. Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study.
25. Current participation in any other investigational drug study or received another investigational drug within 30 days of the screening visit.
26. An immediate family relationship to either sponsor employees, the investigator, or employees of the study site named on the delegation log.
27. Held in an institution by a government or judicial order.

Investigational product, dosage, and mode of administration:

BCX7353 capsules, to be administered orally.

Parts 1 and 2

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

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

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

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

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

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

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

Part 3

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

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

Reference therapy, dosage, and mode of administration:

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

Duration of treatment:

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

Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 until such time as BCX7353 is commercially available at his or her site unless the subject discontinues his or her participation in the study. During this period, BCX7353 will be administered at the dose regimen that is approved in Japan.

Criteria for evaluation:

Efficacy:

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

Safety:

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

Health Outcomes:

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

Pharmacodynamics:

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

Pharmacokinetics:

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

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

Japan has limited statistical power. A supplemental analysis will combine data from this study with data from Study BCX7353-302. The primary efficacy endpoint in Study BCX7353-302 is the monthly investigator-confirmed angioedema event rate in the entire treatment period (Day 1 [post dose] to Day 168) in the ITT population. The angioedema event rate and the treatment comparisons between each BCX7353 dose and placebo in the rate of investigator- or expert-confirmed HAE angioedema events during the entire dosing period will be analyzed using a negative binomial regression model. The number of investigator- or expert-confirmed angioedema events will be included as the dependent variable, the treatment will be included as a fixed effect, the stratification variable (baseline angioedema event rate) will be included as a covariate, and the logarithm of duration on treatment will be included as an offset variable. The estimated rate of angioedema event for each treatment group, the treatment differences expressed as the angioedema event rate ratio (BCX7353 over placebo rate ratio), and their associated 95% confidence intervals will be provided from the negative binomial regression model. Monthly will be defined as 4 weeks.

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

The safety analyses will be analyzed separately for Part 1 alone; a later data analysis will evaluate long-term safety data for the current study.

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

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Explanation
ABW	absolute body weight
AE	adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BCX7353	berotralstat
BK	bradykinin
BMI	body mass index
BMP	di-docosahexaenoyl (22:6)-bis(mono)acylglycerol phosphate
C1-INH	C1 esterase inhibitor
C3	complement 3
C4	complement 4
CI	confidence interval
CK-MB	creatine kinase MB isoenzyme
CL_{CR}	creatinine clearance
C_{max}	maximum plasma concentration of the drug
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CSR	clinical study report
CYP	cytochrome P450
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases, US National Institutes of Allergy and Infectious Diseases
EC_{50}	concentration that elicits a 50% response
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EOS	end-of-study
EOSI	event of special interest
EQ-5D-5L	EuroQoL 5-dimensional, 5-level questionnaire
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HAE	hereditary angioedema
HBV	hepatitis B virus

Abbreviation	Explanation
HCV	hepatitis C virus
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HK	high-molecular weight kininogen
HLA	human leukocyte antigen
IB	investigator's brochure
IC_{xx}	xx% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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 for repeated measures
NGAL	neutrophil gelatinase-associated lipocalin
NHI	National Health Insurance
NHP	non-human primates
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic
P-gp	p-glycoprotein efflux pump
PK	pharmacokinetic
PKK	prekallikrein
PLD	phospholipidosis
PMDA	Japan Pharmaceuticals and Medical Devices Agency
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

Abbreviation	Explanation
QTcF	QT interval corrected by Fridericia's formula
RR	interval between successive heart beats using the R-wave peaks
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SN	salt nomenclature
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
US	United States
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 tract (GI), genitals, and extremities (Longhurst and Cicardi 2012). The frequency of attacks varies, 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 BK B_2 receptor by BK ultimately results in vasodilatation, increased vascular permeability, and contraction of smooth muscle, all of which lead to the tissue swelling that characterizes HAE (Kaplan 2010).

BCX7353 (berotralstat) 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, pharmacokinetics (PK), and toxicology studies of BCX7353 are found in the investigator's brochure (IB).

Safety pharmacology studies of BCX7353 indicated multiple cardiac ion channel effects, including the human ether-à-go-go-related gene (hERG) 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 to 30 and 20 mg/kg/day, respectively, and these dose levels were the no observed adverse effect levels (NOAELs). In the

NHP, at the NOAEL dose of 30 mg/kg/day, mean maximum plasma concentration (C_{max}) and AUC from time 0 to 24 hours (AUC_{0-24}) values 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 another 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); increased kidney weights, renal tubular epithelial cell degeneration, and renal tubular hyperplasia were also observed. Each of these effects was 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 5 Phase 1 studies (BCX7353-101 and BCX7353-102 [clinical study reports (CSRs) available], BCX7353-103, BCX7353-105, and BCX7353-112 [preliminary data available]) and 1 Phase 2 clinical study [BCX7353-203 (results reported and summarized herein)] relevant to the current study have been conducted. One Phase 3 study (BCX7353-302, summarized herein) has been conducted with results reported for the primary analysis (Part 1). Study BCX7353-302 and a Phase 2, parallel-group, long-term safety study (BCX7353-204) remain ongoing globally.

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 Study BCX7353-302

Study BCX7353-302 is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 3-part study in subjects with Type 1 or 2 HAE. The primary objective of the study was to determine the efficacy of prophylactic BCX7353 110 and 150 mg administered orally once daily (QD) for 24 weeks (Part 1) compared to placebo in subjects with HAE.

In Part 2, all subjects receive active treatment with BCX7353 from Weeks 25 through 48, and Part 3 of the study extends treatment with BCX7353 through 96 weeks. Results for Part 1 are summarized herein; Parts 2 and 3 of the study are ongoing.

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 (85%).

The mean baseline rate was 2.98 attacks per month. The majority of subjects (70%) had ≥ 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 150 mg subjects, 1.65 for BCX7353 110 mg subjects, and 2.35 for placebo subjects. These results were supported by sensitivity analyses and were generally 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.

BCX7353 significantly reduced the use of rescue medication per 28 days vs. placebo by 53.6% ($p < 0.001$) for 150 mg and 46.3% ($p < 0.001$) 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, $p = 0.005$, $p = 0.002$, and $p = 0.073$ 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 events of special interest (EOSI; defined as BCX7353-related rash per protocol).

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 better efficacy at the 150 mg dose compared to the 110 mg dose, and no increase in safety 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 endpoint, 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 endpoints 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 and BCX7353-204

Data from Studies BCX7353-302, BCX7353-204, and the current study, BCX7353-301, 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 was completed on 16 April 2020. The review included data from 120 dosed subjects on Study BCX7353-302, 323 dosed subjects on Study BCX7353-204, and 19 dosed subjects on Study BCX7353-301, with 259 subjects receiving study treatment for > 336 days (> 48 weeks). The DMC recommended that all three studies continue per protocol.

5.4. Rationale for Study

The genetic and clinical features of HAE in Japan mirror Western patients (Yamamoto, Horiuchi et al. 2012). Currently, the only treatment approved for prevention of angioedema attacks in Japan is Berinert, a C1-INH concentrate, which is approved for the treatment of acute episodes and pre-procedure prevention (short-term prophylaxis) of acute episodes of HAE. Therefore, androgens and medications with limited, if any, effectiveness such as tranexamic acid and antihistamines are often used as prophylaxis in Japan (Ohsawa, Honda et al. 2015). Berinert must be administered by a healthcare professional. Icatibant (BK B_2 receptor antagonist) and Berinert have been approved for HAE treatment in Japan.

A survey of Japanese physicians who treat patients with HAE revealed that time to diagnosis is long and licensed treatment options for HAE are underused (Ohsawa, Honda et al. 2015). Ten percent of patients had attacks that required airway management (emergency intubation or tracheotomy), 3% of patients underwent abdominal surgery with an uncertain diagnosis, 21% of patients required hospitalization, 8% of patients had at least 20 HAE attacks per year, and 12% of patients reported the death of a relative due to HAE (Ohsawa, Honda et al. 2015). In Japan, there remains a significant medical need to provide additional HAE treatment options that are efficacious, convenient, and well tolerated, especially given the lack of effective treatments for the prevention of attacks in Japan (Ohsawa, Honda et al. 2015).

BCX7353 is an oral kallikrein inhibitor in development for prevention of angioedema attacks in patients with HAE Type 1 and 2. BCX7353 has activity against plasma kallikrein at low nanomolar concentrations (Section 5.2) that are attainable and sustained in humans following oral administration. In both the randomized, double-blind, placebo-controlled, Phase 3 study (BCX7353-302) and the proof-of-concept, 28-day, placebo-controlled, Phase 2 study (BCX7353-203), 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 the prevention of HAE attacks in patients around the world.

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 angioedema events in Japanese subjects with Type 1 and 2 HAE, as measured by the

rate of expert-confirmed angioedema events during dosing in the entire 24-week treatment period in Part 1. The current study expands upon the scope of APeX-1 by evaluating the safety and efficacy of BCX7353 over a longer duration (24 weeks in Part 1 and 28 weeks in Part 2). Moreover, in the current study, the efficacy of BCX7353 will be evaluated in an HAE population potentially characterized by a wider range of angioedema event frequency (a minimum of 2 angioedema events in 8 weeks are required for entry). The current study will be conducted as a parallel cohort assessment of active doses vs. placebo. The current study was designed similarly to Study BCX7353-302, following consultation with and guidance from the Pharmaceuticals and Medical Device Agency (PMDA).

Subjects randomized to Treatment Groups 1 and 2 in Part 1 will continue to be administered their same dose of BCX7353 in Part 2. Subjects randomized to placebo in Part 1 will be randomized to receive an active dose in Part 2. Conduct of Part 2, the blinded extension on active drug, in part satisfies regulatory authorities' requirement to obtain safety data at each dose over an extended treatment duration to support the intended indication 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 the Part 1 analysis is complete, at the earliest.

Conduct of Part 3, an unblinded extension on active drug at the 150 mg QD dose, based on better efficacy and no increase in safety risk in Study BCX7353-302. This will provide additional safety and effectiveness data at the 150 mg QD dose over an extended treatment period. The extension also offers subjects access to BCX7353 treatment for up to 104 weeks, until another mechanism is available to provide drug to the subject (eg, market access), or until the sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first.

Efficacy and safety data from the randomized, double-blind, placebo-controlled, Phase 3 study (BCX7353-302) and accumulating safety data on subjects enrolled in the Phase 2, long-term safety study (BCX7353-204) support long-term treatment with BCX7353 (Section 5.3.3).

