BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-202

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF SINGLE DOSES OF BCX7353 AS AN ACUTE ATTACK TREATMENT IN SUBJECTS WITH HEREDITARY ANGIOEDEMA

EudraCT Number: 2016-001424-55

Version 4.0: 16 March 2018

BioCryst Pharmaceuticals, Inc.
4505 Emperor Blvd., Suite 200
Durham, NC 27703, USA
Phone: +1 (919) 859-1302
Fax: +1 (919) 851-1416

CONFIDENTIAL

Protocol Number:	BCX7353-202
Study Title:	A randomized, double-blind, placebo-controlled, dose-ranging, study to evaluate the efficacy, safety and tolerability of single doses of BCX7353 as an acute attack treatment in subjects with hereditary angioedema
IND Number:	N/A
EudraCT No.	2016-001424-55
Investigational Product:	BCX7353
Indication Studied:	Hereditary Angioedema
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA
Development Phase:	2
Sponsor Medical Officer:	Sylvia Dobo, MD Executive Director, Product Safety and Clinical Development BioCryst Pharmaceuticals Office: +1 (919) 226-5860 Cell: +1 (773) 304-8942 Email: sdobo@biocryst.com
Principal Investigator:	Dr Hilary Longhurst Email: hlonghurst@doctors.org.uk
Sponsor Project Manager:	Sharon VanDyke BioCryst Pharmaceuticals Office: +1 (919) 859-7914 Cell: +1 (919) 830-8019 Email:sdyke@biocryst.com
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and International Conference on Harmonization Guidelines. Essential study documents are currently archived in accordance with applicable regulations
Final Protocol Date:	Version 1.0: 16 December 2016 Version 2.0: 24 February 2017 Version 3.0: 02 August 2017 Version 4.0: 16 March 2018

1.1. Protocol Approval Signature Page

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Date: Version 4.0: 16 March 2018

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

for 16 MAR 2018

William Sheridan, MB BS
Senior Vice President, Chief Medical Officer
BioCryst Pharmaceuticals, Inc.

Date

for 16 March 2018

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

Date

1.2. Clinical Study Protocol Agreement

Protocol No: BCX7353-202

Protocol Title: A randomized, double-blind, placebo-controlled, dose-ranging, study to evaluate the efficacy, safety, and tolerability of single doses of BCX7353 as an acute attack treatment in subjects with hereditary angioedema

Date: Version 4.0: 16 March 2018

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

_____

Investigator's Signature Date

_____

Name (Print)

2. SYNOPSIS

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
BCX7353

Name of Active Ingredient:
(R)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

Title of Study:
A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety and tolerability of single doses of BCX7353 as an acute attack treatment in subjects with hereditary angioedema

Study centers: Study centers in Europe and Israel

Principal Investigator: Dr Hilary Longhurst

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: July 2017 Estimated date last patient completed: September 2018	2

Objectives:

Primary:

- To evaluate the efficacy of single oral doses of BCX7353 in treating acute attacks in subjects with hereditary angioedema (HAE)

Secondary:

- To evaluate the safety and tolerability of single oral doses of BCX7353 in subjects with HAE
- To evaluate the relationship of BCX7353 dose with clinical responses
- To evaluate subject satisfaction with BCX7353 treatment
- Substudy: to describe the natural history and temporal pattern of symptoms of untreated attacks and those treated with commercially available attack medications

Efficacy Endpoints:

- Proportion of subject attacks with an improved or stable 3-symptom composite visual analogue scale (VAS) score at 4 hours post-dose. The 3-symptom composite will be calculated as the average of the VAS scores for abdominal pain, skin pain and skin swelling. A subject is considered improved or stable if the change from baseline (time of drug administration) in VAS is less than or equal to 0.
- Proportion of subject attacks with a patient global assessment of improved or stable symptoms at 4 hours post-dose
- Proportion of subject attacks with no symptoms or mild symptoms of an HAE attack at 4 hours post-dose

- Proportion of subject attacks requiring standard of care attack treatment through 24 hours post-dose
- Time to use of standard of care acute attack treatment through 24 hours
- Time to stable or improved symptoms by composite VAS score through 24 hours post-dose
- Time to symptom relief (first documented time point when a subject experiences a 50% reduction in the 3-symptom composite VAS score from the pretreatment composite score)
- Time to almost complete symptom relief (first documented time point when a subject records a VAS score < 10 mm in the 3-symptom composite VAS score)
- Time to initial symptom relief (time from ingestion of study medication to report that the worst symptoms of the attack are over)
- Time to complete symptom relief (time from ingestion of study medication to no HAE attack symptoms)

Methodology:

This is a 3-part, Phase 2, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of single oral doses of a liquid formulation of BCX7353 in the treatment of acute HAE attacks. All subjects enrolled will receive both active and placebo blinded study drug in a randomized sequence. Part 1 of the study will evaluate single doses of 750 mg BCX7353; Part 2 will evaluate single doses of 500 mg BCX7353 and Part 3 will evaluate single doses of 250 mg BCX7353.

Randomization

Up to 36 subjects with Type 1 or 2 HAE with a documented history of HAE attacks will be sequentially enrolled into Part 1 of the study and randomized to receive a treatment sequence containing one of the following:

Treatment A^1: Single oral dose of BCX7353, 750 mg (Part 1)
Treatment B: Single oral dose of placebo

Note: Treatment A^1 = single oral doses of BCX7353 750 mg in Part 1; Treatment A^2 = single oral doses of BCX7353 500 mg in Part 2; or Treatment A^3 = single oral doses of BCX7353 250 mg in Part 3.

Initially, in Part 1,12 subjects will be randomized to one of 3 treatment sequences (n = 4 per sequence):

Sequence 1: A→B→A
Sequence 2: B→A→A
Sequence 3: A→A→B

If required, additional subjects will be enrolled into Part 1 (as outlined below) using the same 1:1:1 ratio for the 3 sequences, with a maximum total number of 36 subjects for Part 1.

Part 2 will evaluate a dose of 500 mg (Treatment A^2) and placebo (Treatment B). A maximum of 12 subjects will be enrolled, using the same 1:1:1 ratio for the 3 sequences. Part 3 will evaluate a dose of 250 mg (Treatment A^3) and will enroll a maximum of 12 subjects in a 1:1:1 ratio for each of the 3 sequences.

If tolerability issues prevent enrollment of Part 1 as described, additional subjects in Part 1 may be dosed with active study drug at a dose of 500 mg. If the dose in Part 1 is reduced and at least 12 subjects are treated with an active study drug dose of 500 mg, a 250 mg active dose may be assessed in Part 2. Any further dose level changes warranted for Part 2 and Part 3 will be instituted via protocol amendment.

Enrollment and Analyses

Up to 36 subjects will be enrolled in Part 1. Upon full enrollment, enrollment into Part 2 of the study (maximum of 12 subjects) may immediately commence. Part 3 (n = up to 12) may immediately commence upon enrollment of Part 2.

Following the 12th subject completing Part 1, the treatment effect may be estimated. The predefined

endpoint, determined by the Haybittle-Peto method, is the proportion of subjects with a stable or improved composite VAS at 4 hours post-dose. A Haybittle-Peto boundary of $p < 0.001$ is considered clinically significant.

If the Haybittle-Peto analysis is run and the boundary is not crossed with 12 subjects, the treatment effect may be estimated with cumulative data after each treated attack in accordance with the fully sequential analysis method assessing the estimate of treatment effect using the Haybittle-Peto boundary ($p < 0.001$).

Alternatively, if the boundary is not crossed with 24 subjects or the Heybittle-Peto analyses are not performed, treatment differences may be assessed using available data in Parts 1, 2 and 3 in order to plan subsequent studies.

Study Conduct Overview

At the Screening visit, subjects will be provided a diary and receive instruction on the correct completion of the diary in real-time to record attack symptoms and severity and any medication usage during an acute attack. During the 35-day screening period, subjects will be required to: 1) phone the Investigator at the onset of pain or swelling associated with an HAE attack; 2) complete diary details in real time of this HAE attack; and 3) phone the Investigator at the 4 hour post-call timepoint. Completion of these procedures will confirm that the subject is able and competent to perform on-study requirements in early identification of an attack and treating and documenting an appropriate attack with study drug.

Eligible subjects will return to the clinic to attend a Baseline visit. At the conclusion of the baseline visit, subjects will receive their first randomized dose of study drug for treatment of attacks by self-administration. The investigational medicinal product (IMP; BCX7353 or placebo) is supplied as a powder form drug product, presented in a bottle, that will require reconstitution to a liquid formulation with vehicle by the subject prior to administration.

At the Baseline visit, all subjects will be instructed on how to prepare and use study drug to treat a protocol-qualified acute HAE attack and will receive further instruction on the correct completion of a diary in real-time immediately prior to and after study drug administration.

Subjects will be instructed to contact the on-call Investigator (or designee) at the first symptom of swelling or pain associated with a potentially protocol-qualified HAE attack.

Protocol-qualified attacks approved for study drug treatment must meet all of the following:

- have pain and/or swelling associated with an HAE attack reported as a symptom
- subject has contacted Investigator within approximately 1 hour of onset time of HAE pain and/or swelling not involve pain or swelling in the throat or mouth. Such attacks should be treated using the subject's standard of care acute attack treatment (e.g., C1 INH, icatibant) without delay.
- not be an abdominal attack that has already resulted in vomiting. Such attacks should be treated using the subject's standard of care acute attack treatment (e.g., C1 INH, icatibant).
- have an identifiable onset time, with the exception that abdominal attacks with an onset during sleep may be permitted for study drug treatment. Onset time for abdominal attacks will be time the subject woke up with symptoms. Peripheral attacks starting with an onset during sleep will not be approvable for study drug treatment.
- occur during an HAE symptom-free period as follows:
    - if the previous HAE attack was treated with a bradykinin B2 receptor antagonist (i.e. Firazyr) OR treated with human recombinant C1 INH (i.e. Ruconest) OR any non-

targeted therapy (i.e. pain medication, anti-spasmodic, anti-emetic, tranexamic acid) OR was not treated with any medication: new attack can be treated with IMP if has been 48 hours since the complete resolution of all symptoms of the previous HAE attack AND the Investigator believes it is a new (de novo) attack.

OR

- if the previous HAE attack was treated with plasma-derived purified C1 INH (i.e. Berinert or Cinryze) OR plasma preparation (fresh frozen or solvent detergent plasma): new attack can be treated with IMP if it has been 96 hours since the complete resolution of all symptoms of the previous HAE attack

- occur at least 96 hours after complete recovery from a procedure or injury
- occur at least 14 days from a previous dose of study drug

After approval of the attack for study drug administration, subjects will reconstitute and take study drug preferably within one hour of the onset of symptoms. Subjects will complete the diary questionnaire, record any additional medications taken, and a 3-component VAS on a 100 mm scale for abdominal pain, cutaneous pain, and cutaneous swelling at the time of administration and 1, 2, 3, 4, approximately 8 and at 24 hours after study drug administration. Subjects will then phone the on-call Investigator (or designee) at approximately 4 hours after study medication to review their response to study drug and diary completion.

At each visit following treatment of an attack with study drug, the completed diary will be reviewed and any re-education required to ensure correct diary completion will be performed. Safety assessments will be completed and the next randomized dose of study drug will be dispensed to the subject.

Each subject will continue on study to treat 3 attacks with study drug. Clinic visits will be scheduled 10 to 14 days after each attack that is treated with study drug. Any additional attacks that occur in the intervening periods between study visits may be treated according to standard of care for the subject. Subjects will also be asked to track the start and stop times of any attacks not treated with study drug that occur after the baseline visit through the last study visit (Post-Attack 3 visit).

Optional Observational Substudy

Subjects will be asked to participate in an optional observational substudy to obtain diary data on all HAE attacks, through 12 weeks commencing from the last study visit. Consenting subjects will receive a diary and instruction for completion at the Post-Attack 3 visit. For the next 12 weeks, subjects will complete their diaries, with periodic subject contact (telephone) to ensure diary adherence.

A schedule of assessments is presented in Table 4.

Number of subjects (planned):

Up to 36 evaluable subjects with Type 1 or 2 HAE are planned to be enrolled in Part 1, up to 12 evaluable subjects in Part 2 and up to 12 evaluable subjects in Part 3. An evaluable subject is one who treats 3 attacks with study drug and for which there is diary information recorded.

Subjects who complete Part 1 will not be eligible to participate in Parts 2 or 3. Subjects completing Part 2 will not be eligible to participate in Part 3 of the study.

Criteria for inclusion:

1. Able to provide written, informed consent.
2. Males and non-pregnant, non-lactating females age 18 to 70 years.

3. A clinical diagnosis of hereditary angioedema Type 1 or Type 2, defined having a C1 INH functional level below 50% of normal and a C4 level below the lower limit of the normal reference range, as assessed at the Screening visit.
4. Access to and ability to use standard of care acute attack treatment. Standard of care acute attack treatment is defined as a medication approved by the relevant competent authority for the treatment of attacks of HAE (e.g. icatibant, ecallantide, plasma-derived C1INH, recombinant C1INH).
5. Female and male subjects must agree to the contraception requirements and must meet the inclusion criteria regarding contraception, and contraception of female partners (as applicable), as outlined in Section 8.2.
6. Any regularly administered concomitant medication recorded at the Screening visit and not stated as prohibited must be anticipated to be continued through the entire study and be of a stable dose and regimen for the duration of the entire study (screening through follow-up).
7. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. To be dispensed study drug at baseline, the subject must demonstrate adequate compliance with all study procedures required from the Screening visit through randomization, including phoning the Investigator and diary recording of at least one HAE attack during the screening period.
8. Must have a documented HAE attack rate of at least 1 unique attack per month for 3 months (up to 93 days) within the 4 months prior to the Screening visit.

