Part 1 Exploratory Efficacy Endpoints:

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

Part 1 Safety Endpoints:

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

Part 1 Health Outcome Endpoints:

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

Part 2 Primary Objective:

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

Part 2 Secondary Objectives:

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

Part 2 Primary Endpoints:

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

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

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

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

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

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

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

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

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

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

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

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

[f] Table 5 lists parameters to be assessed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[f] Table 5 lists parameters to be assessed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11.2.8. HLA Typing

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

11.2.9. Pregnancy Testing

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

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

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

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

11.2.10. HAE Diagnostic Confirmation

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

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

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

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

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

5.4.3. Study Population Rationale

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

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

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

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

6.1.4. Part 2 Secondary Objectives

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

6.1.5. Part 3 Primary Objective

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

6.1.6. Part 3 Secondary Objectives

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

7. OVERALL STUDY DESIGN AND PLAN

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

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

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

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

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

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

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

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

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

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

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

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

The main study will be comprised of adult subjects (aged ≥ 18 years of age); a substudy in participating regions will be included that allows adolescent subjects (≥ 12 to 17 years of age) to screen and enroll. Main study and substudy subjects will be randomized via a separate

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

7.1.4. Part 1 Safety Endpoints

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

7.1.5. Part 1 Health Outcome Endpoints

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

7.1.6. Part 2 Primary Endpoints

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

7.1.7. Part 2 Secondary Endpoints

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

- Durability in TSQM scores
- Durability in WPAI scores

7.1.8. Part 3 Primary Endpoints

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

7.1.9. Part 3 Secondary Endpoints

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

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

8.2. Subject Selection

8.2.1. Inclusion Criteria

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

1. Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy).
2. Able to provide written, informed consent. Subjects who are aged 12 to 17 years of age at screening for the substudy must be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent.
3. Subject weight of ≥ 40 kg.
4. A clinical diagnosis of HAE Type I or Type II, defined as having a C1-INH functional level below 50% and a complement 4 (C4) level below the lower limit of the normal (LLN) reference range, as assessed during the Screening period.
   In the absence of a low C4 value drawn during the intercritical period (ie, subject is not having an HAE attack), 1 of the following is acceptable to confirm the diagnosis of HAE: 1) a SERPING-1 gene mutation known or likely to be associated with HAE Type I or II assessed during the screening period; 2) a confirmed family history of C1-INH deficiency; 3) a C4 redrawn and retested during an attack in the screening period with the results below the LLN reference range.

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

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

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

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

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

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

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

10.3.2. Period Between Screening and Baseline

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

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

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

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

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

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

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

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

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

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

10.3.3.4. Week 24 Visit

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

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

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

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

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

10.3.4.3. Week 40 and 44 Phone calls

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

10.3.5. Part 3

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

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

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

The following assessments will be performed:

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

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

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

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

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

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

10.3.6. Follow-up/Early Termination Visit

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

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

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

11.2.3. Weight/Body Mass Index

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

BMI should be calculated using the following formula:

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

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

11.2.4. 12-lead Electrocardiograms

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

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

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

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

11.2.5. Vital Signs

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

11.2.6. Clinical Laboratory Evaluations

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

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

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

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

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

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

Possible SERPING genetic analysis is discussed in Section 11.2.10.

11.2.14. Rash Assessment

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

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

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

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

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

11.3. Patient-Reported Outcomes

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

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

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

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

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

11.4. HAE Attack and Dosing Diary and Attack Confirmation

11.4.1. Screening and Parts 1 and 2

11.4.1.1. HAE Attack and Dosing Diary

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

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

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

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

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

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

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

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

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

11.4.1.2. Investigator Confirmation of Attacks

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

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

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

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

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

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

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

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

11.4.2.2. Scheduled Telephone Contact

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

12. ADVERSE EVENT MANAGEMENT AND REPORTING

12.1. Adverse Events

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

12.1.1. Definitions

12.1.1.1. Adverse Event

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

This includes the following:

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

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

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

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

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

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

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

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

12.1.1.2. Serious Adverse Event

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

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

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

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

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

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

12.1.1.3. Adverse Events of Special Interest

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

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

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

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

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

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

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

12.1.3. Definition of Severity

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

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

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

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

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

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

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

12.1.5.1. Reporting Events of Special Interest

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

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

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

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

12.1.6. Pregnancy

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

12.1.7. Serious Breaches of Good Clinical Practice

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

12.1.8. Treatment Interruptions

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

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

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

12.1.9. Emergency Procedures

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

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

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

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

14.1.3. Subject Informed Consent: Adults

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

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

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

14.1.4. Subject Informed Consent: Adolescents

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

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

Part 2 Secondary Endpoints:

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

Part 3 Primary Objective:

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

Part 3 Secondary Objectives:

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

Part 3 Primary Endpoints:

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

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

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

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

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

[h] Table 5 lists parameters to be assessed.