5.4.2. Rationale for BCX7353 Doses and Regimen

The BCX7353 dosage regimens selected for evaluation in this study are 110 and 150 mg QD BCX7353 (equivalent to 125-mg and 175-mg QD [SN]). Exposure to BCX7353 was similar in Japanese and Western subjects in Study BCX7353-101 (Investigator Brochure); therefore, dosing will be the same in Parts 1 and 2 as in the ongoing Phase 3 Study BCX7353-302. The dose levels assessed in this study have been agreed upon with the PMDA.

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 generally safe and 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 pivotal Phase 3 clinical trial (BCX7353-302) and the Phase 2 long-term safety study (BCX7353-204). In the 24-week Phase 3 study (BCX7353-302), the rate of angioedema attacks in subjects randomized to BCX7353 was statistically significantly lower than in placebo subjects, with the 150 mg 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 BCX7353-302 study, with better efficacy at the 150 mg dose compared to the 110 mg dose, and no increase in safety risk.

As a result of these safety and efficacy findings in Study BCX7353-302 indicating a more favorable benefit: risk profile for 150 mg QD, all subjects in Studies BCX7353-302 and BCX7353-204 are being transitioned to a 150 mg QD dose after a year of either 110 or 150 mg QD (ie, completion of Parts 1 and 2). Because the steady-state exposure of BCX7353 in Western subjects is similar to Japanese subjects (Investigator Brochure), the DMC has identified no safety issues in this ongoing study, and the current study is not sufficiently powered on its own to detect a treatment difference between placebo and BCX7353, subjects in Study BCX7353-301 will be similarly transitioned to 150 mg QD after 1 year of treatment (ie, completion of Parts 1 and 2), when they enter Part 3 of the study.

5.4.3. Rationale for Study Population

The current study is limited to adults and adolescents (≥ 12 years of age) of both sexes with HAE Type 1 and 2. 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. 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 subjects with HAE, it is anticipated that female subjects will comprise at least 50% of the subject population. 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 embryofetal developmental toxicity with BCX7353 in reproductive toxicology studies (Section 5.2), appropriate precautions are still warranted with respect to administration of BCX7353 to women of reproductive age, in accordance with International Council for Harmonisation (ICH) guidelines. Women of childbearing potential may be enrolled in this trial 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). Breastfeeding women will also be excluded from this study.

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

In the current study, all participants must have access to an effective, approved treatment for attacks or episodes of angioedema as part of their routine medical care. Each subject will continue to use his or her prescribed acute medication to treat attacks, under the medical

management plan advised by his or her 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 in some countries (not including Japan) there are approved therapies for prophylaxis against HAE attacks, such as C1-INH, consensus recommendations do not exist for either prophylactic treatment as a standard of care or a definition of indications for prophylaxis.

The International World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines for the management of HAE recommends prophylaxis be considered for patients who "face events in life that are associated with increased disease activity," specifically C1-INH for first-line, long-term prophylaxis (Maurer, Magerl et al. 2018). Given the lack of wide availability of such a treatment in Japan and the limitations of intravenous (IV) therapy, a study of an orally available product such as BCX7353 is appropriate.

A subject randomized to placebo in the current study who has access to effective attack medications is therefore considered to be treated in line with current guidelines.

Unapproved prophylactic therapies may be used by some HAE patients in Japan. To guard 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 is not allowed within 28 days of the screening visit; C1-INH prophylaxis is not permitted within 14 days of the screening visit. 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 the angioedema event rate after discontinuing prophylactic therapies before prospective collection of angioedema events required for eligibility and for the baseline angioedema event rate, which begins at screening. However, it should be noted that subjects may receive approved C1-INH therapies for acute treatment of angioedema attacks, if available, 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 and ongoing Phase 1, 2, and 3 studies, 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 angioedema events 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, the pharmacology of BCX7353, and Phase 3 data from 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 BCX7353 110 and 150 mg QD administered for 24 weeks compared to placebo in the prevention of angioedema events in subjects with HAE

6.1.2. Part 1 Secondary Objectives

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

6.1.3. Part 2 Primary Objective

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

6.1.4. Part 2 Secondary Objectives

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

- To evaluate subject satisfaction with BCX7353 over a 24- to 52-week administration period

6.1.5. Part 3 Primary Objectives

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

6.1.6. Part 3 Secondary Objectives

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

7. OVERALL STUDY DESIGN AND PLAN

This is a randomized, placebo-controlled, double-blind, parallel-group, 3-part study. Part 1 is designed to test the hypothesis that the angioedema event rate during 24 weeks of prophylactic BCX7353 treatment at 2 dosage levels will be less than that observed during 24 weeks of placebo. An angioedema event is defined as an attack, symptoms, or swelling due to a subject's underlying hereditary angioedema disease. The primary efficacy endpoint will be assessed after the last subject completes Part 1 (through Week 24). Part 2 is designed to primarily evaluate the long-term safety of BCX7353. Part 3 is open-label and designed to primarily evaluate the long-term safety of BCX7353. Parts 1, 2, and 3 will be conducted in sequence. All subjects will receive BCX7353 in Parts 2 and 3, including those randomized to receive placebo in Part 1.

In addition, efficacy data in Part 1, where appropriate, will be statistically analyzed by combining data from this study with data from Study BCX7353-302 to ensure adequate statistical power.

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

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

Approximately 24 treatment-eligible subjects ≥ 12 years of age will receive study drug (BCX7353 or placebo) in Part 1 of the study based on randomization in a 1:1:1 ratio into one of 3 treatment groups:

- Group 1 (N=8): BCX7353 110 mg QD administered orally for 24 weeks
- Group 2 (N=8): BCX7353 150 mg QD administered orally for 24 weeks
- Group 3 (N=8): Placebo administered orally QD for 24 weeks

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

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

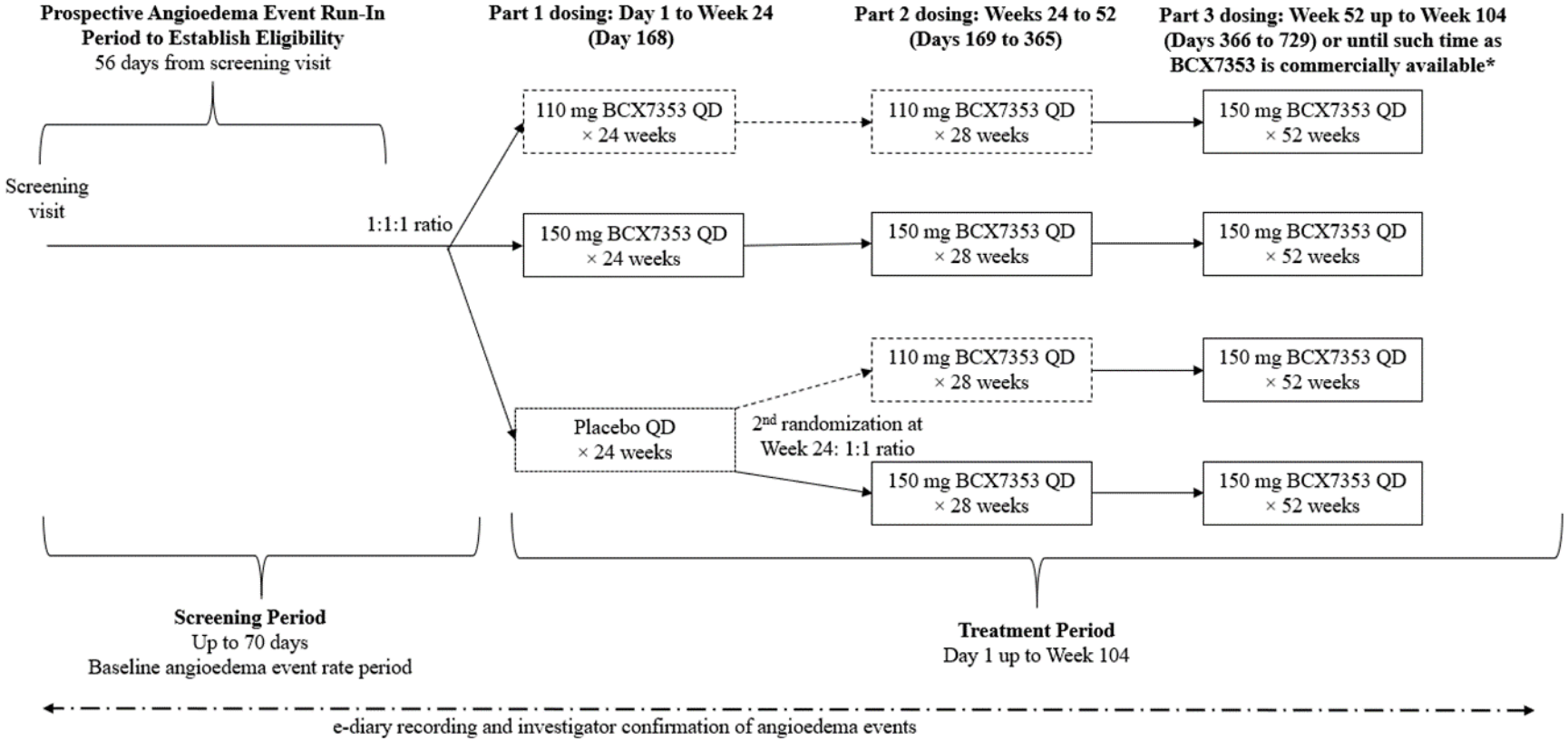
- The angioedema events must be unique, which is defined as an angioedema event that does not begin within 48 hours of the end of a previous angioedema event.
- The angioedema events must have either been treated, required medical attention, or have been documented to cause functional impairment, based on the subject's entry in the electronic diary (e-diary). Functional impairment is defined as the subject not being able to perform his or her daily activities without restriction (ie, subject records that he/she is at least slightly restricted in daily activities during an angioedema event).
- The angioedema events must include symptoms of swelling. The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling.
- The angioedema events are otherwise confirmed by an independent expert to be angioedema events.

A study schematic can be found in Figure 1.

Throughout the entire study, details of all angioedema events (attacks, symptoms, or swelling due to HAE) and compliance with study drug will be recorded in an e-diary. Angioedema events will be treated in accordance with the subject's normal standard of care. Within approximately 2 business days of the end of each angioedema event that occurs from the screening visit through the Week 52 visit in Part 2, subjects will be contacted by the investigator (or appropriately trained designee) to discuss the clinical characteristics of the angioedema event, any questions on the entered data, or to gain additional details on the event that are not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable. The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each angioedema event recorded in the e-diary as a confirmed angioedema event. All expert-confirmed angioedema events must include symptoms of swelling; prodromal symptoms in the absence of swelling are not considered angioedema events, regardless of treatment. The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling. Under no circumstances should the run-in angioedema event requirement for eligibility be disclosed to study subjects.