Criteria for exclusion:

1. No HAE attack reported to the on-call Investigator (or designee) through the 35 days of the Screening period.
2. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.
3. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
4. Clinically significant abnormal electrocardiogram (ECG) at the Screening visit. This includes, but is not limited to, a $QT_cF > 470$ msec for women, a $QT_cF > 450$ msec for men, a PR > 220 msec (both sexes), or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
5. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.
6. Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.
7. History of or current implanted defibrillator or pacemaker.
8. Any laboratory parameter at screening that, in the opinion of the Investigator, is clinically

significant and relevant for this study. A calculated creatinine clearance of ≤ 60 mL/min or AST or ALT value ≥ 2 times the upper limit of the normal reference range value obtained during screening is exclusionary.

9. Suspected C1INH resistance in the opinion of the Investigator and Sponsor.
10. History of alcohol or drug abuse within the previous year prior to the Screening visit, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 drinks/day).
11. Positive serology for human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
12. Pregnant, planning to become pregnant within 30 days of the study, or nursing.
13. Positive drugs of abuse screen (unless as used as medical treatment, e.g., with a prescription).
14. History of severe hypersensitivity to any medicinal product, which was associated with a non-HAE related swelling, a severe rash requiring treatment/hospitalization, or anaphylaxis.
15. Hypersensitivity reaction to BCX7353.
16. Use of tranexamic acid, androgens or C1 INH for prophylaxis of HAE attacks within the 7 days prior to the Screening visit or initiation during the study. Use of a C1 INH therapy for treatment of attacks is not excluded at any time, nor is C1 INH for pre-procedure prophylaxis.
17. Use of concomitant medications that are metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the Baseline visit or planned initiation during the study.
18. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
19. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to baseline or initiation during the study.
20. Current participation in any other investigational drug study or received another investigational drug within 30 days of the Screening visit.
21. An immediate family relationship to either Sponsor employees, the Investigator or employees of the study site named on the delegation log.

Investigational product, dosage and mode of administration:

BCX7353 powder for reconstitution at doses of 750 mg, 500 mg, and 250 mg. BCX7353 powder in bottle will require reconstitution with vehicle by the subject prior to oral administration.

All clinical doses of BCX7353 provided in this protocol are in reference to the hydrochloride (HCl) salt.

Duration of treatment:

Participating subjects will receive 3 single oral doses of study drug to treat an HAE attack approved for study drug treatment: 2 doses of BCX7353 and 1 dose of placebo.

Reference therapy, dosage and mode of administration:

Matched placebo powder for reconstitution. Placebo will be lactose monohydrate powder in a bottle that will require reconstitution with vehicle by the subject prior to oral administration.

Criteria for evaluation:

Efficacy: 3-symptom composite VAS score, patient global assessment of symptoms, qualitative symptom severity, use of standard of care treatment.

Safety: adverse events **(**AEs), laboratory analyses [clinical chemistry, hematology, coagulation, urinalysis, creatine kinase-MB (CK-MB), troponin I and T], vital signs, ECGs, and physical examinations.

Subject satisfaction: Treatment Satisfaction Questionnaire for Medication (TSQM)

Statistical methods:

Due to the exploratory nature of this study, no formal power or sample size calculations were used to determine sample size. Descriptive statistics for disposition, demographics, and baseline characteristics will be presented by treatment sequence. All analyses of efficacy and safety will be attributed to the treatment assignment at the time of the assessment.

Efficacy Analyses:

Resolution of attacks will be analyzed by treatment arm. The endpoint that may be assessed using a Heybittle-Peto boundary for significance is the proportion of subject treated attacks with improved or stable composite VAS at 4 hours post-dose in the full analysis set (i.e., all subject treated attacks). The number and proportion of subject treated attacks that stabilize or improve at 4 hours will be summarized by treatment group. Attacks that require standard of care acute attack treatment prior to the 4-hour time point will be considered as failure (i.e., not having a stable or improved VAS at 4 hours). To assess treatment differences, a logistic mixed effect model including treatment, period and sequence as fixed effects, and subject within sequence as a random effect will be utilized. Other binary endpoints will be analyzed in a similar manner.

The 3-symptom composite VAS and its associated changes from baseline will be summarized by attack, time point and treatment group. Treatment differences in the change from baseline values at each time point will be assessed with a mixed effect linear model with factors for treatment, period, sequence, and baseline value as fixed effects, and subject within sequence as a random effect. Analyses of other continuous variables will be analyzed in a similar manner.

The time to use of standard of care acute attack treatment will be estimated using the Kaplan-Meier method. Subjects who do not use standard of care acute attack treatment will be censored at the end of the attack observation period (i.e., 24 hours). Treatment differences will be assessed using an appropriate proportional hazards model.

Safety Analyses:

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. The occurrence of treatment-emergent AEs will be summarized by treatment group using MedDRA preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events (SAEs) and AEs considered to be related to study drug will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries of vital signs, ECG parameters, and clinical laboratory results will be presented by study visit and treatment group. Laboratory abnormalities will be graded according to the Division of Microbiology and Infectious Diseases [DMID] Adult Toxicity Table [November 2007]. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by

treatment group. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized by study visit and treatment group.

Physical examination results will be presented in listings.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary. These data will be summarized by treatment group.

Subject Satisfaction:

A TSQM global satisfaction score will be calculated as validated. Data on the global score as well as relevant subscales will be listed, summarized, and appropriately tested for differences between active treatment and placebo and between active and current acute therapy utilized at baseline.

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

LIST OF TABLES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1. Abbreviations and specialist terms

Abbreviation	Explanation
AAS	angioedema activity score
ABW	actual body weight
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration versus time curve from time zero to time "t"
$AUC_{0\text{-}inf}$	area under the concentration versus time curve extrapolated to infinite time
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
% AUC_{exp}	percentage of AUC extrapolated between $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$
BCRP	Breast cancer resistance protein
BID	twice daily
BK	bradykinin
BMI	body mass index
BMP	Bis(mono)acylglycerol phosphate
C1 INH	C1 esterase inhibitor
C_{last}	last measurable concentration of drug
CK-MB	creatine kinase-MB
CLcr	creatinine clearance
CLr	renal clearance of unchanged drug in a specific interval (CLr[interval]) or cumulatively over all collection intervals
C_{max}	maximum plasma concentration of the drug
CPK	creatine phosphokinase
CRA	clinical research associate
CRO	clinical research organization
$C_{av,ss}$	average steady-state plasma drug concentration during multiple-dose administration
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CYP	cytochrome P450
DMC	Data monitoring committee

Abbreviation	Explanation
DMID	Division of Microbiology and Infectious Diseases
% $Dose_{excreted}$	percentage of given dose excreted in the urine as unchanged drug
eCRF	Electronic case report form
EC_{50}	Half-maximal effective concentration
ECG	electrocardiogram
EQ-5D-5L	EuroQoL five-dimensional, 5-level questionnaire
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulation hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HAE	hereditary angioedema
HBV	hepatitis B virus
HCl	hydrochloride
HDPE	High density polyethylene
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HK	high-molecular weight kininogen
IB	Investigator's brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device

Abbreviation	Explanation
IUS	intrauterine system
IV	intravenous
K_a	absorption rate constant
K_i	inhibition constant value
$K_{RBC/P}$	partitioning constant between erythrocytes and plasma
λ_z	terminal elimination rate constant
LDH	lactate dehydrogenase
LLN	lower limit of normal
MCH	mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NGAL	neutrophil gelatinase–associated lipocalin
P-gp	p-glycoprotein
PBMC	Peripheral blood mononuclear cell
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
PKK	prekallikrein
PLD	phospholipidosis
PO	oral
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PT	prothrombin time
QD	once daily
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
QTcF	QT interval corrected by Fridericia's formula
RR	interval between successive heart beats using the R-wave peaks
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Explanation
SUSAR	suspected unexpected severe adverse reaction
$T_{1/2}$	estimate of the terminal elimination half-life of the drug
TEAE	treatment emergent adverse event
T_{max}	time to maximum plasma concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
Vz/F	apparent volume of distribution of the drug
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

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

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

The primary inhibitor of kallikrein in plasma is the *SERPING1* gene product, C1 esterase inhibitor (C1 INH) (Cicardi and Johnston 2012). C1 INH is a serine protease inhibitor (serpin) that normally prevents uncontrolled contact activation and BK production by covalently binding to and inactivating kallikrein (Patston, Gettins et al. 1991). Patients with HAE have mutations in the regulatory or coding regions of the C1 INH gene that result in either a failure to produce C1 INH or the production of nonfunctional C1 INH (Pappalardo, Cicardi et al. 2000). The amount of functional C1 INH produced by the unaffected allele is insufficient to control serine protease activity, including that of kallikrein, that is induced by even asymptomatic levels of vascular endothelial contact activation (Cicardi and Johnston 2012). As a result, even when a patient does not experience any symptoms, plasma HK levels may be lower than normal and BK is detectable (Cugno, Hack et al. 1993, Nussberger, Cugno et al. 1998, Kaplan, Joseph et al. 2002, Nussberger, Cugno et al. 2002, Suffritti, Zanichelli et al. 2014). During symptomatic attacks, which may be triggered by trauma, infection, changes in hormone levels (e.g., with oral contraceptive use or with the menstrual cycle), or emotional stress, kallikrein activation, HK cleavage and BK production increase, and circulating BK levels are dramatically elevated (Cugno, Nussberger et al. 2003, Bork, Meng et al. 2006, Cicardi and Johnston 2012, Martello, Woytowish et al. 2012).

The effective management of HAE involves the prevention and/or treatment of symptomatic attacks (Cicardi, Bork et al. 2012). Kallikrein is a proven target in the treatment of HAE.

As noted above, C1 INH is a covalent kallikrein inhibitor, and plasma-derived purified C1 INH (Cinryze®, Berinert®) and a human recombinant C1 INH (Ruconest®) are licensed for the treatment of acute HAE attacks in the European Union (EU). In the United States (US), Berinert® and Ruconest® are licensed for this indication. Kalbitor® (ecallantide) is an engineered recombinant protein noncovalent binding kallikrein inhibitor with homology to tissue factor pathway inhibitor and is licensed in the US for treatment of acute attacks of HAE by subcutaneous injection (Martello, Woytowish et al. 2012, Riedl 2012). In addition, Firazyr® (icatibant) is a bradykinin B2 receptor antagonist and is licensed in the EU and the US for treatment of acute attacks of HAE by subcutaneous injection.

The goal of acute treatment is to resolve angioedema symptoms as quickly as possible. There are no comparative (head-to-head) studies of therapies to treat an acute attack. Double-blind, randomized placebo-controlled trials have demonstrated superiority of Berinert, Cinryze Ruconest, Firazyr, and Kalbitor over placebo. These data are briefly described below.

Data from both the Berinert and the Cinryze trials suggest that higher doses (i.e., 20 U/kg Berinert, and more than 1 dose of Cinryze 1000 U) have a shorter median time to onset of relief with secondary outcomes consistently supported by the efficacy of the higher doses (Craig, Levy et al. 2009, Zuraw, Busse et al. 2010, Wasserman, Levy et al. 2011). With C1 INH, serious arterial and venous thromboembolic events have been reported at the recommended dose of C1 INH products. A general concern over transmission of blood-borne infections is inevitable when using human plasma–derived products. Hypersensitivity and allergic/pseudo-allergic systemic reactions have also been reported in a few patients. Berinert is approved in Europe for self-administration to treat all acute attacks and in the US to treat facial, laryngeal and abdominal attacks. Cinryze is approved in Europe to treat all acute attacks.

Ruconest also demonstrated a treatment effect and the time to minimal symptoms was significantly shorter in patients receiving rhC1 INH compared to placebo with no subject in the rhC1 INH treatment group experiencing therapeutic failure (Zuraw, Cicardi et al. 2010). Hypersensitivity, including anaphylaxis in a single healthy volunteer with an undisclosed rabbit allergy, has been reported with the use of Ruconest. Ruconest is approved in Europe for treatment for all acute attacks and the US package insert has a limitation of use clause in the indication statement that states effectiveness was not established in HAE patients with laryngeal attacks.

Icatibant (Firazyr) is also an acute attack medication option for most patients in the US and EU. Icatibant is a subcutaneously-administered synthetic peptide that works distinctly from the other HAE treatments in that it functions as a bradykinin B2 receptor antagonist. In 3 published multicenter clinical trials (FAST 1, 2, and 3) patients were randomized to icatibant or comparator (placebo or tranexamic acid). Time to almost complete resolution was shorter with icatibant than with the comparator in all 3 trials and was statistically significant in the FAST 2 and FAST 3 trials (Cicardi, Levy et al. 2010, Lumry, Li et al. 2011). Open label studies have shown the benefit of different treatments for attacks at all sites. However, approximately 10% of patients require a second dose for re-emergent symptoms, usually 10 to 27 hours after the initial treatment (Longhurst 2010). Icatibant was generally well tolerated and is approved for the treatment of all HAE attacks.