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

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

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

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

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

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

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

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

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

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

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

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

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

10.3. Study Visits

10.3.1. Screening Visit

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

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

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

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

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

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

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

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

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

11.2.11. Other Laboratory Assessments

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

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

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

11.2.12. Pharmacokinetics and Pharmacodynamics

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

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

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

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

11.2.13. Pharmacogenomic Testing

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

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

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

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

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

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

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

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

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

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

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

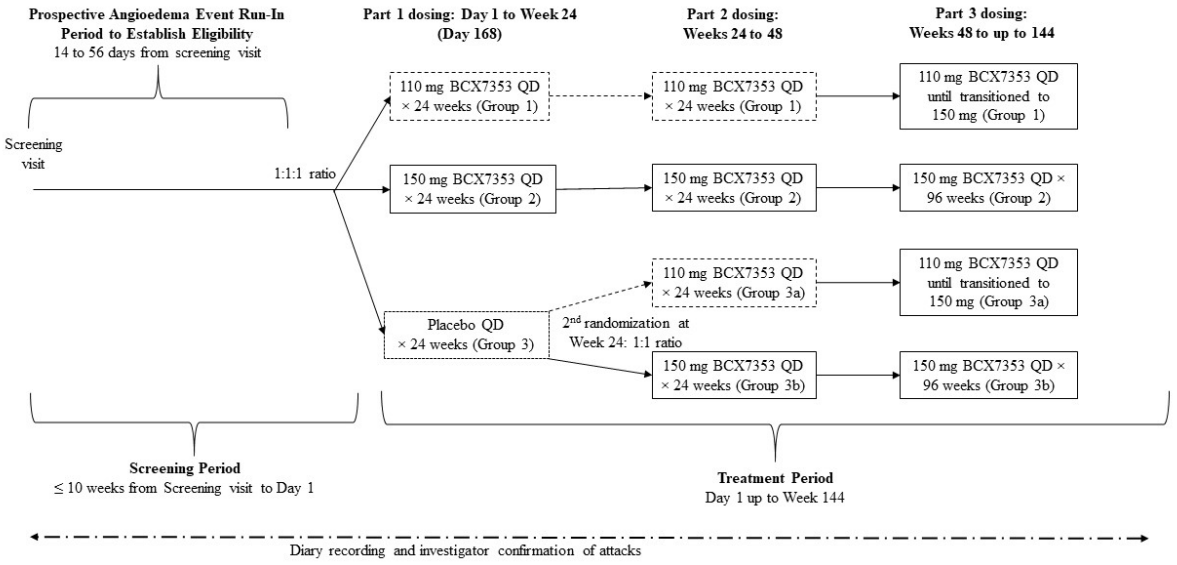
Study visits in Part 1 will occur at screening, baseline and Weeks 2, 4, 8, 12, 18, and 24. The primary efficacy analysis will occur after the last subject completes their Week 24 visit and will include all data through Week 24. Subject treatment will remain blinded to the subject, site, and Sponsor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

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

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

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

Figure 1. Study Schema



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

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

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

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

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

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

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

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

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

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

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

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

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

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

10.3.4. Part 2

10.3.4.1. Week 26 Visit

The Week 26 visit (± 2 days) will consist of monitoring liver function tests only (ALT, AST, GGT, total and direct bilirubin, ALP); urine and additional tubes of blood may be required to accommodate reflex testing for abnormal GGT, AST, or ALT (see Table 5). If preferred by the subject and clinical site, laboratory values may be drawn and resulted locally, with results entered into the CRF.

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

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

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

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

The following assessments will be performed:

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

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

11. ASSESSMENTS

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

11.1. Chronology of Assessments

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

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

11.2. Investigator-Completed Assessments

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

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

11.2.1. HAE Medical and Medication History

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

11.2.2. Physical Examination

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

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

Table 5. Clinical Laboratory Evaluations

Chemistry

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

Urinalysis

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

Hematology

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

Coagulation

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

Pregnancy Test

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

Drug screen

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

Additional Tests

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

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

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

11.2.15. Adverse Events

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

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

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

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

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

11.4.1.3. Scheduled Telephone Contact

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

11.4.2. Part 3

11.4.2.1. HAE Attack Diary

The Sponsor will supply diaries to sites.

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

12.1.4. Definition of Relationship to Study Drug

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

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

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

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

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

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

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

12.2. Toxicity Management

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

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

12.2.1. Rash

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

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

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

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

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

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

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

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

14.1.5. Investigator Reporting Requirements

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

14.2. Study Monitoring

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

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

14.3. Quality Assurance

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

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