Study visits in Part 1 will occur at screening, baseline, and Weeks 2, 4, 8, 12, 18, and 24. The primary efficacy analysis will occur after the last subject completes the Week 24 visit and will include all data through Week 24.

Figure 1: Study Schema



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

* In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended with additional telephone contacts conducted at 4-week intervals (Weeks 108, 112, etc.) and clinic visits completed at 12-week intervals (Week 116, etc.) to allow the subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study. After marketing authorization, BCX7353 will be administered at the dose regimen that is approved in Japan.

Part 2 (evaluation of safety of blinded BCX7353)

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

Study visits in Part 2 will occur during Weeks 26, 28, 32, 36, 48, and 52, with telephone contact at Weeks 40 and 44. Subjects will continue to document all angioedema events that occur while on study drug, as well as compliance with the study drug, in their e-diary and will have regular visits to assess safety and tolerability; investigator confirmation of angioedema events will continue to be required for Part 2. Interim safety analyses will be conducted while Parts 2 and 3 are ongoing to support regulatory filings.

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

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

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

Subjects will continue to document all angioedema events that occur in their diary throughout Part 3 and will have regular visits to assess safety and tolerability. However, subjects will not be required to document compliance with the study drug. In addition, investigator and expert confirmation of angioedema events will not be required in Part 3. All angioedema events recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in effectiveness analyses. These rules will be outlined in the Statistical Analysis Plan (SAP).

Post-Marketing Study

Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 through Week 104 or until such time as BCX7353 is commercially available at his or her site, whichever occurs first, unless the subject discontinues his or her participation in the study. During this period, BCX7353 will be administered at the dose regimen that is approved in Japan. In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended with additional telephone contacts conducted at 4-week intervals (Weeks 108, 112, etc.) and clinic visits completed at 12-week intervals (Week 116, etc.) to allow each subject to continue

treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study. Once BCX7353 is commercially available at each site, an end-of-study (EOS) visit will be scheduled for each subject to complete his or her participation in the study and transition to commercial drug product. Subjects will not have to wait for their next scheduled clinic visit to complete the EOS visit. Subjects may not continue on study for more than 3 months after National Health Insurance (NHI) price listing in Japan. Subjects who choose not to continue their participation in the study at any time will be asked to complete an early termination visit within 3 weeks (+ 1 week) after their last dose of BCX7353.

7.1. Endpoints

7.1.1. Part 1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is as follows:

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

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 expert-confirmed angioedema events 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 angioedema events over 24 weeks
- Use of medications to treat angioedema events over 24 weeks
- The proportion of responders to study drug, separately defined as at least a 50%, 70%, or 90% relative reduction in the rate of expert-confirmed angioedema events during treatment compared with the baseline expert-confirmed angioedema event rate

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

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
- 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 angioedema events
- Durability of response (angioedema event rate trend over time)

- Number and proportion of days with angioedema symptoms
- Use of medications to treat angioedema events
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

Approximately 24 subjects are planned to be enrolled in the study.

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

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

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

   SERPING-1 gene analysis results indicating a “possibly pathogenic” mutation will be considered on a case-by-case basis by the medical monitor and may require additional testing for eligibility.
4. Access to and ability to use an acute treatment for angioedema events approved by the Japan Ministry of Health, Labor, and Welfare (plasma-derived C1-INH or icatibant).

5. Subjects must be medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study; that is, subjects must be medically appropriate to be managed without prophylactic treatments for HAE.
6. The subject must have at least 2 angioedema events as assessed by an independent expert that meet all requirements below during the run-in period of 56 days beginning at the screening visit:

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

   Under no circumstances should the run-in angioedema event requirement for eligibility be disclosed to study subjects.
7. Female subjects must 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 1 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)
      – Combined (estrogen and progesterone containing) oral hormonal contraception associated with inhibition of ovulation. It must be noted that estrogen-containing hormonal contraception cannot be initiated within 56 days of the screening visit. Also, they cannot be initiated until the end of the study.
      – Male condom with or without spermicide
      – Use of male condom with or without spermicide, together with diaphragm

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

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).
c. Be a woman who, as a lifestyle choice, chooses to not engage in heterosexual intercourse or is a woman who exclusively has female sexual partners.

8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate adequate compliance with all study procedures required from the screening visit through randomization, including diary recording of angioedema events 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 events for a pre-planned procedure during the screening or study periods.
4. Concurrent diagnosis of any other type of recurrent angioedema.
5. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a QTcF > 470 msec for women, a QTcF > 450 msec for men, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
6. Any clinically significant history of angina, myocardial infarction, syncope, cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
7. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
8. History of or current implanted defibrillator or pacemaker.
9. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the investigator, is clinically significant and relevant for this study. A calculated creatinine clearance (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 or planning to become pregnant during the study.
15. Currently breastfeeding. Women who want to enter the study must agree to suspend breastfeeding at the screening visit. Women must wait at least 3 weeks after the last dose of BCX7353 to commence breastfeeding.
16. Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).
17. History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
18. Use of androgens or tranexamic acid for prophylaxis of angioedema events within the 28 days prior to the screening visit or initiation during the study.

    Prophylaxis is defined as administration of a medication in the absence of symptoms of an angioedema event.
19. Use of C1-INH for prophylaxis of angioedema events within the 14 days prior to the screening visit or initiation during the study. Use of a C1-INH therapy for treatment of angioedema events is not excluded at any time, nor is C1-INH for preprocedural prophylaxis for an unplanned/unforeseen procedure.

    Prophylaxis is defined as administration of a medication in the absence of symptoms of an angioedema event.
20. Use of concomitant medications that are metabolized by cytochrome P450 (CYP) 2D6, CYP2C9, CYP2C19, and/or 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).
21. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study (see Section 9.7.1).
22. Use of a medication that is transported by P-glycoprotein (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).
23. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
24. Initiation of an estrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study. Established use (initiation ≥ 56 days prior to screening) during the study is permitted.

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

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 EOS evaluations. Although a subject may withdraw from the study at any time without specifying a reason for withdrawal, the reason for withdrawal, if provided by the subject, will be recorded in the subject's medical records (source documents) and also in the electronic case report form (eCRF). 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 his or her 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 eCRF.

- 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 benefit-risk profile.
- Reoccurrence 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 (male) or 470 msec (female).
- 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 and Table 3 through the end of the study part (ie, Part 1 or 2) in which they were currently 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 52. Subjects who discontinue in Part 3 will have an EOS visit 3 weeks after the 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 study visit.

Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 until such time as BCX7353 is commercially available at his or her site, unless the subject discontinues his or her participation in the study. Once the last subject is able to access commercial drug product or discontinues from the study, the study will be terminated.

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 a dose of BCX7353 (150 or 110 mg) or matching placebo (Part 1 only) capsules for oral administration once daily for up to 104 weeks (placebo capsules will be administered for 24 weeks followed by once daily treatment with BCX7353 for up to 80 weeks). Study drug or investigational medicinal product (IMP) 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 as a 150 mg capsule in Part 3. The capsules are composed 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 capsules. The matching placebo will contain microcrystalline cellulose and magnesium stearate.

In Parts 1 and 2, subjects will be instructed to take 2 capsules of study drug (55 or 75 mg capsules) together at the same time daily. In Part 3, subjects will take a single capsule of study drug (150 mg capsule) daily. After the study has been transitioned to a post-marketing study following marketing authorization of BCX7353, BCX7353 will be administered at the dose regimen that is approved in Japan.

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 bottle of study drug will be labeled with the information required per local law and may include the following: sponsor name, study protocol number, description of the contents, expiry date, kit number, and either a statement regarding the investigational (clinical trial) or post-marketing clinical study use of the study drug, as applicable.

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

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

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

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

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

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

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

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

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

- The angioedema events must have either been treated, required medical attention, or be documented to cause functional impairment based on subject entry in the e-diary. Functional impairment is defined as the subject being unable to perform his or her daily activities without restriction (ie, subject records that he or she is at least slightly restricted in daily activities during the angioedema event).
- The angioedema events must include symptoms of swelling. The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling.
- The angioedema events must be confirmed by an independent expert to be angioedema events, based upon the e-diary record and investigator-collected information.

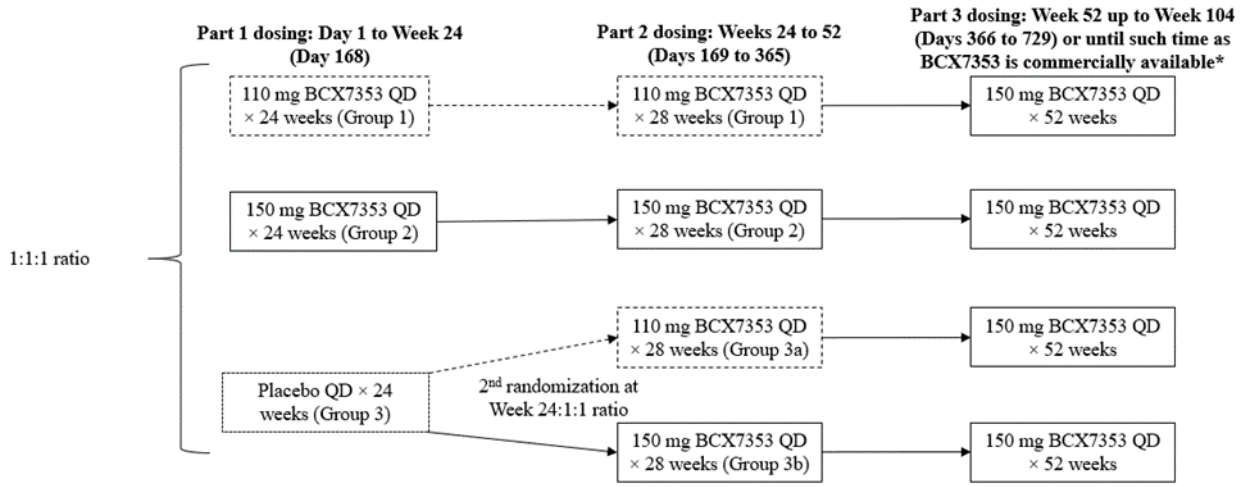
9.3.2.2. Part 2 Randomization

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

Subjects who received placebo during Part 1 will be automatically randomized for Part 2 in the IXRS, which will occur at the time of the Week 24 visit (Figure 2). Sites will assign drug for Part 2 of the study in the IXRS beginning at the Week 24 visit.

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

Figure 2: Study Randomization



Abbreviations: QD = once daily.