Kalbitor (ecallantide) demonstrated a significantly higher improvement over placebo by using 2 measures of patient-reported outcomes and demonstrated efficacy at all attack locations (Riedl, Campion et al. 2010). The open-label extension phase of the studies suggested that the majority of patients benefited from a single dose of ecallantide, although in 29% of attacks a second dose was necessary due to incomplete efficacy (Levy, Lumry et al. 2010). Hypersensitivity (including anaphylaxis) is a known risk of ecallantide treatment for acute HAE attacks and is a black box warning label in the prescribing information, with a 4% incidence in treated patients. Ecallantide is approved for the treatment of all acute attacks of HAE.

BCX7353 is a potent, synthetic, second-generation small molecule inhibitor of plasma kallikrein discovered at BioCryst. In contrast to the parenterally administered options outlined above, inhibition of kallikrein with an orally bioavailable small molecule such as BCX7353 may offer the advantage of oral administration in the rapid and successful treatment of acute HAE attacks.

5.2. Nonclinical Findings for BCX7353

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

BCX7353 is a potent and highly specific inhibitor of human plasma kallikrein activity with a 50% inhibitory concentration (IC_{50}) of BCX7353 against plasma kallikrein of 0.88 nM.

In activated plasma from subjects with HAE, the mean half-maximal effective concentration (EC_{50}) value was 15.9 ± 0.57 nM.

Safety pharmacology studies were negative except for a positive human ether-à-go-go-related gene (hERG) signal. Doses > 30 mg/kg increased the duration of ECG intervals including the QTc interval, but these effects were not considered adverse as the maximum increase was 10% versus the pretest group mean.

In nonclinical species, orally dosed BCX7353 is recovered in the bile, feces, and urine, and the terminal half-life is long. In the rat and monkey, BCX7353 is metabolized by oxidative deamination, oxidation, and/or conjugation of cyclopropanecarboxylic acid.

In vitro, BCX7353 inhibits cytochrome P450 (CYP) 2C9 and CYP2C19, CYP2D6 and CYP3A. The time-dependent inhibition screen with BCX7353 suggests it may irreversibly inhibit CYP3A, but not CYP2C9 or CYP2C19. BCX7353 is also an inhibitor of the transport protein p-glycoprotein (P-gp) and also breast cancer resistance protein (BCRP), MATE1, and MATE2-K at micromolar concentrations. BCX7353 is a substrate of P-gp and BCRP.

BCX7353 has a low concern for genotoxicity and has no phototoxic potential.

In rats and cynomolgus monkeys, the effects of repeated, daily oral doses for durations of 28 days and 13 weeks have been investigated, in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice (GLP). Twenty-eight day studies in rats and monkeys suggest that the primary target organs of BCX7353 toxicity were liver (both hepatocyte necrosis and bile duct hyperplasia), kidney, and skeletal muscle, with toxicities also observed in cardiac and smooth muscle, and the lymphoid system. However, with longer duration of dosing (13 weeks; a different drug lot than used in the 28-day studies was utilized) there were no significant adverse effects noted. In monkeys administered the highest dose (20 mg/kg/day) for 13 weeks, there were no adverse effects noted. In rats dosed at this same dose level, bile duct hypertrophy,

hyperplasia and vacuolated macrophages in the liver were noted but not considered adverse. Further details can be found in the IB.

Single oral dose non-GLP studies have also been conducted in rats and monkeys. Doses of 150, 250 and 450 mg/kg administered to rats were well tolerated; there were no deaths and no clinical observations. At the highest dose of 750 mg/kg mortality and clinical signs were noted, mainly in females. At the highest tolerated single dose of 450 mg/kg, the mean plasma exposures (C_{max} and AUC_{0-24}) were 560 ng/mL and 11,900 ng•hr/mL, respectively. A single oral dose of BCX7353 to one male and one female cynomolgus monkey was evaluated at 75, 150, 300, 500 and 700 mg/kg. BCX7353 was tolerated at all dose levels but vomiting was noted at 300 mg/kg and higher which may have limited the systemic exposure and hence the toxicity. At 300 mg/kg, the mean plasma exposures (C_{max} and AUC_{0-24}) were 1,030 ng/mL and 14,400 ng•hr/mL, respectively. Exposures were lower at higher doses.

Definitive embryo-fetal development studies were conducted in pregnant Sprague Dawley rats and New Zealand White rabbits. In rats and rabbits there was no evidence of embryo-fetal mortality, fetotoxicity, or dysmorphogenesis at any dose level. There was no evidence of adverse maternal toxicity at 25 mg/kg/day in rats and at 50 mg/kg/day in rabbits.

5.3. Clinical Findings for BCX7353

Two studies in human subjects have completed (Study BCX7353-101 and Study BCX7353-102) and 2 studies are currently ongoing (Studies BCX7353-203 and BCX7353-109). Brief summaries are provided below.

5.3.1. Study BCX7353-101

Study BCX7353-101 was a first-in human, 3-part, Phase 1, double-blind, placebo-controlled dose-ranging study of BCX7353 (solid dosage form) conducted in 96 healthy subjects. Part 1 and Part 2 of the study assessed the safety, pharmacokinetic (PK), and pharmacodynamic (PD) of a single ascending dose of BCX7353 (10 mg–1000 mg) or multiple ascending doses of BCX7353 given to healthy Western subjects over 7 to 14 days (125mg–500 mg once daily [QD]), respectively. Part 3 of the study evaluated the safety, PK, and PD of single (100 and 500 mg) and multiple doses of BCX7353 250 mg given over 7 days in healthy Japanese subjects.

BCX7353 was generally safe and well tolerated with no treatment-emergent serious adverse events (TESAEs) or Grade 4 treatment emergent adverse events (TEAEs). Most TEAEs were Grade 1 in severity. In the multiple dose portion (Part 2), one subject (500-mg group) experienced a Grade 3 TEAE. The TEAE was a diffuse, cutaneous maculo-papular rash with no mucosal involvement, no desquamation, or constitutional symptoms or laboratory abnormalities that was diagnosed after the subject completed 7 days of treatment. This event was consistent with a Type IV hypersensitivity reaction, and resolved following treatment with oral and topical steroids. The event was assessed as probably related to BCX7353. In addition, a Japanese subject treated with BCX7353 250 mg for 7 days experienced a Grade 2 maculo-papular rash after completing treatment; the subject had no mucosal involvement, no desquamation, or constitutional symptoms or clinically significant laboratory abnormalities. The event resolved following treatment with antihistamine and was assessed as probably related to BCX7353.

Overall, 2 subjects (both enrolled in Part 2) discontinued treatment due to Grade 2 TEAEs upper abdominal pain and diarrhea in 1 subject (500-mg group) and upper abdominal pain in 1 subject (350-mg group).

There was no apparent dose response regarding any individual AE; however, more gastrointestinal AEs were reported in the higher dose cohorts. Across all parts of the study, there were no trends in laboratory abnormalities.

Electrocardiograms extracted from the 12-lead Holter monitoring data provided evidence of a dose-dependent increase in mean QTcF occurring after multiple doses of BCX7353 at dose levels of 350 mg QD and higher (250 mg QD in Japanese subjects). This was not seen in the single dose cohorts.

Following single and multiple oral doses of BCX7353, C_{max} was reached approximately 2 to 6 hours after dosing. There was approximately 3- to 5-fold accumulation in BCX7353 plasma exposure with 7 or 14 days of BCX7353 dosing, which is consistent with the observed long half-lives ranging from 67 to 79 hours. Analysis of trough values indicated that steady-state conditions were achieved from 6 to 12 days post first dose.

C_{max} and $AUC_{0\text{-}inf}$ indicated that both C_{max} and $AUC_{0\text{-}inf}$ increased in a more than dose-proportional manner over the 30 mg to 1000 mg dose range while reasonable dose-proportionality between 250 mg and 500 mg for C_{max} was observed. There was a slightly greater than dose proportional increase in exposure (AUC_{tau} and C_{max}) following multiple dose exposure over the 125-mg to 500-mg dose range.

After a high-fat breakfast, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ appeared to be modestly increased although the 90% CIs were wide. No significant changes were observed in the geometric mean C_{max} values.

The effect of BCX7353 on plasma kallikrein activity was generally dose dependent. Higher doses of BCX7353 (≥ 250 mg QD) provided more potent inhibition that was more consistently sustained through a dosing interval, achieving approximately 90% inhibition across an interval on average. Exposure-response analyses demonstrated a high correlation between ex-vivo kallikrein inhibition activity and plasma concentrations of BCX7353 ($r = 0.921$). The BCX7353 concentration and kallikrein inhibition relationship was well described by a sigmoidal E_{max} model with predicted EC_{50} value of 9.71 ng/mL.

There were no clinically relevant safety, PK, or PD differences and/or trends observed between Western and Japanese subjects following dosing with BCX7353.

5.3.2. Study BCX7353-102

Study BCX7353-102 evaluated the effect of multiple oral doses of BCX7353 (solid dosage form) on hepatic and intestinal metabolism by CYP3A4 (as assessed by pharmacokinetics of intravenous [IV] and oral [PO] midazolam, respectively), CYP2C9 (tolbutamide), CYP2C19 (omeprazole) and CYP2D6 (dextromethorphan) enzyme activity using probe substrate drugs in healthy subjects. Study BCX7353-102 has completed dosing.

A total of 21 subjects were enrolled and 18 subjects completed the study; withdrawal from study drug were for nonstudy-drug related reasons. BCX7353 was generally safe and well tolerated. Most AEs were Grade 1 in severity and no SAEs or Grade 3 or 4 AEs were reported. There was 1 Grade 2 TEAE assessed as probably related to BCX7353: a subject developed a diffuse

maculo-papular rash 48 hours after completing 9 days of BCX7353. The rash was pruritic with no mucosal involvement, no desquamation, and no abnormalities on exam. The subject had no constitutional symptoms or clinically significant lab abnormalities. The rash resolved rapidly following a single dose of cetirizine 10 mg.

Preliminary analysis of the PK data indicate that BCX7353 is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6 to varying degrees. Following administration of ≥ 8 days of BCX7353, exposure of all probe substrates were increased, indicating that metabolism was inhibited. Based on the draft US Food and Drug Administration (FDA) Drug Interaction Guidance and preliminary PK of the probe substrates, BCX7353 is a strong inhibitor of CYP2D6 (> 5-fold increase in AUC), a moderate inhibitor of CYP2C9, CYP2C19, and intestinal CYP3A4 (exposure increased between 2- and 5-fold), and a weak inhibitor of hepatic CYP3A4 (< 2-fold increase in exposure).

5.3.3. Study BCX7353-203

Study BCX7353-203 is an ongoing Phase 2, randomized, double-blind, placebo-controlled, 2-part, parallel-group, dose- response study to evaluate the safety, tolerability, PK, PD, and efficacy of BCX7353 (solid dosage form) in subjects with HAE. Up to 36 eligible subjects are to be randomized in Part 1 of the study to BCX 7353 350 mg QD or placebo QD orally for 28 days. In Part 2, approximately 14 eligible subjects will be randomized into 1 of the following 3 treatment groups: 1) placebo QD orally for 28 days, 2) BCX7353 125 mg QD orally for 28 days, and 3) BCX7353 250 mg QD orally for 28 days.

As of 16 December 2016, 29 subjects have been randomized and treated in Part 1 of the study. Fifteen subjects have completed through 28 days of dosing and 2 subjects have discontinued study drug prematurely due to TEAEs, one due to a concurrent illness and one due to a TEAE. The first subject discontinued due to persistently elevated liver enzyme levels that were present at baseline and assessed as not related to study drug by the investigator. The other subject discontinued due to elevated liver enzymes that occurred in the setting of gastroenteritis. To date, no SAEs have been reported.

5.3.4. Study BCX7353-109

Study BCX7353-109, is an ongoing, open-label study in subjects with Type 1 or 2 HAE to evaluate the single dose pharmacokinetics and pharmacodynamics of BCX7353. A single dose of BCX7353 is administered with 2 dose regimens tested. Subjects may participate in one or more of the regimens, although it is preferred to have a subject participate in both regimens. Six subjects will be enrolled in each regimen to receive the following treatments, separated by at least a 14-day washout period:

Regimen A: Single oral dose of BCX7353 350 mg in capsule formulation

Regimen B: Single oral dose of BCX7353 750 mg in capsule formulation

Regimen C: Single oral dose of BCX7353 750 mg in liquid dose formulation

Three subjects have currently screened for enrollment. Regimen B (750 mg capsules) will be administered first given ready availability of IMP for this dosing level. One subject has received Regimen B.

