- 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

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

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

[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).

[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.

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

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

- 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.

- 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).

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

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.

- 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

- 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

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.

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):

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

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).

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.

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.

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

- 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

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 %

- 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

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

(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).

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.

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

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

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.

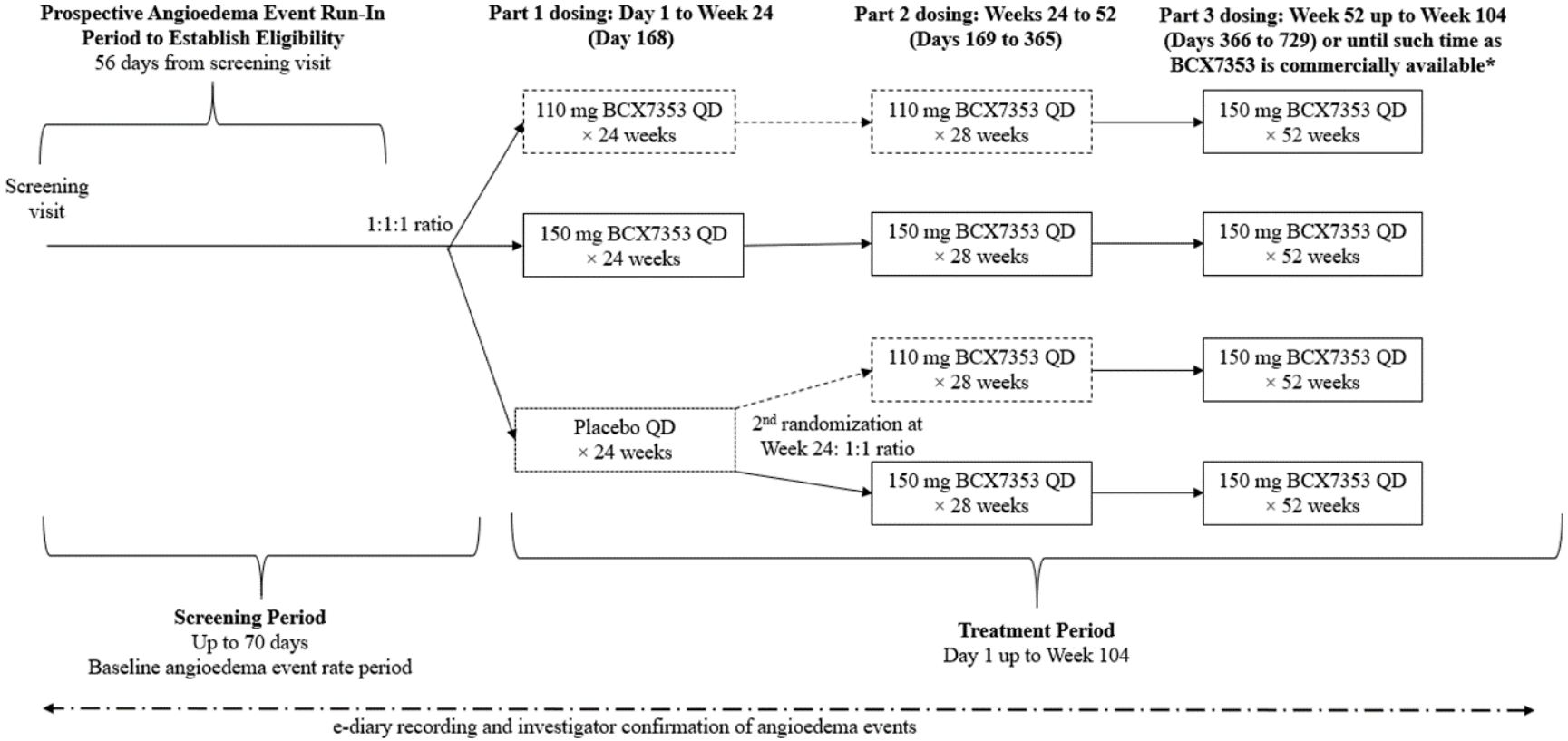
Although there is no evidence of embryofetal developmental toxicity with BCX7353 in reproductive toxicology studies (Section 5.2), appropriate precautions are still warranted with respect to administration of BCX7353 to women of reproductive age, in accordance with International Council for Harmonisation (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

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.

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

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.

- 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

- 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.

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.

- 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

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.

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.

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

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.

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