* In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended with additional telephone contacts conducted at 4-week intervals (Weeks 108, 112, etc.) and clinic visits completed at 12-week intervals (Week 116, etc.) to allow the subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study. After marketing authorization, BCX7353 will be administered at the dose regimen that is approved in Japan.

9.4. Study Drug Administration and Treatment Compliance

Subjects will be instructed to take BCX7353 capsules together orally QD at approximately the same time each day for up to 104 weeks as follows:

- Treatment Group 1 (110 mg QD)
  - Parts 1 and 2: two 55-mg capsules of BCX7353 QD × 52 weeks
  - Part 3: one 150-mg capsule of BCX7353 QD × 52 weeks
- Treatment Group 2 (150 mg QD)
  - Parts 1 and 2: two 75-mg capsules of BCX7353 QD × 52 weeks
  - Part 3: one 150-mg capsule of BCX7353 QD × 52 weeks
- Treatment Group 3
  - Parts 1 and 2 (placebo in Part 1, 110 mg or 150 mg in Part 2): two capsules of placebo QD × 24 weeks (Days 1 to 168) followed by two 55-mg or 75-mg capsules of BCX7353 QD × 28 weeks (Days 169 to 365)
  - Part 3: one 150-mg capsule of BCX7353 QD × 52 weeks
- Post-marketing authorization: Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. BCX7353 will be administered at the dose regimen that is approved in Japan. Subject treatment will continue until Week 104 or until such time as BCX7353 is commercially available at his or her site, unless the subject discontinues his or her participation in the study. In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended to allow each subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study.

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 purposes of analysis in Part 1 is defined as the day that subjects take their first dose of study drug. If the 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 study drug no sooner than the conclusion of the Week 52 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 regular dosing schedule on the next day. Dosing may not be split across a day.

Subjects will be instructed to record in the e-diary the time of day study drug was taken and the number of capsules of study drug taken (Parts 1 and 2 only).

Drug dispensation will occur in-clinic but may be delivered to subjects by other means (eg, traceable courier) if warranted due to extenuating circumstances (eg, coronavirus disease 2019 [COVID-19] restrictions), which will be determined individually for each site and/or subject.

With the exceptions of the Week 2 and Week 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.

9.5. Study Drug Dose Modification

Dose reductions are not permitted. Study drug interruptions are discussed in Section 12.1.8.

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 exceptions of the Week 2 and 26 visits. 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.

Details of all prior medications (taken within 30 days of screening; prior contraceptive medications taken within 56 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/eCRF.

9.7.1. Prohibited Medications

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

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 (potential for increasing angioedema event 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: aliskiren, digoxin, posaconazole, and talinolol.
- Use of a concomitant medication that is metabolized by CYP2D6, CYP2C9, CYP2C19, and/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: warfarin, phenytoin, s-mephenytoin, thioridazine, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. Note: Topical or ophthalmic tacrolimus or sirolimus and use of testosterone replacement therapy 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: donepezil, haloperidol, methadone, procainamide, and amitriptyline.
- Androgens or tranexamic acid for prophylaxis of angioedema events within the 28 days prior to the screening visit or initiation during the study. Androgens must not be used at all during the study.

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 at least 107 weeks, with an additional 56 to 70 days for the screening period and a dosing period of up to 104 weeks, or until another mechanism is available to provide BCX7353 to the subject (eg, market access). Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 until such time as BCX7353 is

commercially available at his or her site, unless the subject discontinues his or her participation in the study.

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 and 28 weeks of blinded BCX7353 (110 or 150 mg) in Part 2. All subjects will receive BCX7353 150 mg in Part 3. All subjects will undergo a screening period (including a prospective angioedema event run-in period of 56 days) of up to 10 weeks. During the up to 104-week dosing period, all subjects will be required to attend at least 18 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), Week 28 (Day 197), Week 32 (Day 225), Week 36 (Day 253), Week 48 (Day 337), Week 52 (Day 365), Week 60 (Day 421), and approximately every 12 weeks thereafter.

Once BCX7353 is commercially available at each site, an EOS visit will be scheduled for each subject to complete his or her participation in the study and transition to commercial drug product. Subjects will not have to wait for their next scheduled clinic visit to complete the EOS visit. Subjects may not continue on study for more than 3 months after NHI price listing in Japan. Subjects who choose not to continue their participation in the study at any time will be asked to complete an early termination visit 3 weeks (+ 1 week) after their last dose of BCX7353 (eg, subjects who do not extend their treatment at Week 104 should complete the early termination visit at Week 107 [+ 1 week]).

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) and procedures are described in Section 11.

Table 2: Schedule of Assessments: Part 1 of Study BCX7353-301

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

Assessment	Screening Period		Baseline	Part 1 Double-Blind, Placebo-Controlled Study Drug Administration					
	Screening Visit[a,b] (up to Week -10)	Run-in Period[a]	Day 1[a]	Week 2[c] Day 15 ± 2 days	Week 4 Day 29 ± 2 days	Week 8 Day 57 ± 2 days	Week 12 Day 85 ± 2 days	Week 18 Day 127 ± 2 days	Week 24 Day 169[d]
EQ-5D-5L[r,s]			X		X	X	X	X	X
AE-QoL, TSQM, and WPAI[s]			X		X	X	X	X	X
Concomitant medications	◄	———	———	———	———	———	———	———	►
AEs	◄	———	———	———	———	———	———	———	►
Randomization[t]			X						X
e-diary instruction/review/ set-up[u]	X	X	X		X	X	X	X	X
e-diary completion[v]	◄	———	———	———	———	———	———	———	►
Study drug dosing[w]			◄	———	———	———	———	———	►
Investigator review of angioedema events[x]	◄	———	———	———	———	———	———	———	►
Study drug accountability/ dispensing			X		X	X	X	X	X
Plasma for PK and PD analysis[y]			X		X	X	X	X	X

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

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

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

[c] The Week 2 visit will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, ALP); urine and additional tubes of blood will be required to accommodate possible reflex testing for abnormal GGT, AST, or ALT.

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

[e] The investigator (or designee) must call and talk to the subject at least weekly in between the Screening and Baseline visits and on-treatment through Week 24; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of angioedema event details

(if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an angioedema event as the investigator must call and confirm or reject the angioedema event (see Footnote 'x').

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

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

[h] Table 5 lists parameters to be assessed.

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

[j] For all women of childbearing potential (including adolescents), a serum pregnancy test will be administered at screening. Urine pregnancy tests will be assessed at all subsequent visits as indicated in the table. Demonstration of a negative urine pregnancy test will be required prior to the subject taking study drug on Day 1.

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

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

[m] A clinical diagnosis of HAE Type 1 or 2 must be demonstrated during screening for this study as outlined in Inclusion Criterion 3 (Section 8.2.1).

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

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

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

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

[r] The EQ-5D-5L will be administered once at baseline and 1 to 2 × at Weeks 4, 8, 12, 18, and 24 visits. The subject will fill out the first EQ-5D-5L at baseline and on-study to describe his or her 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 his or her health state during an average angioedema event experienced since the last study visit. If the subject has not had an angioedema event since the last study visit, the subject is not required to fill out the second, angioedema event-related EQ-5D-5L.

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

[t] Sites will randomize eligible subjects in the IXRS at the Day 1 visit, preferably after all baseline assessments have been completed. Sites using a centralized pharmacy may randomize the subject the day prior to the baseline visit. The baseline event rate generated from the date of screening through the time of randomization must be calculated at this time (Section 9.3.2.1).

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

[v] At any time the e-diary is in a subject's possession, they will enter angioedema events (attacks, symptoms or swelling due to HAE) and relevant details and dosing information (as applicable) at least once per day.

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

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

[y] Concentration and PD blood samples will be drawn on all subjects at the scheduled visits. For at least one of these time points, a PK and PD sample should be drawn approximately 3 to 6 hours after the last dose of study drug. The remaining time points can be drawn with no particular relationship to the timing of study drug dosing. The investigator (or designee) must ensure that the time of the last dose prior to PK and PD draw is recorded in the subject's e-diary (this may also be captured in the eCRF).

Table 3: Schedule of Assessments: Part 2 of Study BCX7353-301

Assessment	Part 2 Double-Blind, Active Study Drug Administration[a]							
	Week 26[b] Day 183 ± 2 days	Week 28 Day 197 ± 2 days	Week 32 Day 225 ± 2 days	Week 36 Day 253 ± 2 days	Week 40	Week 44	Week 48 Day 337 ± 7 days	Week 52 (Day 365) ± 2 days
In-clinic evaluation	X	X	X	X			X	X
Telephone contact[c]					X	X		
Subject weight		X	X	X			X	X
Physical examination[d]		X	X	X			X	X
Urine pregnancy test		X	X	X			X	X
Vital signs[e]		X	X	X			X	X
Safety laboratory evaluations[f]	X[b]	X	X	X			X	X
Troponin I & troponin T		X	X	X			X	X
NGAL		X	X	X			X	X
CK-MB		X	X	X			X	X
Urinalysis[f]	X[b]	X	X	X			X	X
12-lead ECG[g]		X	X	X			X	X
EQ-5D-5L[h,i]		X	X	X			X	X
AE-QoL, TSQM, and WPAI[i]		X	X	X			X	X
Concomitant medications	←	—	—	—	—	—	—	→
AEs	←	—	—	—	—	—	—	→
e-diary instruction/review[j]		X	X	X	X	X	X	X
e-diary daily completion[k]	←	—	—	—	—	—	—	→
Study drug dosing[l]	←	—	—	—	—	—	—	→
Investigator review of angioedema events[m]	←	—	—	—	—	—	—	→
Study drug accountability/ dispensing		X	X	X			X	X
Plasma for BCX7353 concentration and PD analysis[n]		X	X	X			X	X

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

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

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

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

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

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

[f] Table 5 lists parameters to be assessed.

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

[h] The EQ-5D-5L will be administered 1 to 2 × at Weeks 28, 32, 36, 48, and 52. The subject will fill out the first EQ-5D-5L at baseline and on-study to describe his or her 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 his or her health state during an average angioedema event experienced since the last study visit. If the subject has not had an angioedema event since the last study visit, the subject is not required to fill out the second, angioedema event-related EQ-5D-5L.

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

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

[k] At any time the e-diary is in a subject's possession, they will enter angioedema events (attacks, symptoms or swelling due to HAE) and relevant details and dosing information (as applicable) at least once per day.