5.4. Rationale for Study

BCX7353 is a second-generation small molecule developed as an orally administered inhibitor of plasma kallikrein that is being evaluated for the treatment of acute angioedema attacks in adult patients with HAE. Kallikrein is a proven target for the treatment of HAE; the kallikrein inhibitor ecallantide is approved in the US for subcutaneous injection for the treatment of acute HAE attacks, and C1 INH treatments also target kallikrein. BCX7353 has activity at low nM concentrations against plasma kallikrein (see Section 5.4.1). Phase I PK data describe a plasma concentration profile that supports treatment of acute attacks: following oral administration, BCX7353 is rapidly absorbed and has a long terminal elimination half-life.

Study BCX7353-202 is an initial proof-of-concept study of BCX7353 in the oral treatment of acute attacks in adult subjects with HAE. Administration of a liquid formulation of BCX7353 was chosen for this study to eliminate the time required for disintegration of capsules and dissolution of powdered drug substance, in order to optimize the time to effective drug levels in the systemic circulation after oral dosing.

This study is designed to evaluate the treatment effect of BCX7353 750 mg on the resolution of acute attacks. Up to 2 additional doses of BCX7353 (500 mg and 250 mg) will be evaluated in the dose-ranging parts of the study.

5.4.1. Rationale for Study Drug Doses

5.4.1.1. Rationale for Achievement and Maintenance of Target Concentrations Proposed as Efficacious

In healthy subjects in Study BCX7353-101, inhibition of plasma kallikrein was highly correlated with plasma BCX7353 concentrations (r = 0.92). Therefore, achieving BCX7353 concentrations at or above an appropriate target level is hypothesized to effectively treat attacks in HAE subjects with little or no functional C1 INH, the endogenous inhibitor of kallikrein and ultimately, bradykinin production. Moreover, maintaining these concentrations over the target level for a duration of time to prevent recurrence of an attack will be required.

Selection of appropriate target plasma level of BCX7353

In the plasma kallikrein inhibition assay using HAE patient plasma, the EC_{50} of C1 INH was measured to be 213 nM and for BCX7353 was 15.9 nM, a 13.4-fold potency difference. The lower limit of the normal range (LLN) of C1 INH is approximately 1680 nM; therefore, the LLN for C1 INH corresponds to a BCX7353 concentration of approximately 125 nM, or 71 ng/mL. It would be expected that BCX7353 concentrations above approximately 71 ng/mL, would restore phenotypically normal total plasma kallikrein inhibitory activity.

Selection of duration that BCX7353 concentrations must exceed the target plasma level

To abate an attack, it is desirable to exceed the target plasma concentrations of BCX7353 as quickly as possible after a dose. HAE attacks typically follow a predictable time course. Swelling classically worsens slowly but relentlessly over the first 24 hours, and gradually subsides over the subsequent 48 to 72 hours. Following administration of a single dose formulated in a capsule in Study BCX7353-101, BCX7353 was rapidly absorbed. Mean plasma concentrations exceeded 71 ng/mL by 0.5 to 1 hour postdose at doses ranging from 250 to 1000 mg. Administration of a

liquid formulation in the current study is expected to achieve target levels earlier. In summary, target concentrations of BCX7353 are achievable early in the development of an HAE attack.

Current treatments for acute attacks of angioedema in HAE patients are administered parenterally, and sometimes retreatment is required after a period to time due to a lack of symptom relief. The label for Firazyr (icatibant) specifies that patients should administer additional doses every 6 hours if symptoms have not improved, and analysis of the open-label extension period of FAST-1 showed that 11.8% of treated attacks required more than one injection of Firazyr (icatibant) (Malbran, Riedl et al. 2014). The need for redosing could indicate that adequate plasma concentrations of icatibant are not of a sufficient duration to alleviate the symptoms of the attack or that a rebound effect is occurring. For an acute treatment, it would be advantageous to rapidly achieve plasma concentrations of BCX7353 at levels that lead to potent inhibition of plasma kallikrein, and maintain these concentrations above this level for longer than 6 hours.

Given that BCX7353 is rapidly absorbed from the gastrointestinal tract and has a long half-life (approximately 50 hours after a single dose), it is expected that BCX7353 plasma concentrations could be maintained above the target of 71 ng/mL for up to 24 hours with an appropriate dose. Following administration of a single 250-mg dose in Study BCX7353-101, BCX7353 was rapidly absorbed, and mean plasma concentrations exceeded 71 ng/mL by 1 hour postdose and fell below target by 8 hours. After administration of a 500-mg dose, mean BCX7353 plasma concentrations exceeded 71 ng/mL after 0.5 hours postdose and remained above that concentration through 12 hours. Mean plasma concentrations were above 71 ng/mL at 1 hour postdose and remained above this level until the 24-hour time point following administration of the 1000-mg dose. In addition, rapid inhibition of plasma kallikrein was observed following a single dose of BCX7353 at doses of 250 mg or higher. At doses of 500 and 1000 mg, maximal inhibition of plasma kallikrein was sustained through 24 hours postdose.

The rapid onset and maintenance of kallikrein inhibition with a single dose gives support that BCX7353 could be a potent oral option for treatment of acute HAE attacks.

5.4.1.2. Rationale for Proposed Doses

This study will evaluate the safety and efficacy of a single dose treatment of BCX7353 for an acute HAE attack at doses of 750 mg, 500 mg, and 250 mg compared to placebo. The rationale for selection of these doses is based upon the safety observed in Study BCX7353-101 and the achievement and maintenance of potentially efficacious BCX7353 plasma concentrations. Single doses of up to 1000 mg were generally safe and well-tolerated in healthy subjects. Gastrointestinal effects were reported more frequently at higher dose levels, although these events were predominantly mild. No other dose-related safety concerns were noted, and the maximum tolerated dose was not reached in Study BCX7353-101, supporting selection of single doses up to 750 mg for clinical evaluation in the current study. Assuming linear exposure between a single 500 mg dose and a 1000 mg dose administered in Study BCX7353-101, the $AUC_{0\text{-}24}$ for a single 750 mg dose is predicted to be approximately 4219 ng*h/mL with a C_{max} of approximately 330 ng/mL. This exposure is expected to be less than the steady-state exposure at a 350 mg and 500 mg daily dose as measured in the first in human study (517 ng/mL [C_{max}] and 8230 ng*h/mL [AUC_{tau}] for a 500 mg dose administered for 7 days and 363 ng/mL [C_{max}] and

5720 ng*h/mL [AUC_{tau}] for a 350 mg dose administered for 14 days). As previously mentioned, the doses of BCX7353 imparting this exposure were well-tolerated.

Simulation of plasma drug levels over a range of doses of BCX7353 after single dose administration

Superposition with linear extrapolation was first used to simulate individual plasma concentration-time profiles of BCX7353 following single dose administration at dose levels ranging from 250 to 750 mg using available pharmacokinetic data from Study BCX7353-101. The main purpose of this simulation was to obtain more concentration-time points of BCX7353 at early times following the dose administration. Simulated mean concentrations (Figure 1) facilitated determination of the percentage of theoretical subjects predicted to have concentrations over a target concentration of 71 ng/mL at various timepoints postdose (SAS Version 9.2 [SAS, USA)], assuming a normal distribution, with 1000 simulations performed at each time point for each dose level). These data are presented in Table 2. Following administration of a capsule-formulated dose of 750 mg, plasma concentrations are predicted to exceed the target concentration of 71 ng/mL within 1.2 hours of dosing in approximately 90% of subjects. At this dose, plasma concentrations are predicted to be sustained above 71 ng/mL for 24 hours, which also provide sustained levels of kallikrein inhibition (Table 3).

Figure 1. Simulated Mean Exposure of BCX7353 over Target Concentration

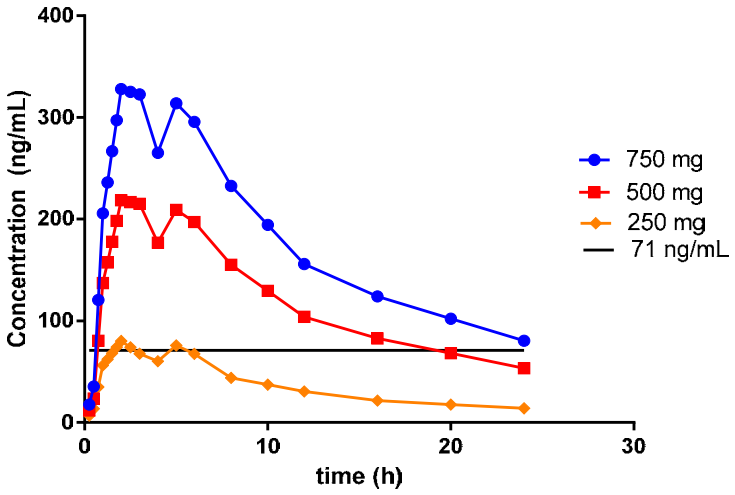


Table 2. Simulated first time postdose to achieve BCX7353 concentration ≥71 ng/mL following single dose administration of 250, 500, and 750 mg BCX7353

Dose (mg)	Mean time (hr) to first achieving target BCX7353 concentration (≥71 ng/mL)	Estimated percentiles (1st percentile to 99th percentile) of simulated subjects (1,000 at each dose level) for time (hr) to first achieving target drug concentration (≥71 ng/mL), based on plasma concentrations observed in study BCX7353-101 after dosing solid dosage form (powder in capsule)								
		p1	p5	p10	p25	p50	p75	p90	p95	p99
250	1.56	0.00	0.20	0.36	0.87	1.56	2.22	2.75	2.99	3.66
500	0.92	0.00	0.12	0.30	0.59	0.91	1.25	1.56	1.70	2.18
750	0.76	0.00	0.17	0.29	0.53	0.76	1.02	1.23	1.36	1.56

Table 3. Simulated duration of BCX7353 concentrations exceeding target concentration of 71ng/mL following single dose administration of 250, 500, and 750 mg BCX7353

Dose (mg)	Mean duration (hr) of BCX7353 concentration ≥ target (71 ng/mL)	Estimated percentiles (1st percentile to 99th percentile) of simulated subjects (1,000 at each dose level) for duration (hr) at or above the target drug concentration (≥71 ng/mL), based on plasma concentrations observed in study BCX7353-101 after dosing solid dosage form (powder in capsule)								
		p1	p5	p10	p25	p50	p75	p90	p95	p99
250	4.0	0.0	0.2	1.1	2.4	4.1	5.6	6.9	8.0	9.6
500	17.7	6.3	9.5	11.1	14.2	17.6	21.0	24.0	24.0	24.0
750	21.2	12.6	15.0	16.5	18.5	21.2	23.8	24.0	24.0	24.0

5.4.2. Rationale for Study Design

This is a Phase 2 study designed to assess the efficacy and safety of single oral doses of BCX7353 for the treatment of acute attacks in subjects with Type 1 or Type 2 HAE.

A dose-ranging design that incorporates sequential testing was chosen to ensure that a treatment effect could be demonstrated while allowing exploration of the potential utility of a range of doses. Further, evaluating a total of 3 attacks for each subject (1 of which is treated with placebo) enhances the ability to detect a treatment effect at each dose. The study allows for initial evaluation of the treatment effect during Part 1, the highest planned dose level (750 mg), and employs a Haybittle-Peto boundary for detection of drug effect. Treatment effect will be measured by comparing BCX7353-treated and placebo-treated attacks, using the proportion of subjects with a stable or improved composite visual analogue scale (VAS) of HAE attack symptoms at 4 hours postdose. If conducted, a convincing treatment effect will be demonstrated if the p value for the comparison crosses the Haybittle-Peto boundary of < 0.001. This treatment effect may be estimated beginning when 12 subjects completing the study at the 750-mg dose

level and. If the boundary is not crossed, the treatment effect may be re-estimated based on cumulative data after data on each additional attack on study are available.

Given the C_{max} levels achieved with the BCX7353 doses proposed in this study and its long terminal half-life, a washout period of at least 14 days between treatments is necessary to minimize carryover of a previously administered active dose.

Risk mitigation built into the protocol includes medical assessment of suitability of the attack, prohibiting treatment with study drug of any attack involving the throat or mouth, or any abdominal attack that has already resulted in vomiting. Lastly, subjects are allowed to self-treat with a standard of care attack medication 4 hours after dosing with study drug or sooner if the subject feels that the attack is progressing rapidly after administration of study drug.

A 3-month optional substudy, commencing at the conclusion of the study drug phase of the study, is included with the goal to learn more about the progression of untreated attacks and those treated with commercially available attack medications.

5.4.3. Study Population Rationale

The current study is limited to adults of both sexes with HAE. Adolescents and children are excluded from participation since the long term benefit/risk profile has not been sufficiently characterized in adults.

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 males and females in this clinical trial to gain an early assessment of potential safety and efficacy differences. Based on past and ongoing studies conducted in HAE patients, it is anticipated that female subjects will comprise at least 50% of the patient population in this study.

Although there is no evidence of embryofetal developmental toxicity with BCX7353 in reproductive toxicology studies, appropriate precautions are still warranted with respect to administering BCX7353 to women of reproductive age, in accordance with International Conference on Harmonization) ICH guidelines. Women of childbearing potential may be enrolled in this trial provided they meet the contraceptive requirements and have negative pregnancy tests prior to receiving each dose of study drug.

As BCX7353 is early in clinical development, the benefit/risk profile has not been sufficiently characterized to allow pregnant women to receive BCX7353, therefore pregnant women will be excluded from participation. 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.

5.4.3.1. Rationale for Use of Standard of Care Attack Medication

In the current study, all participants must have access to effective, approved treatments for acute attacks of angioedema as part of their routine medical care. Each subject will continue to use

their prescribed acute attack medication to treat any acute attacks that do not meet the eligibility requirements for treatment in this study. For the protection of the safety of the subjects, subjects will not utilize study drug to treat any HAE attack with the symptoms of pain or swelling involving the throat or mouth; for these attacks, subjects will be instructed to use their standard of care acute attack treatment. Abdominal attacks that have resulted in vomiting may be expected to reduce or abrogate absorption of an orally administered drug, and are therefore also restricted from study drug treatment. For these attacks, subjects will be instructed to use their standard of care acute attack treatment. Lastly, subjects who experience progression or do not experience improvement of the HAE attack will also be instructed to use their acute attack treatment per their standard of care.

Subjects will be requested to treat early with study drug (within approximately 1 hour of symptom onset) and use standard of care, if necessary, no sooner than 4 hours post-study drug administration. Requesting a delay in administration of standard of care for 4 hours after administration of study drug and maximally 5 hours after the onset of known symptoms is necessary for demonstration of a treatment effect of BCX7353 versus placebo and is a reasonable request of subjects as part of the protocol for the following reasons:

1. An HAE attack develops with a worsening of swelling over the first 24 hours with a resorption of the edema over the subsequent 48-72 hours. Therefore, four to five hours from the onset of symptoms to administration of standard of care attack treatment is within a symptom-modifiable timeframe based upon the development of symptoms of HAE.
2. A four to five hour timeframe from the onset of symptoms to administration of standard of care attack treatment in the current study is less than the delay in treatment observed in pivotal studies of acute attack medications in which treatments were found to be efficacious. For instance, in the FAST-3 study of icatibant, the mean (SD) time from onset of symptoms to blinded study drug treatment in 43 subjects was 7.07 (3.17) hours; in FAST-3, icatibant-treated attacks had a median time to onset of symptom relief of 2 hours (Lumry, Li et al. 2011).
3. After administration of study drug, subjects may treat an attack with their standard of care attack medication before 4 hours post administration of study drug, if they feel that the attack symptoms warrant earlier treatment.

Exclusion of approved kallikrein inhibitor attack prophylaxis with C1 INH is required to clearly demonstrate proof of concept of BCX7353. Additionally, use of androgens is prohibited due to possible interference of androgen metabolism by CYP3A4 from the inhibitory effect of BCX7353, resulting in higher androgen concentrations (see Section 9.7.1).

5.4.4. BCX7353 Risk/Benefit Analysis

5.4.4.1. Risks for Potential Severe Adverse Reactions

BCX7353 is a small molecule kallikrein inhibitor and given the previous experience with this class of agents in man, there is an acceptably low risk of severe adverse reactions, especially with two single active doses separated by at least 14 days. Potential risks are outlined below.

5.4.4.2. Risks of Potential Adverse Events with BCX7353

Initial toxicology studies in rats and monkeys suggest that the primary target organs of BCX7353 toxicity were liver (both hepatocyte necrosis and bile duct hyperplasia), kidney, and skeletal muscle, with toxicities also observed in cardiac and smooth muscle, and the lymphoid system. However, with longer duration of dosing (13 weeks) (albeit with a different drug lot than used in the 28-day studies) there were no significant adverse effects noted. In monkeys dosed 20 mg/kg/day, and for 13 weeks, there were no adverse effects noted. In rats dosed at 20 mg/kg/day, only bile duct hypertrophy, hyperplasia and vacuolated macrophages in the liver were noted and these were not considered adverse. No clinically significant toxicities in these organs have been noted during the first in human trial. Mild gastrointestinal symptoms, including diarrhea, abdominal pain, and nausea were noted with single doses, particularly at higher doses. With multiple days of dosing, similar gastrointestinal effects were seen as well as a delayed hypersensitivity drug rash, both occurring in the higher dose cohorts. In addition, at multiple dosing with 350 mg and higher, QT prolongation was seen. While the mechanisms of delayed hypersensitivity drug rash and QT prolongation following multiple dosing with BCX7353 have not yet been elucidated, it is currently considered unlikely that either of these findings will occur following administration of single doses of study drug.

Liver: At 20 mg/kg/day of BCX7353 dosed to rats for 13 weeks, liver bile duct hypertrophy, hyperplasia, and vacuolated macrophages were present in the liver with evidence of phospholipidosis (PLD) in Kupffer cells on EM. There were no hepatic enzyme or biliary lab marker changes and all these effects were reversible as evidenced in the 6-week recovery animals. At 25 mg/kg/day of BCX7353 dosed to rats for 28 days, there was minimal to mild bile duct degeneration/necrosis and inflammation. At higher doses of 75 mg/kg day, there was minimal bile duct hyperplasia, hepatocyte necrosis, and hepatocellular vacuolation that correlated to increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) on clinical chemistry.

At 20 mg/kg/day dosed to monkeys for 13 weeks, ALT levels were mildly increased in both sexes at Week 4 but demonstrated partial resolution at the terminal collection despite continued dosing, lacked correlative microscopic changes in the liver at the terminal necropsy, and were normal at the recovery collection. In the previous study where monkeys were dosed for 28 days there were enlarged hepatocytes with foamy to large cytoplasmic vacuoles and hyperplasia of oval cells at 100 mg/kg/day. Hepatocellular necrosis was noted at 30 mg/kg/day, but only those effects at 100 mg/kg/day were considered adverse. These changes also correlated with increased transaminases on clinical chemistry. In addition, monkeys had mild decreases in albumin and mild increases in globulin levels at 100 mg/kg/day.

Liver enzymes, bilirubin, gamma-glutamyltransferase (GGT) and alkaline phosphatase are being followed closely in clinical trials to monitor for any hepatocellular and biliary system changes. There have been no clinically significant abnormalities observed in any of these analytes during the completed and unblinded Phase 1 studies. In the 68 subjects treated with BCX7353 for 7 to 14 days, the highest ALT (104 IU/L) and AST (48 IU/L) occurred on Day 14 in 1 subject who was in the 350 mg × 14-day cohort. There was no evidence of any clinically significant abnormality in hepatic synthetic function as monitored by prothrombin time, albumin, and total protein levels in blood.

Liver function will be monitored after each dose administered in this study, although no toxicity is anticipated from single doses of study drug, separated by 14 days at a minimum.

Kidney: Although there was no evidence for any renal injury in the 13-week studies in either rats or monkeys, in the 28-day studies both rats and monkeys had renal tubular degeneration/ regeneration with vacuolated cells, which was adverse at 75 mg/kg/day for rats and 100 mg/kg/day for monkeys. This appeared to correlate to glycosuria noted in the 28-day monkey study. In addition, female monkeys had significant mononuclear infiltration resulting in a 35% increase in kidney weight from controls at 100 mg/kg/day.

In the Phase 1 trials, no clinically significant abnormalities of renal function, as measured by serum creatinine and creatinine clearance have been found. Additional measurements to date of renal injury were also performed; serial evaluations of spot urine microalbumin to creatinine ratio, a marker for glomerular injury, and neutrophil gelatinase–associated lipocalin (NGAL), a novel marker for tubular injury, did not demonstrate any evidence of renal injury.

Renal assessments including creatinine and urine microalbumin will be assessed after each dose of study drug administered in this study, although no toxicity is anticipated from single doses of study drug, separated by 14 days at a minimum.

Skeletal muscle: Although there was no evidence for any skeletal muscle injury in the 13-week studies in either rats or monkeys, in the 28-day studies both rats and monkeys had degeneration/necrosis and/or regeneration noted in multiple skeletal muscle groups. In the rat, these changes were also noted in cardiac muscle. Both the skeletal and cardiac muscle changes were adverse at 75 mg/kg/day in rats. The skeletal muscle changes were adverse in the monkey at 100 mg/kg/day. The muscle degeneration was suspected to contribute to the elevated AST on serum chemistry.

In the Phase 1 trials neither AST nor creatine phosphokinase (CPK) demonstrated any clinically significant elevations. All CPK changes were associated with muscular exertions. In addition, no subjects have experienced any AEs of potential muscular injury.

Given the preclinical data, AST and CPK will be monitored after each dose of study drug administered in this study, although no toxicity is anticipated from single doses of study drug, separated by 14 days at a minimum.

Heart: Although there was no evidence for any cardiac muscle injury in the 13-week studies in either rats or monkeys, in the 28-day study in rats, degeneration/necrosis and/or regeneration were noted in cardiac muscle and was considered adverse at 75 mg/kg/day. At high doses of BCX7353, monkeys did have decreases in blood pressure and heart rate, with corresponding ECG changes consisting of slowing of the heart rate and lengthening of the RR, QT and QTc intervals and QRS duration.

In addition to cardiac muscle changes and physiologic changes in heart rate and blood pressure, it should be noted that there is a small risk of hERG channel inhibition, although the cardiac action potential was not prolonged.

In the Phase 1 study BCX7353-101 study, no single ECG in subjects dosed with BCX7353 had a clinically significant abnormality. All QRS intervals were < 120 msec. There was a small but discernible QT prolongation seen only with multiple day dosing at doses higher than 250 mg; no QT prolongations were noted following single doses of BCX7353 up to 1000 mg. After multiple

daily doses, there was a dose-dependent increase in QTcF evident at 350 mg QD and higher in Western subjects and at 250 mg QD in Japanese subjects, and a concentration-dependent increase that was not predicted by analysis of QTcF data for single high doses that produced overlapping BCX7353 concentrations. No subject dosed in this study had an absolute QTcF value > 448 msec or change from baseline > 37 msec. There were 9 subjects in the entire trial with 21 events of QTcF change from baseline > 30 msec. The majority (16/21) of events occurred in 4 subjects after 7 days of dosing with 500 mg. The rest of the events occurred in 5 subjects at lower doses at a single timepoint. In summary, these data indicate that the change observed with multiple doses is not likely to be clinically significant in any population with normal QTcF and no underlying cardiac conductivity issues, even at a supratherapeutic daily doses such as 500 mg QD.

Troponin T values were normal at all time points in all Phase 1 subjects. One subject in the single-dose 1000-mg group had a transient elevation in Troponin I on Day 2 to 0.06 µg/L (ULN = 0.04 µg/L) that returned to within normal limits on Day 4 and remained < 0.01 µg/L through follow-up. The subject was clinically asymptomatic, had no Troponin T or CK-MB elevations, and had no ECG evidence of ischemia.

Six subjects treated with BCX7353 in the Phase 1 study BCX7353-101 study had treatment emergent elevations from baseline of CK-MB, 2 receiving single doses of 100 mg,2 subjects receiving 250 mg for 7 days, 1 subject receiving 500 mg for 7 days and 1 subject receiving 350 mg for 14 days. In 5 of the 6 subjects this corresponded to elevated CK ranging from 1.3 to 7.6 × ULN. In addition, 3 of these 5 subjects had elevated CK-MB at baseline. None of these subjects had an elevation of Troponin I or Troponin T or any evidence of ischemia or cardiac muscle damage. In all cases this was noted at the follow-up visit after sequestration was complete. In 1 subject receiving 350 mg for 14 days, the CK-MB was elevated to 6.5 µg/L (normal range = 0.0–2.9 µg/L) at the follow-up visit which was not due to an abnormal CK level. This subject had an elevated CK-MB at baseline of 4.0 µg/L, which improved during study drug dosing. All other labs were normal at the follow-up visit. In particular, Troponin I and Troponin T were normal and there was no evidence of cardiac ischemia. It is unclear why the CK-MB was elevated in this subject but cardiac ischemia is unlikely. No significant ECG or laboratory changes were seen in BXC7353-102 study.

As a precaution, this study will exclude subjects with evidence of cardiac disease as indicated by medical history, family history of sudden death or abnormal screening ECG. ECGs, troponin and CK-MB will be regularly monitored in this study. No cardiac toxicity or QT prolongation is anticipated from single doses of study drug, separated by 14 days at a minimum.

Lymphoid system: Although there was no evidence for any lymphoid system abnormalities in the 13 week studies in either rats or monkeys, in the rat 28-day study lymphoid depletion was noted in the thymus and spleen at 75 mg/kg/day. In contrast, the monkeys generally had hyperplastic lymphoid tissue (spleen and lymph nodes) which was not considered adverse.

In the Phase 1 studies, no clinically significant changes in any hematologic parameter or lymphoid tissue were noted. No organomegaly and no lymphadnopathy were noted on physical exam.

In this study, complete blood counts and general physical examinations will be monitored after each dose of study drug administered.

Presumed Phospholipidosis (PLD):

In the 28 day studies in both rats and monkeys, foamy macrophages and vacuolated infiltrates were found in multiple organs and various tissues, and presumed to be signs of PLD. PLD can only be confirmed with electron microscopy which was not done in the 28 day study. In most tissues, these infiltrates did not appear to be adverse and there were no clinical or blood chemistry findings that correlated. Importantly, the infiltrates were fully or partially reversible in both species. The partial reversibility in monkeys may have been due to the continued presence of BCX7353 in plasma even at Day 50 of the 28-day dosing study.