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

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

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

Table 4: Schedule of Assessments: Part 3 of Study BCX7353-301

Assessment	Part 3 Open-Label, Active Study Drug Administration[a]												Early Termination Visit/Follow-Up/EOS[c]
	Week 56	Week 60 Day 421 ± 6 days	Weeks 64 and 68	Week 72 Day 505 ± 6 days	Weeks 76 and 80	Week 84 Day 589 ± 6 days	Weeks 88 and 92	Week 96 Day 673 ± 6 days	Week 100	Week 104 (Day 729 ± 7 days)	+each 4 wks[b]	+each 12 wks[b]	
In-clinic evaluation		X		X		X		X		X		X	X
Telephone contact[d]	X		X		X		X		X		X		
Subject weight/height[e]		X		X		X		X		X		X	X
Physical examination[f]		X		X		X		X		X		X	X
Urine pregnancy test		X		X		X		X		X		X	X
Vital signs[g]		X		X		X		X		X		X	X
Safety laboratory evaluations[h]		X		X		X		X		X		X	X
Troponin I & troponin T		X		X		X		X		X		X	X
NGAL		X		X		X		X		X		X	X
CK-MB		X		X		X		X		X		X	X
Urinalysis[h]		X		X		X		X		X		X	X
12-lead ECG[i]		X		X		X		X		X		X	X
EQ-5D-5L[j,k]		X		X		X		X		X			
AE-QoL, TSQM, and WPAI[k]		X		X		X		X		X			
Concomitant medications		←	—	—	—	—	—	—	—	—	—	→	
AEs		←	—	—	—	—	—	—	—	—	—	→	
Diary instruction/review[l]		X	X	X	X	X	X	X	X	X	X	X	X
Diary daily completion[m]		←	—	—	—	—	—	—	—	—	—	→	
Study drug dosing[n]		←	—	—	—	—	—	—	—	—	→		
Study drug accountability/ dispensing		X		X		X		X		X		X	X[o]
Plasma for BCX7353 concentration and PD analysis[p]													X[q]

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

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

[b] In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended with additional telephone contacts conducted at 4-week intervals (Weeks 108, 112, etc.) and clinic visits completed at 12-week intervals (Week 116, etc.) to allow each subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study.

[c] Once BCX7353 is commercially available at each site, an EOS visit will be scheduled for each subject to complete his or her participation in the study and transition to commercial drug product. Subjects will not have to wait for their next scheduled clinic visit to complete the EOS visit. Subjects may not continue on study for more than 3 months after NHI price listing in Japan Subjects who choose not to continue their participation in the study at any time will be asked to complete an early termination visit and/or a follow-up visit 3 weeks (+ 1 week) after their last dose of BCX7353 (eg, subjects who do not extend their treatment at Week 104 should complete the follow-up visit at Week 107 (+ 1 week). Subjects who transition to commercial BCX7353 will not need to return 3 weeks after their last dose of study drug.

[d] The investigator (or designee) must call and talk to the subject during Weeks 56, 64, 68, 76, 80, 88, 92, and 100; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of angioedema event details (if applicable), or any usability issues with the e-diary. If needed, additional telephone contacts will be conducted at 4-week intervals post-Week 104 to allow the subjects to continue treatment with BCX7353 until commercially available.

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

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

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

[h] Table 5 lists parameters to be assessed.

[i] 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.

[j] The EQ-5D-5L will be administered 1 to 2 × at Weeks 60, 72, 84, 96, and 104. The subject will fill out the first EQ-5D-5L at baseline and on-study to describe his or her 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 his or her health state during an average angioedema event experienced since the last study visit. If the subject has not had an angioedema event since the last study visit, the subject is not required to fill out the second, angioedema event-related EQ-5D-5L.

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

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

[m] At any time the e-diary is in a subject's possession, they will enter angioedema events (attacks, symptoms or swelling due to HAE) and relevant details (as applicable) at least once per day. Subjects are not required to enter dosing information in the e-diary in this part.

[n] 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.

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

[p] PK and PD blood samples will be drawn on all subjects with no particular relationship to the timing of study drug dosing through the Week 52 visit only. The investigator (or designee) must ensure that the time of the last dose prior to PK and PD draw is recorded in the subject's e-diary (this may also be captured in the eCRF).

[q] PK and PD blood samples will be drawn at the ET visit, only if the ET visit occurs prior to Week 52.

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 ICF (if not done prior to the visit) and assent (as applicable)
- Review of inclusion and exclusion criteria
- Medical and medication history (including HAE medical, medication history and prohibited medications)
- Complete physical examination
- 12-lead ECG
- Height/weight/BMI estimation
- Vital signs (blood pressure, pulse rate, temperature, and respiratory rate)
- Serum pregnancy test for all female subjects of childbearing potential (including adolescents)
- Blood collection for clinical chemistry, hematology, coagulation, HBV/HIV/HCV serology, C-INH function level, C4 level, C1-INH antigenic 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 GGT, AST, or ALT
- Recording of AEs and concomitant medications
- Provision and instruction of the e-diary

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

In the case of limitations for conduct of the screening visit to occur on a single day, a site is permitted to perform screening assessments over more than one screening visit. However, an

e-diary to capture angioedema events 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 angioedema event within approximately 3 days of the visit as C1-INH functional level is more likely to come back normal or to not meet inclusion criterion 3.

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 angioedema events will be determined during the run-in period; the baseline angioedema event 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 angioedema events that are recorded following the screening visit, subjects will be contacted within approximately 2 business days of the end of the angioedema event to discuss the clinical characteristics of the angioedema event, any questions on the entered data, or to gain additional details on the event not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable. The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each event as a confirmed angioedema event. The investigator e-diary data review and subject contact summary worksheets will be documented in the source records and made available to an independent expert for their verification (confirmation or rejection) of the event.

For the subject to qualify for the study, the subject must have at least 2 angioedema events as assessed by an independent expert during the run-in period (56 days beginning at the screening visit) that meet all of the following requirements below:

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

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

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 angioedema event details (if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an angioedema event, as the investigator must call and confirm or reject the angioedema events.

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 C4 level during an angioedema event. Normal C4 drawn during an angioedema event 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. 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 1 or 2 HAE is acceptable to confirm the diagnosis of HAE. A SERPING-1 analysis that does not identify a likely or pathologic mutation indicative of HAE excludes the subject from study participation.

For a C1-INH 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. A C1-INH functional level < 50% or a SERPING-1 mutation known or likely to be associated with HAE Type 1 or 2 HAE is acceptable to confirm the diagnosis of HAE. A SERPING-1 analysis that does not identify a likely or pathologic mutation indicative of HAE excludes the subject from study participation.

SERPING-1 gene analysis results indicating a "possibly pathogenic" mutation will be considered on a case-by-case basis by the medical monitor and may require additional testing for eligibility.

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 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 angioedema event requirements during the run-in period.

A screening failure eCRF 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, and prohibited medications
- Subject weight
- Vital signs (blood pressure, temperature, respiratory rate, and pulse rate)
- 12-lead ECG (in triplicate)
- Full physical examination
- Blood collection for clinical chemistry, hematology, coagulation, C3, troponin I and troponin T, NGAL, human leukocyte antigen (HLA) typing, and CK-MB
- PK concentration 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 all female subjects of childbearing potential. A negative urine pregnancy result must be recorded before the subject can be dosed.
- Review of concomitant medications and AEs
- e-diary instruction and review. Where required, the e-diary should be turned to the dosing phase in Part 1 at the conclusion of these assessments, prior to randomization and study drug dispensing.
- Calculation of baseline angioedema event rate for stratification in IXRS
- 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 or should be administered at home on the day of the visit (see Section 9.3.2). 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 discuss details of all angioedema events recorded in the e-diary within approximately 2 business days of the end of the angioedema event. 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 angioedema event details (if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an angioedema event, as the investigator must call and confirm or reject the angioedema event.

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, 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 eCRF.

During Part 1, investigators will contact subjects to discuss details of all angioedema events recorded in the e-diary within approximately 2 business days of the end of the angioedema event. 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 concentration and PD plasma samples
- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT, and urine pregnancy test for all female subjects of childbearing potential

- Review of concomitant medications and AEs
- Review of angioedema event and dosing e-diary completion and study drug compliance
- Study drug accountability and dispensing

During the Part 1 dosing period, investigators will contact subjects to discuss details of all angioedema events recorded in the e-diary within approximately 2 business days of the end of the angioedema event. 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 angioedema event details (if applicable), or any usability issues with the e-diary. A weekly phone call may be omitted if the subject records an angioedema event, as the investigator must call and confirm or reject the angioedema event.

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 in Part 1 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 (1-2 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 concentration and PD plasma samples
- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT, and urine pregnancy test for all female subjects of childbearing potential. A negative urine pregnancy result must be recorded in order for the subject to be dosed.
- Review of concomitant medications and AEs
- Part 1 study drug collection/accountability

- e-diary instruction and review and set up. The e-diary should be turned to Part 2 at the conclusion of these assessments, prior to randomization and study drug dispensing for Part 2.

After completion of the above bulleted items at the conclusion of the visit, Part 2 study drug may be dispensed from the IXRS 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 given at the visit, should be taken the day of the visit.

During the Part 2 dosing period, investigators will contact subjects to discuss details of all angioedema events recorded in the e-diary within approximately 2 business days of the end of the angioedema event. 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 (Day 183 ± 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 eCRF.

During the Part 2 dosing period, investigators will contact subjects to discuss details of all angioedema events recorded in the e-diary within approximately 2 business days of the end of the angioedema event. Moreover, any noncompliance will warrant contact with the subject.

10.3.4.2. Week 28, 32, 36, 48, and 52 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), Week 48 (Day 337 ± 7 days), and Week 52 (Day 365 ± 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 (1-2 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 concentration and PD plasma samples

- Urine collection for urinalysis, possible reflex testing for abnormal GGT, AST, or ALT, and urine pregnancy test for all female subjects of childbearing potential
- Review of concomitant medications and AEs
- Review of angioedema events and dosing e-diary completion and study drug compliance. The e-diary should be turned to Follow-up at the conclusion of the Week 52 visit.
- Study drug accountability and dispensing.

During the Part 2 dosing period, investigators will contact subjects to discuss details of all angioedema events recorded in the e-diary within approximately 2 business days of the end of the angioedema event. Moreover, any noncompliance will warrant contact with the subject.

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 angioedema event details (if applicable), or any usability issues with the e-diary. The phone call may be omitted if the subject records an angioedema event as the investigator must call and confirm or reject the angioedema event.

10.3.5. Part 3

10.3.5.1. Week 60, 72, 84, 96, and 104 Visits

Subjects will return to the clinic during Week 60 (Day 421 ±6 days), Week 72 (Day 505 ± 6 days), Week 84 (Day 589 ± 6 days), Week 96 (Day 673 ± 6 days), and Week 104 (Day 729 ± 7 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. 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 48 and 96)
- 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 all female subjects of childbearing potential
- Review of concomitant medications and AEs
- Review of e-diary data, to include recording of angioedema events.
- Study drug accountability and dispensing (collection only at Week 104)

During the Part 3 dosing period, investigator confirmation of angioedema events recorded in the e-diary is not required nor is recording of daily dosing. The e-diary should be reviewed with the subject at all study visits. Any noncompliance will warrant contact with the subject.