In the 13-week studies in rats, the liver showed vacuolated macrophages with electron microscopic features consistent with PLD. In the monkey 13-week study there were no microscopic abnormalities, and no foamy macrophages or vacuolated cellular infiltrates were observed. Increased urinary levels of di-docosahexaenoyl (22:6)-Bis(mono)acylglycerol phosphate (BMP), an investigational biomarker for PLD, were demonstrated in both rats and monkeys dosed with BCX7353 for 13 weeks. This increase was dose related and reversible upon cessation of BCX7353 in both species. These data suggest that the urinary BMP changes induced by BCX7353 in both rats and monkeys may not be associated with PLD, given the differences seen microscopically between the two species.

PLD is not adverse in and of itself and there are many approved products that cause this phenomenon without any unmanageable toxicities. Since PLD requires accumulation of drug, it is highly unlikely that subjects are at any risk of this phenomenon with individual doses of study drug, separated by at least 14 days at a minimum. The primary method of ensuring subject safety will be to monitor organ toxicity and subject well-being through adverse event reporting and vital signs including weight. Since phospholipidosis is not toxic in and of itself, organ health including function and signs of inflammation will be monitored. Monitoring of renal, liver, cardiac, and muscle health will be achieved with routine safety assessments, including ECGs.

Gastrointestinal (GI) symptoms: Gastrointestinal symptoms, all mild, were noted in half of the subjects receiving a single 1000 mg single dose in the Phase 1 BCX7353-101 study. The events were both upper GI (nausea, dyspepsia, and vomiting) and lower GI (diarrhea). The events resolved without treatment. No pertinent GI events occurred in the 500 mg single dose cohort but 2 subjects reported GI symptoms at 100 mg. During multiple day dosing (part 2), all cohorts experienced GI symptoms when BCX7353 was given over 7 to 14 days. Symptoms were primarily lower gastrointestinal (diarrhea and flatulence) at 500 mg QD × 7 days and primarily upper gastrointestinal (abdominal pain, dyspepsia) at 350 mg QD × 14 days without any pertinent laboratory or physical exam findings. In the Japanese 250 mg × 7-day cohort, a single subject had abdominal pain. All subjects reporting these events took study drug in a fasting state. Two subjects discontinued study drug, one after a single 500-mg dose of BCX7353 due to diarrhea and abdominal pain, and one after 10 days of 350 mg BCX7353 due to abdominal pain. Neither subject had any clinically significant laboratory abnormalities. The Phase 1 study demonstrated no adverse impact on the extent of drug exposure from taking BCX7353 with food in 6 subjects who received a dose of BCX7353 (250 mg) under fed and fasting conditions. However, the time to achieve maximal blood concentrations was delayed when BCX7353 was administered with food (median T_{max} increased from 2 to 5 hours, with 4 of 6 subjects experiencing a delay in T_{max} with food relative to fasting). Therefore, since food may materially delay achievement of effective blood levels and the gastrointestinal effects to date have been a

tolerability issue but not a safety issue, BCX7353 is recommended to be taken without food and to delay food at least one hour (to allow for gastric emptying). However, due to the unpredictability of onset and location of HAE attacks, recent food intake will not necessarily prohibit an attack from being approved for treatment with study drug in this study. The time of the last meal prior to the attack will be captured to assess whether recent food ingestion prior to an attack may affect efficacy.

Subject well-being with respect to possible gastrointestinal symptoms will be monitored through adverse event reporting and laboratory assessment.

Drug rash: A benign maculopapular exanthema consistent with a delayed type drug rash has been seen in 3 subjects taking multiple doses of BCX7353 to date. In Studies BCX7353-101 and BCX7353-102, a total population of BCX7353 exposed subjects who have received at least 7 days of BCX7353 doses is 68, equating to an incidence rate of 4.4%. In all cases, symptoms were observed or reported approximately 2 days after daily BCX7353 dosing ended: one subject who completed 500 mg QD BCX7353 x 7 days (Study BCX7353-101), one subject of Japanese heritage who completed 250 mg QD BCX7353 x 7 days (Study BCX7353-101), and one subject who recently completed 9 days of BCX7353 350 mg QD (Study BCX7353-102). In all cases, no systemic or constitutional symptoms, no organ involvement, no desquamation or mucosal involvement was observed, no clinically significant laboratory abnormities were present and the rash rapidly resolved. Two subjects received an oral antihistamine and 1 subject received oral and topical steroids.

Hypersensitivity is a risk with any drug. In all three cases, the rashes have been limited and resolved quickly. Subjects should report any rashes, pruritus, or skin changes. Evaluation of any suspected drug-induced rash will be required with high resolution photography and clinical laboratory assessments in order to better define this risk; skin biopsy of a fresh lesion should be obtained for histopathologic examination, where possible. The management of rash is specifically addressed in Section 11.1.11. It is unknown if repeat exposure of single doses will result in hypersensitivity.

5.4.5. Benefits of Trial Participation

Study subjects will receive regular medical care for the duration of the study. Subjects may experience a resolution in their acute attacks after receiving active study drug; however, subjects will be blinded to their treatment sequence so they will not know if they are receiving BCX7353 or placebo for any given treated attack.

The development of BCX7353 may be of benefit to the wider community/patients with HAE.

5.4.6. Overall Benefit-Risk Assessment

The risks seen to date in both preclinical and clinical studies at the study doses were primarily mild, monitorable, and reversible. Although there may be no direct benefit to any individual subject, the information obtained from this study will support the development of BCX7353 for treatment of acute attacks in patients with HAE, a life-threatening disease. The overall risk benefit balance is therefore considered to be acceptable.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of single oral doses of BCX7353 in treating acute attacks in subjects with HAE

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of single oral doses of BCX7353 in subjects with HAE
- To evaluate the relationship of BCX7353 dose with clinical responses
- To evaluate subject satisfaction with BCX7353 treatment
- Substudy: to describe the natural history and temporal pattern of symptoms of untreated attacks and those treated with commercially available attack medications

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 3-part, Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of single oral doses of a liquid formulation of BCX7353 in the treatment of acute HAE attacks. All subjects enrolled will receive both active and placebo blinded study drug in a randomized sequence. Part 1 of the study will evaluate single doses of BCX7353 750 mg; Part 2 will evaluate single doses of BCX7353 500 mg and Part 3 will evaluate single doses of BCX7353 250 mg.

HAE patients with a documented recent history of angioedema attacks who have provided written informed consent will be evaluated for participation in this study at a screening visit.

Up to 36 subjects with Type 1 or 2 HAE with a documented history of HAE attacks will be sequentially enrolled into Part 1 of the study and randomized to a treatment sequence containing the following:

- Treatment A^1: Single oral dose of BCX7353 750 mg
- Treatment B: Single oral dose of placebo

Note: Treatment A^1 = single oral doses of BCX7353 750 mg in Part 1; Treatment A^2 = single oral doses of BCX7353 500 mg in Part 2; or Treatment A^3 = single oral doses of BCX7353 250 mg in Part 3.

Initially in Part 1, 12 subjects will be randomized 1:1:1 to 1 of 3 treatment sequences (n = 4 subjects per treatment sequence):

- Sequence 1: A→B→A
- Sequence 2: B→A→A
- Sequence 3: A→A→B

Both subjects and site staff will be blinded to which treatment sequence a subject is randomized to receive.

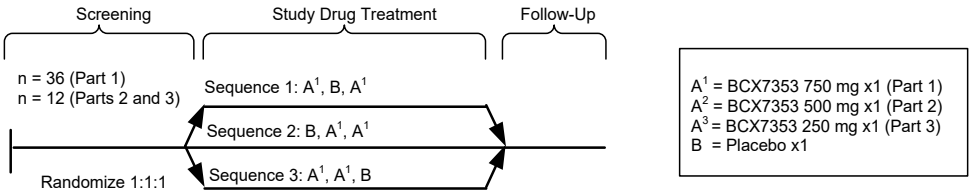
If required, additional subjects will be enrolled into Part 1 (see below) using the same 1:1:1 ratio for the 3 treatment sequences, with a maximum total number of 36 subjects for Part 1.

Part 2 will evaluate a dose of 500 mg (Treatment A^2) and placebo (Treatment B). A maximum of 12 subjects will be enrolled, using the same 1:1:1 ratio for the 3 sequences. Part 3 will evaluate a dose of 250 mg (Treatment A^3) and will enroll a maximum of 12 subjects in a 1:1:1 ratio for each of the 3 treatment sequences.

If tolerability issues prevent enrollment of Part 1 as described, additional subjects in Part 1 may be dosed with active study drug at a dose of 500 mg. If the Part 1 dose is reduced and at least 12 subjects are treated with an active study drug dose of 500 mg, a 250 mg active dose may be assessed in Part 2. Any further dose level changes warranted for Part 2 and Part 3 will be instituted via a protocol amendment.

The overall study design is presented in Figure 2.

Figure 2. Study Design Through Follow-up (Post-Attack 3 Visit)



7.1.1. Enrollment and Analyses

Up to 36 subjects will be enrolled in Part 1. Upon full enrollment, enrollment into Part 2 of the study (maximum of 12 subjects) may immediately commence. Likewise, Part 3 (n = up to 12) may immediately commence upon enrollment of Part 2.

Following the 12th subject completing Part 1, the treatment effect may be estimated. The predefined endpoint, determined by the Haybittle-Peto method, is the proportion of subjects with a stable or improved composite VAS at 4 hours postdose of an HAE attack. A Haybittle-Peto boundary of $p < 0.001$ is considered clinically significant.

If the Haybittle-Peto analysis is run and the boundary is not crossed with 12 subjects, the treatment effect may be re-estimated with cumulative data after each treated attack in accordance with the fully sequential analysis method. At each evaluation, the treatment effect may be assessed using the Haybittle-Peto boundary ($p < 0.001$).

Alternatively, if the boundary is not crossed with 24 subjects enrolled or the Heybittle-Peto analyses are not performed, treatment differences may be assessed using available data in Parts 1, 2 and 3 in order to plan subsequent studies.

7.1.2. Study Conduct Overview

At the Screening visit, potential subjects will be given a diary and receive instruction on the correct completion of the diary in real-time to record attack symptoms and severity and any medication usage during an attack. During the 35-day screening period, subjects will be required to: 1) phone the on-call Investigator (or designee) at the onset of pain or swelling associated with an HAE attack; 2) complete details in real time of this HAE attack; and 3) phone the on-call Investigator (or designee) again in at least 4 hours time. Completion of these procedures will confirm that the subject is able and competent to perform on-study requirements in early identification of an attack and treating and documenting an HAE attack.

Eligible subjects will return to the clinic to attend a Baseline visit. At the conclusion of the Baseline visit, subjects will receive their first (single) randomized dose of study drug for treatment of attacks by self-administration. The IMP is supplied as a powder form of drug in a bottle that will require reconstitution to a liquid formulation with vehicle, by the subject, prior to self-administration.

At the Baseline visit, all subjects will be instructed on how to prepare and use study drug to treat a protocol-qualified HAE attack and will receive further instruction on the correct completion of a diary in real-time immediately prior to and after study drug administration.

Specifically, subjects will be instructed with respect to treatment of attacks with study drug by self-administration as follows:

1. At the first symptom of swelling or pain known to be associated with a potentially protocol-qualified attack, the subject will phone their on-call study Investigator (or designee) who will review the subject's symptoms by phone. The Investigator will confirm that their symptoms constitute an acute attack that qualifies for treatment with study drug.

   Protocol-qualified attacks approved for study drug treatment must meet all of the following:

   - have pain and/or swelling associated with an HAE attack reported as a symptom
   - subject has contacted Investigator within approximately 1 hour of onset time of HAE pain and/or swelling
   - not involve pain or swelling in the throat or mouth. Such attacks should be treated using the subject's standard of care acute attack treatment (e.g., C1 INH, icatibant) without delay.
   - not be an abdominal attack that has already resulted in vomiting. Such attacks should be treated using the subject's standard of care acute attack treatment (e.g., C1 INH, icatibant).
   - have an identifiable onset time, with the exception that abdominal attacks with an onset during sleep may be permitted for study drug treatment. Onset time for abdominal attacks will be time the subject woke up with symptoms. Peripheral attacks starting with an onset during sleep will not be approvable for study drug treatment.
   - occur during an HAE symptom-free period as follows:
     - if the previous HAE attack was treated with a bradykinin B2 receptor antagonist (i.e. Firazyr) OR treated with human recombinant C1 INH (i.e. Ruconest) OR any non-targeted therapy (i.e. pain medication, anti-spasmodic, anti-emetic, tranexamic acid) OR was not treated with any medication: new attack can be treated with IMP if has been 48 hours since the complete resolution of all symptoms of the previous HAE attack AND the Investigator believes it is a new (de novo) attack.

       OR

     - if the previous HAE attack was treated with plasma-derived purified C1 INH (i.e. Berinert or Cinryze) OR plasma preparation (fresh frozen or solvent detergent plasma): new attack can be treated with IMP if it has been 96 hours since the complete resolution of all symptoms of the previous HAE attack
   - occur at least 96 hours after complete recovery from a procedure or injury

- occur at least 14 days from a previous dose of study drug

2. Only after receiving confirmation by the on-call Investigator (or designee) should a subject reconstitute study drug with vehicle and take it to treat the HAE attack. Reconstitution and ingestion of the study drug should occur almost immediately (within 5 minutes) following the phone call, with the goal for subjects to take study drug within approximately one hour of the onset of symptoms.
3. At 4 hours post study drug intake, subjects who are not experiencing improvement or who are experiencing progression of the HAE attack can use their standard of care acute attack treatment, if warranted. However, if the subject feels that an attack is progressing rapidly after administration of study drug or intraoral symptoms develop, the subject may treat the attack with their standard of care attack medication prior to 4 hours.
4. The subject will call the on-call study Investigator (or designee) at least 4 hours after taking study medication (or earlier if they have any concerns over the course of their symptoms) to review their response to study drug and diary completion. The on-call study Investigator (or designee) will call the subject if they have not heard from the subject within 5 hours of their initial phone call. Subjects who did not require standard of care at 4 hours will be reminded at the telephone call, by the Investigator, that they may use standard of care at any time point at their own discretion if not experiencing improvement or if they are experiencing progression of the HAE attack. An exception to the requirement of a phone call follow-up at 4 hours may be made if the 4 hour timepoint occurs during the typical period of sleep and the subject is asleep at 4 hours post-study medication. In this case, the subject will be required to call the on-call Investigator (or designee) upon waking.

Subjects will complete a diary questionnaire and a 3-component VAS on a 100 mm scale for abdominal pain, cutaneous pain, and cutaneous swelling immediately prior to study drug administration and at 1, 2, 3, 4, approximately 8 and at 24 hours after study drug administration. Subjects sleeping during these timepoints (see #4 exception above) will be required to complete the diary questionnaire upon waking. Subjects will also be asked to track the start and stop times of any attacks not treated with study drug that occur after the baseline visit through the last study visit (Post-Attack 3 visit).

At each clinic visit following treatment of an attack with study drug, the diary will be reviewed. Any re-education required to ensure correct diary completion will be performed and safety assessments will be completed. At Post-Attack 1 and Post-Attack 2 clinic visits, the subject will be dispensed their next randomized dose of study drug and a new attack diary. Completed diaries will be collected at each visit to avoid subjects referencing back to previous attack entries.

Each subject will continue on study to treat 3 protocol-qualifying attacks with study drug. Clinic visits will be scheduled 10 to 14 days after each attack that is treated with study drug. Any additional attacks that occur in the intervening periods between study visits may be treated according to standard of care for the subject.

Sites must attempt to contact subjects every 7 days from the last clinic visit to inquire about the occurrence of an attack if the subject has not contacted the site during this timeframe.

Subjects will be asked to participate in an optional observational substudy to obtain diary data on all HAE attacks, commencing from the Post-Attack 3 visit. Consenting subjects will receive a diary and instruction for completion at the Post-Attack 3 visit. For the next 12 weeks, subjects will complete diaries provided on an as-needed basis with periodic subject contact to ensure adherence with diary completion.

7.2. Endpoints

7.2.1. Efficacy Endpoints

The efficacy endpoints of this study are as follows:

- Proportion of subject attacks with an improved or stable 3-symptom composite VAS score at 4 hours post-dose. The 3-symptom composite will be calculated as the average of the VAS scores for abdominal pain, skin pain, and skin swelling. A subject is considered improved or stable if the change from baseline (time of drug administration) in VAS is less than or equal to 0
- Proportion of subject attacks with a patient global assessment of improved or stable symptoms at 4 hours post-dose
- Proportion of subject attacks with no symptoms or mild symptoms of an HAE attack at 4 hours post-dose
- Proportion of subject attacks requiring standard of care attack treatment through 24 hours post-dose
- Time to use of standard of care acute attack treatment through 24 hours post-dose
- Time to stable or improved symptoms by composite VAS score through 24 hours post-dose
- Time to symptom relief (first documented time point when a subject experiences a 50% reduction in the 3-symptom composite VAS from the pretreatment composite score)
- Time to almost complete symptom relief (first documented time point when a subject records a VAS score < 10 mm in the 3-symptom composite VAS score)
- Time to initial symptom relief (time from ingestion of study medication to report that the worst symptoms of the attack are over)
- Time to complete symptom relief (time from ingestion of study medication to no HAE attack symptoms)

7.2.2. Safety Endpoints

Safety endpoints will include the number and proportion of subjects who: discontinue due to a treatment-emergent AE; experience a treatment-emergent SAE; experience a Grade 3 or 4 treatment-emergent AE; and experience a treatment emergent Grade 3 or 4 laboratory abnormality.

7.2.3. Other Secondary Endpoints

Other secondary endpoints will include treatment satisfaction, as assessed by the TSQM.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

Up to 36 evaluable subjects with Type 1 or 2 HAE are planned to be enrolled in Part 1, up to 12 evaluable subjects in Part 2, and up to 12 evaluable subjects in Part 3. An evaluable subject is one who treats 3 attacks with study drug and for which there is diary information recorded for each treated attack.

Subjects who complete Part 1 will not be eligible to participate in Parts 2 or 3. Likewise, subjects who complete Part 2 will not be permitted to participate in Part 3.

Subjects who prematurely withdraw from the study may be replaced at the Sponsor's discretion. Any subject who has withdrawn from the study as a result of a treatment-emergent AE (regardless of severity or causality) may not be replaced.

The following inclusion and exclusion criteria will be used to screen subjects for the study.

8.2. Subject Selection

8.2.1. Inclusion Criteria

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

1. Able to provide written, informed consent
2. Males and non-pregnant, non-lactating females age 18 to 70 years
3. A clinical diagnosis of hereditary angioedema Type 1 or Type 2, defined having a C1 INH functional level below 50% of normal and a C4 level below the lower limit of the normal reference range, as assessed at the Screening visit.

   Should the C4 level be within the normal range, as is the case in a small percentage of subjects with HAE, C4 may be drawn during an attack for re-testing or the SERPING-1 gene may be analyzed for a known mutation associated with HAE Types 1 or 2. Either will be considered confirmation of eligibility.
4. Access to and ability to use standard of care acute attack treatment. Standard of care acute attack treatment is defined as a medication approved by the relevant competent authority for the treatment of attacks of HAE (e.g., icatibant, ecallantide, plasma-derived C1INH, recombinant C1INH).
5. Female participants must meet at least 1 of the following requirements:
   a. Be a woman of childbearing potential (defined as a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) who agrees to use 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 (i.e., bilateral tubal ligation 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) hormonal contraception associated with inhibition of ovulation, initiated at least 60 days prior to the screening visit
- 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 screening follicle-stimulating hormone (FSH) ≤ 40 mIU/mL must agree to use an acceptable effective contraceptive method (as defined above) during study and for 30 days after the last dose of study drug.

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

c. Be a woman declaring herself as either sexually abstinent or exclusively having female sexual partners. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."

6. Male participants must comply with the following requirements through the end of the study:

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

- surgical sterilization (ie, vasectomy or bilateral tubal ligation of a female partner)
- partner’s placement of an IUD or IUS
- partner’s use of any form of hormonal contraception that is associated with inhibition of ovulation (oral, injectable, intravaginal, implantable or transdermal)
- use of a condom with or without spermicidal foam/gel/film/cream/suppository
- partner’s use of an occlusive cap [diaphragm, or cervical/vault caps] with spermicidal (foam/gel/film/cream/suppository)

b. Male subjects who declare themselves as sexually abstinent or exclusively having male sexual partners are acceptable for the purposes of this study. Abstinence in

this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."

7. Any regularly administered concomitant medication recorded at the Screening visit and not stated as prohibited must be anticipated to be continued through the entire study and be of a stable dose and regimen for the duration of the entire study (screening through follow-up).
8. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. To be dispensed study drug at baseline, the subject must demonstrate adequate compliance with all study procedures required from the Screening visit through randomization, including phoning the investigator and diary recording of at least one HAE attack during the screening period.
9. Must have an HAE attack rate of at least 1 unique attack per month for 3 months (up to 93 days) within the 4 months prior to the Screening visit. A unique attack is defined as an attack that is not recorded on contiguous days to another attack. For the purposes of this protocol, two attacks that are recorded on contiguous days are one attack with an onset day/time of the first attack.

   Any of the following will be acceptable source records of HAE attacks: clinic notes with a numerical rate of attacks, acute attack medicine administration records, or a historically-completed subject record of attacks. This record should indicate the dates of attacks, at a minimum.

8.2.2. Exclusion Criteria

Subjects must meet none of the following exclusion criteria to be eligible for participation in this study:

1. No HAE attack reported to the on-call Investigator (or designee) during the 35-day screening period.
2. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.
3. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
4. Clinically significant abnormal ECG at the Screening visit. This includes, but is not limited to, a QTcF > 470 msec for women, a QT_cF > 450 msec for men, a PR > 220 msec (both sexes), or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
5. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.

6. Known family history of sudden cardiac death from causes other than HAE. Family history of sudden death from HAE is not exclusionary.
7. History of or current implanted defibrillator or pacemaker.
8. Any laboratory parameter at screening that, in the opinion of the Investigator, is clinically significant and relevant for this study. A calculated creatinine clearance of ≤ 60 mL/min or AST or ALT value ≥ 2 times the upper limit of the normal reference range value obtained during screening is exclusionary.
9. Suspected C1 INH resistance in the opinion of the Investigator and Sponsor.
10. History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 drinks/day).
11. Positive serology for human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
12. Pregnant, planning to become pregnant within 30 days of the study, or nursing.
13. Positive drugs of abuse screen (unless as used as medical treatment, e.g., with a prescription).
14. History of severe hypersensitivity to any medicinal product, which was associated with swelling, a severe rash requiring treatment/hospitalization, or anaphylaxis.
15. Hypersensitivity reaction to BCX7353.
16. Use of tranexamic acid, androgens or C1 INH for prophylaxis of HAE attacks within the 7 days prior to the Screening visit or initiation during the study. Use of a C1 INH therapy for treatment of attacks is not excluded at any time, nor is C1 INH for pre-procedure prophylaxis.
17. Use of concomitant medications that are metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study. For the purpose of this protocol, these include, but are not limited to the following: warfarin, phenytoin, s-mephenytoin, thioridazine, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine and desogestrel.
18. Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.
19. Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to baseline or initiation during the study.
20. Current participation in any other investigational drug study or received another investigational drug within 30 days of the Screening visit.
21. An immediate family relationship to either Sponsor employees, the Investigator or employees of the study site named on the delegation log.

Medications prohibited for use during the study are addressed in Section 9.7.1.

8.3. Subject Withdrawal Criteria

8.3.1. Subject Discontinuation from Study

Participation in the study is strictly voluntary; a subject may withdraw consent to contribute additional study information at any point. A subject who withdraws consent prior to study completion will be requested to attend an early termination visit to complete all end-of-study evaluations. In all cases, the reason for withdrawal from the study must be recorded in the subject's medical records (source documents) and also in the electronic case report form (eCRF). If at any point in the study the clinic is unable to contact the subject after appropriate attempts have been made according to local clinic standards, the subject will be considered to have withdrawn consent. If the reason for subject withdrawal is not known, the subject must be contacted to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 12.

Once subjects have discontinued the study, the Sponsor will no longer provide treatment through the study. Following withdrawal from the study, a subject will be able to receive further treatment as recommended by their treating physician and according to the accepted standard of care.

8.3.2. Subject Discontinuation from Study Drug

A subject will be withdrawn from study drug for any of the following bulleted reasons, which will be recorded in the source documents and eCRF. In all cases, subjects who discontinue study drug will be requested to complete an Early Termination visit and all procedures as outlined in Section 10.3.5.

- Intercurrent illness or emergence of a new illness/medical condition that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Subsequent determination that inclusion/exclusion criteria were not met
- Emergence of any laboratory abnormality or AE that in the judgment of the Investigator compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest due to an altered risk/benefit profile
- Subject noncompliance with study drug or to the protocol
- Discontinuation at the request of the Sponsor, competent authorities in the Member State(s) concerned, or the institutional review board (IRB)/independent ethics committee (IEC)
- Criteria outlined in Sections 8.3.2.1 and 8.3.2.2.

8.3.2.1. Discontinuation Due to QT Prolongation

Any subject will be discontinued from further dosing if the following QTcF criteria are met:

- The subject has a QTcF > 500 msec (confirmed on repeat testing)

  or

- The subject has a QTcF increase of more than 60 msec (confirmed by repeat ECG) from the value obtained predose at baseline

8.3.2.2. Discontinuation Due to Rash

All subjects with a suspected drug rash should undergo specific rash evaluation as described in Section 11.1.11. Subjects with a study drug related Grade 3 or 4 rash as described by the DMID criteria "Skin-mucocutaneous" will be discontinued from study drug and treated according to best medical practice. A Grade 3 rash is defined as vesiculation or moist desquamation or ulceration and a Grade 4 rash is defined as exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson or necrosis requiring surgery Subjects with a Grade 1 or 2 study-drug related rash may be continued on BCX7353 if both investigator and subject deem it appropriate.