Post-Marketing Study

Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 through Week 104 or until such time as BCX7353 is commercially available at his or her site, whichever occurs first, unless the subject discontinues his or her participation in the study. In the event that BCX7353 is not commercially available when the first and each subsequent subject at each site reaches Week 104, then the treatment period will be extended to allow each subject to continue treatment with BCX7353 until commercially available, unless the subject discontinues his or her participation in the study. Once BCX7353 is commercially available at each site, an EOS visit will be scheduled for each subject to complete his or her participation in the study and transition to commercial drug product. Subjects may not continue on study for more than 3 months after NHI price listing in Japan.

10.3.5.2. Week 56, 64, 68, 76, 80, 88, 92, and 100 Phone Calls

The investigator (or designee) must call and talk to the subject once during Weeks 56, 64, 68, 76, 80, 88, 92, and 100; alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the investigator (or designee) will assess the subject's overall welling, discuss compliance (if applicable), proper recording of angioedema event details (if applicable), or any usability issues with the e-diary.

If needed, additional telephone contacts will be conducted at 4-week intervals post-Week 104 to allow the subjects to continue treatment with BCX7353 until commercially available.

10.3.5.3. Early Termination Visit/Follow-Up/End-of-Study

The following assessments will be performed for study completers at the EOS or at the Early Termination/Follow-Up visit (as applicable) for those subjects who discontinue, held approximately 3 weeks following the last dose of study drug.

Subjects who will transition to commercial drug product will have an EOS visit once BCX7353 is commercially available at each site. Subjects who transition to commercial BCX7353 will not need to return 3 weeks after their last dose of study drug. These assessments will also be conducted at an Early Termination Visit for those withdrawing consent (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 all female subjects of childbearing potential
- Review of concomitant medications and AEs
- Review and collection of e-diary
- Blood for plasma PD and PK concentration analysis (early termination visit before Week 52 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.

Assessments in the study are intended to be conducted in-clinic; they may be conducted remotely under extenuating circumstances (eg, COVID-19 restrictions), which will be determined individually for each site and/or subject. At a minimum, a subject must be contacted to assess whether he or she has experienced any changes in his or her physical health or concomitant medications, and to review the adequacy of his or her existing study drug supply. If drug dispensation in-clinic is not possible, study drug may be delivered to the subject by other means (eg, traceable courier) as described in Section 9.4.

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.

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 eCRF 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:

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

BMI and height are only to be captured at the screening visit.

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 interval 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, with 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 time point, only the central laboratory results will be used for study purposes. Additionally, urine pregnancy tests will be provided by the central laboratory 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	**Coagulation**
• 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, phosphorus) • Lipid panel (total cholesterol, triglycerides) • Creatine kinase • Creatinine and calculated CL_{CR} • Gamma-glutamyltransferase (GGT) • Lactate dehydrogenase (LDH) • Total serum protein • Uric acid • Amylase • *If amylase is > 2 × ULN, reflex to* lipase	• Prothrombin time (PT) and international normalized ratio (INR) • Activated partial thromboplastin time (aPTT)
	Pregnancy Test
	Serum (screening) and urine (other scheduled visits) β-hCG for women of childbearing potential (including adolescents) only
	Drug screen
	• Amphetamines • Barbiturates • Benzodiazepines • Cocaine • Opiates • Methamphetamine • Ecstasy
Urinalysis	
• Specific gravity • Blood • Bilirubin • Glucose • Leukocytes • Ketones • Nitrites • pH • Protein • Urobilinogen • Microalbumin to creatinine ratio • *Reflex microscopy if dipstick is abnormal*	**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 functional level • 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
Hematology	
• Hemoglobin • Hematocrit • Erythrocytes • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) • Platelets	

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

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

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 all women and adolescents of childbearing potential, a serum pregnancy test will be administered at screening. This will be done regardless of contraceptive or lifestyle choice (ie, those choosing not to engage in heterosexual activity or exclusively having female partners). Urine 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.

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 (as used for treatment of an angioedema event). Last use of C1-INH for treatment of an angioedema event prior to this measurement should be denoted in the eCRF.

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 C4 level during an angioedema event. A normal C4 level drawn during an angioedema event 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 1 or 2 HAE is acceptable to confirm the diagnosis of HAE. A SERPING-1 analysis that does not

identify a likely or pathologic mutation indicative of HAE excludes the subject from study participation.

For a C1-INH 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. A C1-INH functional level < 50% or a SERPING-1 mutation known or likely to be associated with HAE Type 1 or 2 HAE is acceptable to confirm the diagnosis of HAE. A SERPING-1 analysis that does not identify a likely or pathologic mutation indicative of HAE excludes the subject from study participation.

SERPING-1 gene analysis results indicating a "possibly pathogenic" mutation will be considered on a case-by-case basis by the medical monitor and may require additional testing for eligibility.

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 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 a study drug-related rash (see Section 11.2.14)

A C1-INH antigenic level will be measured at screening; last use of C1-INH for treatment of an angioedema event prior to this measurement should be denoted in the eCRF.

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 concentration samples obtained from subjects randomized to placebo may be limited. The bioanalytical laboratory 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 52 (except Weeks 2 and 26).

The samples ordinarily can be drawn at any time post-dose; however, during Part 1, at least 1 sample should be drawn at the approximate C_{max} of the drug, approximately 3 to 6 hours post-dose. Actual date and time of sample collection will be recorded in the eCRF. Sites will ensure that the time of the previous dose prior to the blood draw is recorded in the e-diary (may also be captured in the eCRF).

Instructions for collection, processing, storage, and shipment of PK and PD 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 1 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.

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. In addition, it is preferable that sites have the ability to obtain or to refer to a specialist who can obtain an appropriate skin biopsy. 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 maculo-papular (eg, urticarial) or not related to BCX7353 (ie, has a clear alternative etiology), then the rash is reported as an AE, 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 desires more rapid results, a second set of blood tubes may be sent to the local laboratory for faster processing.
- Vital signs including temperature
- Urine sent to local laboratory for urine eosinophils (if evaluation is available locally).

- While not mandated, subjects should be requested to undergo a standard dermatologic punch biopsy for hematoxylin and eosin (H&E) staining and immunofixation. The biopsy should be obtained from a fresh lesion for diagnostic and scientific purposes, after obtaining specific informed consent from the subject. 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 benefit-risk 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 nonstudy 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 communicated to the study sites. Note: If the rash is no longer present by the time of medical evaluation, biopsy is not necessary. In addition, if the rash is classically urticarial, biopsy is not necessary.

  If a subject with drug-related treatment-emergent rash does not agree to undergo skin punch biopsy, study drug dosing may be continued if clinical benefit is being derived but the subject must undergo weekly monitoring until the rash resolves to assess for any worsening of symptoms, particularly mucosal involvement or systemic symptoms.

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 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 (pre-dose) and at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 48, 52, 60, 72, 84, 96, and 104.

The EQ-5D-5L will be administered once at baseline (pre-dose) and at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 48, 52, 60, 72, 84, 96, and 104. 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 angioedema event since the previous visit. The subject will be instructed to fill out this second questionnaire based on a

recollection of his or her health state during an average angioedema event that they experienced since the previous visit.

Each questionnaire will be translated into Japanese. For all subject-completed forms, clinic staff should ensure the subject reads the instructions and completes the questionnaires in full prior to filling in the source documentation. For the baseline TSQM, separate guidance will be provided such that subjects complete their assessment with reference to their satisfaction with their usual standard of care treatment of HAE, prior to screening for the study.

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

11.4. Angioedema Events and Dosing e-Diary, Investigator Event Follow-up and Confirmation

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 his or her possession, the subject will fill out the angioedema event e-diary daily, recalling whether or not symptoms of an angioedema event were experienced in the previous 24 hours. Subjects will fill out the e-diary regardless of the presence of HAE symptoms. If the subject does report an angioedema event, additional details about the angioedema event will be entered into the e-diary including start and stop time of the angioedema event, angioedema event symptoms, anatomical location of swelling (if applicable), severity, treatment(s) administered and times of administration, and whether additional medical care was sought for the angioedema event. During study drug administration in Parts 1 and 2, subjects will also record the times of day study drug was taken in the e-diary on a daily basis.

All subjects will fill out an HAE e-diary during the run-in period of 56 consecutive days from the screening visit to enable the qualifying angioedema event rate to be established. Subjects will continue to fill out their e-diary after the run-in period in advance of the baseline visit. 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 end Part 1/begin Part 2 or to end Part 2/begin Part 3). Subjects should be instructed to bring their e-diary with them to each study visit, up to and including Week 104, 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 angioedema event details (if applicable), or any usability issues with the e-diary.

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

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 angioedema event 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 angioedema event that occurs.

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

11.4.1. Screening and Parts 1 and 2

11.4.1.1. Investigator Follow-up of Angioedema Events and Expert Confirmation of Angioedema Events

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

For all angioedema events that are recorded from screening through the end of Part 2, the investigator (or appropriately-trained designee) will review the e-diary record of the angioedema event details. Subjects will then be contacted within approximately 2 business days of the end of the angioedema event to discuss the clinical characteristics of the angioedema event and any questions the investigator has on the entered data, or to gain additional angioedema event details not included in the e-diary that the investigator deems important to clinically evaluate the event, as applicable. The investigator-collected information, in conjunction with the e-diary record, will be used by an independent expert to verify or reject each event recorded in the e-diary as a confirmed angioedema event.

The investigator e-diary data review and subject contact summaries will be documented in the source records and made available to an independent expert for their verification (confirmation or rejection) of the event.

During the run-in period of 56 days beginning at the screening visit, angioedema events used to establish eligibility must meet the following stipulations, in addition to expert confirmation that the recorded event is an angioedema event:

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

During the entire screening period (run-in period and the period after eligibility has been established during the run-in period but prior to randomization), angioedema events must meet the following stipulations to be counted in the baseline angioedema event rate calculation necessary for stratification, in addition to the expert confirmation:

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

After randomization through the end of Part 2, the expert will use their judgment to confirm or reject a reported event as an angioedema event; however, all angioedema events must include symptoms of swelling. The expert will consider that symptoms of swelling, in addition to visible swelling, may also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling.

The selection of the independent expert(s) who will confirm or reject attacks will be made by the sponsor and may or may not be an investigator in the current study. Expert expectations for turn-around times of the event confirmation or rejection and how the event confirmation or rejection will be received by the investigator and site staff, especially in the period between screening and baseline, will be communicated separately.

11.4.1.2. Scheduled Telephone Contact

The investigator (or designee) must call and talk to the subject once weekly during Part 1 and during Part 2 at Weeks 40 and 44. Alternative forms of interactive communication such as returned email and cellular text correspondence are acceptable. During all calls, the investigator (or designee) will assess the subject's overall wellbeing, discuss compliance (if applicable), proper recording of angioedema event details (if applicable), or any usability issues with the e-diary. The phone call may be omitted if the subject records an angioedema event, as the investigator must call and confirm or reject the angioedema event.

11.4.2. Part 3

11.4.2.1. Confirmation of Angioedema Events

Subjects will continue to document all angioedema events that occur in their e-diary throughout Part 3. Investigator follow-up of angioedema events and expert confirmation of events will not be required for Part 3. All angioedema events recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in effectiveness analyses. These rules will be outlined in the SAP.

11.4.2.2. Scheduled Telephone Contact

The investigator (or designee) must call and talk to the subject once during Weeks 56, 64, 68, 76, 80, 88, 92, and 100. If needed, additional telephone contacts will be conducted at 4-week intervals post-Week 104 to allow the subjects to continue treatment with BCX7353 until commercially available. 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 angioedema event 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 will not meet the definition of an adverse event.

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 angioedema event. 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 be reported only 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, angioedema events and their associated symptoms will not be defined as AEs, even if the subject requires hospitalization. This information, as well as all HAE attacks and associated symptoms, are reported in the subject's e-diary and is a reflection of the disease under study. The events that may trigger an angioedema event 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 an HAE patient).
- 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
- 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 (> 1 dose per calendar day) 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, 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 in the AE eCRF.

AEs should be documented in the eCRF as investigators become aware of them. AEs are to be followed until the event resolves, as follows. 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 at least 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 entering the event into the AE eCRF and by completion of the SAE eCRF within 24 hours of their knowledge of the event (see Section 12.1.5). The SAE eCRF form is an additional form to the AE eCRF that provides important details on the SAE.

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 by deleting the previous symptoms and entering the diagnosis. The rapid reporting of SAEs 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 Appendix 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 via the AE and SAE eCRFs within 24 hours of the investigator's awareness of the SAE. All additional follow-up evaluations of the SAE must be reported to BioCryst or its designee as soon as they are available by amending these eCRFs. The SAE notification should be reported to:

Phone (24 hours): +1 919-859-7905

Email: safety@biocryst.com and mmj@biocryst.com

In the event the eCRF system is not functioning, the reporting of an SAE **must not** be delayed. Sites will have SAE report forms (electronic Word document) that can be completed and emailed to the above recipients. As soon as the eCRF system is functioning, that particular SAE must be entered into the AE eCRF. The SAE eCRF for that particular event does not need to be completed if the site communicates all follow-up on the separate SAE report form that was initially completed. If the site wishes to enter follow-up information on the SAE via the SAE eCRF, then the SAE eCRF must be completed with the initial as well as the follow-up information.

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.

Japan-specific rules and requirements for safety management will be described in the Safety and Medical Management Plan prepared for the current protocol.

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

BioCryst or its designee 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 ICH regions, and to the institutional review boards (IRBs) or independent ethics committees (IECs), and in any case no later than 7 days after knowledge by BioCryst of such a case, in accordance with all applicable local laws. All other SUSARs shall be reported to the competent authorities concerned and to the IRBs/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. Investigators are responsible for retaining a copy in their files, unless otherwise instructed.

12.1.5.1. Reporting Adverse Events of Special Interest

All skin disorders or abnormal findings of the skin are adverse events and should be reported in the usual manner on the eCRF as per Section 12.1.2. However, events of maculopapular rash assessed as related to study drug/IMP, regardless of severity, are considered to be EOSIs which require additional reporting. Any new maculo-papular rash assessed as related to the use of study drug must be reported to the sponsor medical monitor via the eCRFs, specifically both the AE eCRF and the SAE eCRF, within 24 hours of the investigator's *assessment* of the event. The SAE eCRF will also serve as an EOSI Report form, although the rash event itself may not meet seriousness criteria. High resolution photographs must also be submitted via email as described in Section 11.2.14. All additional follow-up evaluations of the event must be reported to BioCryst or its designee as soon as they are available. The notification should be sent to the following email addresses:

Phone (24 hours): +1 919-859-7905

Email: safety@biocryst.com and mmj@biocryst.com

In the event the eCRF system is not functioning, the reporting of an EOSI **must not** be delayed. Sites will have SAE/EOSI Report forms (electronic Word document) that can be completed and emailed to the above recipients. As soon as the eCRF is functioning, the EOSI must be entered into the AE eCRF. The SAE eCRF for that particular event does not need to be completed if the site communicates all follow-up on the separate SAE/EOSI Report form that was initially completed. If the site wishes to enter follow-up information on the EOSI via the SAE eCRF, then the SAE eCRF must be completed with the initial as well as the follow-up information.

This method of reporting should allow BioCryst to obtain more information including a full clinical description and information regarding the evaluation. 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 (GCP) that 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 reported 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 angioedema event 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 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 eCRF 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 that 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. Adverse Event 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 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, and 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 evidence of any hypersensitivity involving the liver or kidney. 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, anti-histamines, 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.

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. Subjects who remain on study drug should be followed closely until the rash resolves.

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 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 when available and the investigative site contacts the subject to ascertain any symptoms. If either ALT or AST continue to increase and the subject remains asymptomatic, study drug must be held if:

- Either ALT or AST is > 5 × ULN for more than 2 weeks, or
- ALT or AST reaches > 8 × ULN.

The subject should continue regular assessments of ALT, AST, total bilirubin, ALP, prothrombin time/INR, and complete blood count for eosinophil levels, as deemed appropriate by the investigator, 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, complete blood count (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 unexpected 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

Data from ongoing studies BCX7353-302 (Phase 3 study), BCX7353-204 (long-term safety study), and the current study (BCX7353-301) are reviewed by the BCX7353 DMC at defined time points. At the time of this amendment, the latest data review was conducted on 16 April 2020 and the DMC recommended that all 3 studies continue per protocol. Since > 200 subjects have completed through 48 weeks across the studies, the DMC members 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. Each DMC member will provide his or her written assessment of the safety data; 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 DMC meeting. Where possible, scheduled DMC meetings for this study may be aligned with those of other studies. The DMC may also be convened if a new clinically significant safety signal emerges or other times as requested.

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

13.1.1. Primary Hypotheses

The primary study hypothesis is that the rate of angioedema events during 24 weeks of prophylactic BCX7353 (at either 150 mg or 110 mg QD) will be less than the corresponding rate on placebo.

As the sample size considered feasible for enrollment in Japan has limited statistical power, hypothesis testing will be performed on a combined analysis of the current study with Study BCX7353-302. The hypothesis will be tested separately for each active dose, comparing to placebo treatment.

The primary null and alternative hypotheses are:

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

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

The primary efficacy endpoint in Study BCX7353-301 is the monthly expert-confirmed angioedema event rate in the entire treatment period (Day 1 [post dose] to Day 168) in the

intent-to-treat (ITT) population, which includes all randomized subjects. The primary efficacy endpoint in Study BCX7353-302 is the monthly investigator-confirmed angioedema event rate in the entire treatment period (Day 1 [post dose] to Day 168) in the ITT population, 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.

13.1.2. Secondary Hypotheses

For each dose separately, the following secondary hypotheses will be tested in a combined analysis of the current study with Study BCX7353-302:

1. Proportion of days with angioedema symptoms
    - H_o: $\beta=0$; active treatment does not have a differential effect on the proportion of days with angioedema symptoms over the entire treatment period
    - H_A: $\beta\neq0$; active treatment does have a differential effect on the proportion of days with angioedema symptoms over the entire treatment period

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

    where R_A is the monthly angioedema event rate for active treatment and R_P is the monthly angioedema event rate for placebo treatment during the effective treatment period.
3. AE-QoL
    - H_o: $\beta=0$; active treatment does not have a differential effect on the change from baseline AE-QoL at Week 24
    - H_A: $\beta\neq0$; active treatment does have a differential effect on the change from baseline AE-QoL at Week 24

    where β is the parameter representing treatment effect for the dose of interest in a mixed effect model for repeated measurements (MMRM).

13.1.3. Controlling for Multiplicity

There are 4 endpoints being tested in the combined analysis, the primary endpoint and 3 secondary endpoints. For each endpoint, there are 2 potential doses to be tested. The Type I error rate will be controlled at the study level by using a combination of hierarchical testing and the Hochberg procedure. The 4 endpoints will be tested in a hierarchical fashion and the 2 doses

will be tested using the Hochberg step-up procedure at each level of the hierarchy to which both doses progress through the hierarchy.

The first endpoint to be tested is the primary endpoint, the rate of investigator or expert-confirmed angioedema events during dosing in the entire 24-week treatment period (Days 1 to 168). Using the Hochberg step-up procedure, each of the 2 doses will be tested at the $\alpha = 0.05$ level, comparing active treatment to placebo. If the maximum of the 2 p-values is ≤ 0.05, the null hypotheses of no difference between the rate of angioedema events for subjects on active and placebo treatment will be rejected for both doses and testing will proceed to the next endpoint in the hierarchy with $\alpha = 0.05$. If the maximum of the 2 p-values is > 0.05 but the minimum of the 2 p-values is < 0.025, the null hypothesis for the dose with $p < 0.025$ will be rejected and testing for that dose only will proceed to the next endpoint in the hierarchy with $\alpha = 0.025$. Otherwise, the null hypotheses for both doses will not be rejected, testing will stop, and the hypothesis for the next endpoint in the hierarchy will not be tested.

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

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

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

13.2. Sample Size Considerations

The planned sample size for the current study is 8 per treatment group for each of three treatment groups. The primary analysis will be conducted on the BCX7353-301 study population. It should be noted that the sample size considered feasible for enrollment in Japan has limited statistical power. Therefore, all efficacy data for Part 1, where appropriate, will also be analyzed by combining data from this study with data from Study BCX7353-302, to ensure adequate statistical power. For the combined analysis with Study BCX7353-302, the sample size is expected to be 40 subjects per treatment group.

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

Power calculations for the primary efficacy endpoint for the current study alone and those for the combined analyses with Study BCX7353-302 are provided in Table 6 and described in Sections 13.2.1 and 13.2.2.

Table 6: Power Calculations to Support Sample Size

Study	Sample Size Per Treatment Group	Attack Rate for Placebo Subjects (attacks/week)	Attack Rate for Active Treatment (attacks/week)	Common SD for Attack Rate	Type I Error Rate (α)	Power for Pairwise Comparison with Placebo
BCX7353-301 alone	8	0.9	0.3	0.5	0.05	61%
Combined BCX7353-301 and BCX7353-302	40	0.9	0.3	0.5	0.05	>99%

Abbreviation: SD = standard deviation.

13.2.1. Sample Size for Study BCX7353-301 Alone

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

13.2.2. Sample Size for the Combined Analysis of Studies BCX7353-301 and BCX7353-302

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

13.3. Stratification

Randomization of subjects will be stratified by the baseline expert-confirmed angioedema event rate (≥ 2 angioedema events per month vs. < 2 angioedema events per month).

13.4. Statistical Methods

A detailed SAP will be developed to describe in detail the methods of analyses. Deviations from the analyses outlined in the SAP will be described in the CSR.

13.4.1. Analysis Populations

The analysis populations are defined below.

13.4.1.1. Screen Failures

Subjects who give informed consent but are not dispensed study medication are considered screen failures. Reason for screen failure will be summarized using this population.

13.4.1.2. 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.

13.4.1.3. 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 at first dose for all subjects for Part 1 or at first dose of Part 2 for subjects originally randomized to placebo.

13.4.1.4. Per Protocol Population

The per protocol (PP) population will include a subset of 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 for Part 1 or at first dose of Part 2 for subjects originally randomized to placebo. The PP population may be used as a secondary population for efficacy analyses.

13.4.1.5. Completers Population

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

13.4.1.6. Pharmacodynamic Population

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

13.4.1.7. PK Concentration/PD Population

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

concentration). This population will be used for all correlation analyses of plasma kallikrein inhibition and plasma BCX7353 concentrations.

13.4.2. General Considerations for Data Analysis

Descriptive summaries, figures, and listings for efficacy, safety, concentration, and PD results will use data from subjects enrolled in this study alone.

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.

Selected summaries will be repeated using data from the current study and BCX7353-302.

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).

13.4.3. Subject Demographic and Disposition Data

Demographic and disposition data will be summarized for the current study alone and using the combined 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.

13.4.4. Analysis of Efficacy Variables

The primary efficacy endpoint will be determined from Part 1 of the current study alone, using the ITT population.

A supplemental analysis will combine data from the current study and Study BCX7353-302. Analysis of data using the PP population will be conducted to support the combined efficacy analysis.

Efficacy data will generally be summarized by treatment group and for both active doses combined. Angioedema events will generally be summarized over the entire dosing period. Selected analyses will be repeated using 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 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 first dose in Part 2) is the date of first dose + 7 days to the date and time of first dose in Part 2 or the date of study treatment discontinuation + 24 hours, for subjects who discontinue treatment prior to Part 2.

13.4.4.1. Primary Efficacy Analysis

The primary efficacy endpoint is the rate of expert-confirmed angioedema events during dosing in the entire treatment period of Part 1 of the current study.

The sample size considered feasible for enrollment in Japan has limited statistical power. Therefore, a supplemental statistical analysis will be conducted using the combined monthly angioedema event rate (investigator-confirmed attacks in Study BCX7353-302 and expert-confirmed events in Study BCX7353-301) in the entire treatment period in the ITT population. The angioedema event rate and the treatment comparisons between each BCX7353 dose and placebo in the rate of investigator- or expert-confirmed angioedema events during the entire dosing period will be analyzed using a negative binomial regression model. The number of investigator- or expert-confirmed angioedema events will be included as the dependent variable, the treatment will be included as a fixed effect, the stratification variable (baseline monthly angioedema event rate) will be included as a covariate, and the logarithm of duration on treatment will be included as an offset variable. The estimated rate of angioedema events for each treatment group, the treatment differences expressed as the angioedema event rate ratio (BCX7353 over placebo rate ratio), and their associated 95% confidence intervals (CIs) will be provided from the negative binomial regression model. Monthly will be defined as 4 weeks.

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 the study and on those in the PP population.

13.4.4.2. 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- or expert-confirmed angioedema events during dosing in the effective treatment period (beginning on Day 8 through Week 24)

Part 1 exploratory efficacy endpoints include:

- Number and proportion of subjects with no angioedema events over 24 weeks
- Use of medications to treat angioedema events over 24 weeks
- The proportion of responders to study drug, separately defined as at least a 50%, 70%, or 90% relative reduction in the rate of expert-confirmed angioedema events during treatment compared with the baseline expert-confirmed angioedema event rate

For the combined analysis with Study BCX7353-302, treatment comparisons in the AE-QoL total score change from baseline will be analyzed using an 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% CI and the associated p-value. Primary inferences will be drawn from treatment differences for the changes from baseline derived from the MMRM model through 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.

Secondary and exploratory efficacy endpoints will be summarized and listed.
The between-treatment comparisons will be performed for the combined analysis with Study BCX7353-302 using a similar negative binomial regression model for the investigator- or expert-confirmed angioedema events 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 endpoints are described in Section 13.1.3.

Additional related details of angioedema events (eg, symptoms, anatomical location, hospitalizations, emergency room visits, and angioedema event 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 angioedema events
- Durability of response (angioedema event rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of medications to treat angioedema events
- Discontinuations due to lack of efficacy (through Week 52 [Part 2] 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 for Parts 2 and 3 will be provided for the current study. For the placebo subjects who switched to an active BCX7353 dose, the change from placebo to the active dosing period will be summarized. Details of the planned efficacy analyses for the entire study will be provided in the SAP.

13.4.5. Planned Analyses

The primary analysis is planned after the last subject completes the 24 weeks of study (last subject completes Part 1).

The investigators, study staff, and subjects will remain blinded until after the database has been locked and the final analysis conducted. The final analysis will occur after the last subject completes 52 weeks of study. Analysis of the 52-week data will be comprised of data from the current study alone.

13.4.6. Analysis of Safety Variables

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

The safety analyses will be analyzed separately for Part 1 alone; a later data analysis will evaluate long-term safety data for the current study.

Safety endpoints that will be summarized include, at a minimum, the number and proportion of subjects: 1) with a TEAE; 2) who discontinue BCX7353 due to a TEAE; 3) who experience a TESAE; 4) who experience a 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 as identified by the investigator will also be summarized.

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The occurrence of TEAEs will be summarized using MedDRA preferred terms, system organ classifications, and severity. Separate summaries of TEAEs, TESAEs, AEs considered to be related to study drug, and AEs leading to study drug interruption 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 Adverse Event Table (Publish Date: Draft, November 2007; Appendix 16.1).

Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. The number and percentage of subjects experiencing 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 $\leq$ 450, > 450 to $\leq$ 480, > 480 to $\leq$ 500, and > 500 msec; or changes of $\leq$ 30, > 30 to $\leq$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 hypotheses are planned for safety data.

13.4.7. Health Outcome Analyses

Health outcome endpoints are as follows:

- Durability in TSQM scores
- Durability in WPAI scores

- Durability in EQ-5D-5L scores

Summaries will be provided for the current study.

The between-treatment comparisons for combined analysis with Study BCX7353-302 for TSQM, WPAI, and EQ-5D-5L will be performed using a mixed effect model including terms of treatment, visit, visit interaction, and baseline score. Details will be provided in the SAP.

13.4.8. Pharmacokinetic Analyses

Plasma samples for determination of BCX7353 concentrations are planned to be collected per Table 2 and Table 3. Concentration data will be listed and summarized by treatment group for the current study alone.

The resulting PK data will then be pooled in a meta-analysis to facilitate population PK analyses. In the population PK analysis, covariates will be tested to determine the effect on PK of BCX7353. Region will be one of the covariates analyzed.

Pharmacokinetic results from the meta-analysis will not be summarized in the statistical reporting of this study.

13.4.9. Pharmacodynamic Analyses

Plasma kallikrein inhibition data will be expressed as percentage 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. Using data from the current study alone, descriptive statistics will be reported. Mean and individual plasma kallikrein inhibition versus time profiles will be plotted by treatment group.

13.4.10. PK Concentration /Pharmacodynamic Analyses

This analysis of PK concentration-PD relationships may be performed using data from this study alone or may be combined with data from Study BCX7353-302. 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; GCPs, including ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH E6); Japan PMDA 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.

Following marketing authorization in Japan and formal transition to a post-marketing study, this study will be conducted in compliance with post-marketing regulations. The sponsor of the study

will be changed from BioCryst to the marketing authorization holder in Japan, OrphanPacific, Inc. However, the clinical conduct of the study will continue to be overseen by BioCryst. Therefore, reference to "the sponsor" in this section may encompass reference to BioCryst and/or OrphanPacific, Inc., as applicable.

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 the sponsor.

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 the sponsor 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 sponsor 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 non-enrollment.

14.1.4. Subject Informed Consent: Adolescents

Signed informed consent must be obtained from each parent/caregiver of adolescent subjects aged 12 to 17 years 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 have 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 the sponsor 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 sponsor policies.

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, the sponsor 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 in the eCRFs are accurate. The investigator and institution will allow sponsor 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 the sponsor 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:

- if the study drug becomes commercially available or another mechanism is available to provide drug to the subject
- changes in scientific knowledge that lead to a negative impact on the benefit-risk profile for subjects
- request of sponsor 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

The sponsor 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 the sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

An individual trial center that is determined to be unsuitable by the 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 will be defined for individual subjects, parts of the trial, or the entire trial. 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.

Once BCX7353 receives marketing authorization in Japan, this study will be transitioned to a post-marketing study. Each subject remaining on study may continue to receive access to BCX7353 via this study until such time as BCX7353 is commercially available at his or her study center. Once the last subject is able to access commercial drug product, the study will be terminated.

14.5. Records Retention

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and medical/hospital records), all original signed ICFs, all original signed assents (where applicable), all eCRFs, 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 the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records and must notify the sponsor before transferring any records to another facility.

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

14.6. Confidentiality of Information and Data

The sponsor 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 the sponsor. However, in compliance with federal regulations, the sponsor requires the investigator to permit the sponsor's representatives and, when necessary, representatives of the PMDA 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. 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.

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 prior 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.

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16. APPENDICES

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

For the purposes of this protocol, the title of the Division of Microbiology and Infectious Disease (DMID) table to be used grade adverse events is referred to as the 'DMID Adult Adverse Event Table.' The criteria contained in the 'DMID Adult Adverse Event Table' has been unaltered from the published DMID table under the name 'DMID Adult Toxicity Table (DRAFT, Publish Date: November 2007).'

Copies of the DMID Adult Adverse Event Table will be available to the medical staff throughout the project.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
DRAFT

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.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
DRAFT

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 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
DRAFT

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