8.3.2.3. End of Trial Definition

The end of the trial will be defined as when the last subject completes the Post-Attack 3 visit.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

The study drug or IMP in this study consists of BCX7353 powder and matching placebo powder for reconstitution as oral solutions. Subjects will be randomized to 1 of 3 treatment sequences and will receive 2 single doses of BCX7353 and 1 single dose of matching placebo:

- Two single oral doses of BCX7353 750 mg and one oral dose of matching placebo (Part 1)
- Two single oral doses of BCX7353 500 mg and one oral dose of matching placebo (Part 2)
- Two single oral doses of BCX7353 250 mg and one oral dose of matching placebo (Part 3)

The active ingredient for this study is BCX7353. All clinical doses of BCX7353 provided in this protocol are in reference to the hydrochloride (HCl) salt. BCX7353 is a white to tan powder. The IMP is formulated as a single unit dose drug in a bottle formulation that will be reconstituted with an oral vehicle prior to dosing. The oral vehicle to be used for reconstitution is a SyrPalta:Sterile Water for Irrigation solution and is supplied with the IMP.

The taste-masked placebo for this study is lactose monohydrate which is an off-white powder. The IMP is formulated as a single unit dose drug in a bottle formulation that will be reconstituted with an oral vehicle prior to dosing. The oral vehicle to be used for reconstitution is a SyrPalta, Sterile Water for Irrigation and Bitrex® 0.256%w/v (50ppm) solution and is supplied with the IMP.

Quotient Clinical (Nottingham, UK) will manufacture the IMP.

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

9.2. Description of Study Drug Packaging, Labeling and Storage

Oral vehicle and study drug will each be packaged in appropriately sized high density polyethylene (HDPE) bottles with tamper evident polypropylene lids. Each kit dispensed to a subject will contain one of each bottle.

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

The IMP will be stored according to the Investigational Medicinal Product Dossier (IMPD).

Study drug will be stored between 15°C–25°C (room temperature).

9.3. Blinding and Randomization

9.3.1. Blinding

This is a double-blind study. As such, study drug treatment sequence will be blinded to the Investigator, study staff, study subjects, and clinical research organization (CRO) staff. Sponsor employee(s) not regularly interacting with the clinical sites will also be blinded to the treatment sequence of individual subjects, with the exception of Sponsor staff responsible for managing clinical supplies.

The project statistician performing the analyses with a Haybittle-Peto boundary for significance may become unblinded after the 12th subject completes Part 1. Sponsor employees may be unblinded at the same time or at any point thereafter.

9.3.2. Randomization

Up to 36 subjects will be sequentially enrolled into Part 1 of the study and randomized to receive a treatment sequence containing one of the following:

- Treatment A^1: Single oral dose of BCX7353 750 mg (Part 1)
- Treatment B: Single oral dose of placebo

Initially in Part 1, 12 subjects will be randomized 1:1:1 to the following treatment sequences (n = 4 subjects per treatment sequence):

- Sequence 1: A→B→A
- Sequence 2: B→A→A
- Sequence 3: A→A→B

Note: Treatment A^1 = single oral doses of BCX7353 750 mg in Part 1; Treatment A^2 = single oral doses of BCX7353 500 mg in Part 2; and Treatment A^3 = single oral doses of BCX7353 250 mg in Part 3.

A subject will be randomized to a treatment sequence at or prior to the Baseline visit.

Subject randomization will occur only after the following steps have been completed and reviewed by the Sponsor:

a) The following data is provided to the Sponsor: qualifying historical HAE attack data, concomitant and past medications, C1INH function and C4 level (or SERPING-1 mutation), and the data collected on the HAE medical and medication history form.
AND
b) A site-documented screening HAE attack has occurred (i.e., subject phones Investigator prior to the attack and approximately 4 hours later)

For the documented attack, the completed diary does not have to be collected to randomize a subject; however, the on-call Investigator (or designee) should ensure the subject has competently completed the attack diary.

Specific details of the randomization and kit shipment processes will be communicated to the sites.

Study drug will be dispensed to subjects in a quantity sufficient for the treatment of one acute attack. Each subject will be assigned study drug a total of 3 times, which will be dispensed at Baseline and at the clinic visits following the first and second attack.

Information on unblinding in the event of a SAE is provided in Section 12.1.8.

9.4. Study Drug (Investigational Medicinal Product) Reconstitution and Administration

Subjects will take all study drug doses by self-administration after approval from the on-call Investigator or designee. After authorization to treat the attack, subjects should reconstitute and ingest study drug and the rinse (see below). Reconstitution and ingestion of the study drug should occur almost immediately (within 5 minutes) following the phone call, with the goal for subjects to take study drug within or approximately one hour of the onset of symptoms.

To prepare drug to ingest, subjects should reconstitute their study drug by pouring the entire contents of the vehicle (liquid) into the bottle containing the powder. The bottle containing the liquid and powder should be recapped and shaken vigorously for at least 15 seconds. After drinking the entire volume of the reconstituted study drug, subjects will rinse the bottle with water (not provided in the study drug kit) by shaking for 5 seconds and ingest the rinse. To the extent possible, the entire dose of study drug plus the rinse should be taken within 5 minutes from the time of reconstitution.

Where practical, study drug is recommended to be taken without food and to delay food at least one hour (to allow for gastric emptying). If the subject desires to further cleanse their pallet after ingesting the water rinse, hard candy, mouthwash, tongue or teeth brushing or chewing gum is recommended. Further instructions on subject preparation of study drug will be provided.

9.5. Study Drug Dose Modification

Subjects will be instructed to take the entire study drug dose as indicated by the protocol.

If tolerability issues prevent enrollment of Part 1 at the 750 mg dose, the Sponsor may reduce the dose of study drug for new subjects in Part 1 to a dose of 500 mg. Written instructions will be communicated to all sites on documentation of the dose to be given to new subjects in Part 1 if this occurs. If the Part 1 dose is reduced and at least 12 subjects are treated with an active study drug dose of 500 mg, a 250 mg active dose may be assessed in Part 2. Any further dose level changes warranted for Part 2 and Part 3 will be instituted via protocol amendment.

9.6. Study Drug (Investigational Medicinal Product) Accountability

Accountability of returned study drug bottles will be performed by site personnel at the study visits following each attack. Returned drug bottles must be retained and reviewed during monitoring visits by the clinical research associate (CRA) (Section 14.2).

The Investigator/pharmacist must maintain accurate records (including date) of the disposition of all IMPs received from the Sponsor. The Sponsor will supply a specific drug accountability form to each site. At the end of the study, information describing study drug supplies and disposition of supplies for each subject must be provided, signed by the Investigator or designee, and collected by the study monitor. If any errors or irregularities in any shipment of study medication

to the site are discovered at any time, the CRO Project Manager and/or Sponsor must be contacted immediately.

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

9.7. Concomitant Medications and Other Restrictions

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

Any regularly administered concomitant medication at screening must be anticipated to be continued through the study and be of a stable dose and regimen for the duration of the study.

Details of all prior (within 30 days of screening) and concomitant medication use, including all medications administered for the treatment of AEs, will be recorded in the source documentation/eCRF.

9.7.1. Prohibited Medications/Restrictions

The following medications are excluded during the study (Section 8.2.2):

- Use of concomitant medications that are metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study. For the purposes of this protocol, these include: warfarin, phenytoin, s-mephenytoin, thioridazine, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine, androgens and desogestrel.

  Additional medications may be added to this list of excluded CYP substrate medications as the Sponsor becomes aware of evolving data. The Sponsor may add to the exclusionary list based upon review of regulatory labelling for individual medications, regulatory guidances, peer-reviewed publications, and regularly-updated drug interaction reference databases (e.g., University of Washington School of Pharmacy Drug Interaction Database Program). Any updates to the excluded list will be shared with clinical sites.

- Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study (potential for exacerbation of HAE).

- Use of C1 INH, tranexamic acid or androgens for prophylaxis of HAE attacks within the 7 days prior to the screening visit or initiation during the study. Use of a C1 INH therapy for treatment of attacks is not excluded at any time.

- Use of a medication that is clinically known to prolong the QT interval and is metabolized by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to baseline or initiation during the study.

  A list of these medications will be shared with the clinical sites. In order to construct this list, drugs with a *known risk of torsades de pointes* from the Arizona Center for

Education and Research on Therapeutics (https://www.crediblemeds.org) will be examined against labelling for CYP substrate specificity.

- Current participation in any other investigational drug study or having received another investigational drug within 30 days of the Screening visit

The following classes of medications are restricted during the study based upon in vitro transporter data:

- Daily use (more than 5 consecutive days) of a medication that is known to induce or inhibit drug transporters P-gp or BCRP to a clinically significant degree 7 days prior to baseline or subsequent initiation during the study. This includes foods or beverages containing grapefruit or Seville oranges
- Use of a medication (more than 5 consecutive days) that primarily relies upon BCRP or P-gp transport proteins for systemic disposition 7 days prior to baseline or subsequent initiation during the study that is known or suspected to have clinically significant safety concerns with increased exposure.

The Sponsor will compile and provide a spreadsheet outlining these restricted medications based upon regulatory labelling for individual medications, regulatory guidances, peer-reviewed publications and regularly-updated drug interaction reference databases (e.g., University of Washington School of Pharmacy Drug Interaction Database Program).

A drug interaction study designed to elucidate the clinical relevance of the inhibition potential of BCX7353 on BCRP and P-gp transport and whether the pharmacokinetics of BCX7353 is affected by P-gp or BCRP inhibitors is planned. If the results of this study indicate that there is no clinically significant transport inhibition on or by BCX7353, these restricted medications will be permissible for use on study. A memo outlining the findings and impact will be sent to each study Investigator.

10. STUDY CONDUCT

10.1. Overview

This is a randomized, double-blind, placebo-controlled study. The duration of a subject's participation in this study is dependent on the timing and frequency of on-study acute attacks eligible for treatment with study drug. Assuming that subjects will have 1 eligible attack every 4 weeks, it is anticipated that minimally a subject's participation would be approximately 19 weeks (inclusive of the screening period, wash-out periods of 10 to 14 days in duration in between treated attacks, and a final follow-up visit [at least 16 days after the third attack]). Each eligible subject who consents to participate in the study will receive a total of 2 single doses of BCX7353 and 1 dose of matching placebo. All subjects will undergo a screening period of up to 35 days, and 4 clinic visits; visits will occur at Baseline, within 10 to 14 days after the first and second study drug treated attacks, and at least 16 days following the last study drug treated attack. Subjects who consent to the optional observational substudy after the last study visit (Post-Attack 3 visit) will participate in study activities for approximately 12 additional weeks.

After the Baseline visit, at the first symptom of swelling or pain associated with an attack, the subject will be asked to phone the on-call study Investigator (or designee) who will review the subject's symptoms by phone and confirm that they constitute an appropriate acute attack that qualifies for treatment with study drug, including ensuring that the subject is in an environment that he/she deems suitable for completion of the timed diary. Following confirmation by the Investigator, subjects should use study drug to treat the HAE attack, within approximately 1 hour from the onset of the first symptoms.

Subjects will fill out a diary questionnaire and a 3-component VAS on a 100 mm scale for abdominal pain, cutaneous pain, and cutaneous swelling prior to and at 1, 2, 3, 4, approximately 8, and at 24 hours after record of study drug administration.

If the subject prematurely discontinues from the study, they will be requested to attend an early termination visit.

10.2. Schedule of Assessments

The schedule of assessments for this study is summarized in Table 4; the optional substudy assessment schedule can be found in Table 5.

Table 4. Schedule of Assessments for Study BCX7353-202

	Screening Day –35 to –1	Baseline	Attack 1 Telephone Contacts	Post-Attack 1 Visit (10-14 days)	Attack 2 Telephone Contacts	Post-Attack 2 Visit (10-14 days)	Attack 3 Telephone Contacts	Post-Attack 3 Visit/ Follow-up (16 days + 3 days)	Early Termination Visit
Informed consent[a]	X							X	
Telephone contact[b]	X		X		X		X		
Clinic visits[c]	X	X		X		X		X	X
Inclusion/Exclusion criteria	X	X							
Medical history	X	X							
HAE attack frequency confirmation	X								
HAE medical and medication history	X								
Height/Weight/BMI	X	X[d]							X[d]
Drugs of abuse screen[e]	X								
HIV/HCV/HBV serology	X								
FSH[f]	X								
C1 INH function and C4	X								
Pregnancy test[g]	X	X		X		X		X	X
Safety laboratory evaluations and urinalysis testing[h]	X	X		X		X		X	X
Troponin I & Troponin T		X		X		X		X	X
CK-MB		X		X		X		X	X
C3		X							
C1 INH antigen level		X							

	Screening Day −35 to −1	**Baseline**	**Attack 1 Telephone Contacts**	**Post-Attack 1 Visit (10-14 days)**	**Attack 2 Telephone Contacts**	**Post-Attack 2 Visit (10-14 days)**	**Attack 3 Telephone Contacts**	**Post-Attack 3 Visit/ Follow-up (16 days + 3 days)**	**Early Termination Visit**
Randomization[i]	X								
Physical examination	X	X		X[j]		X[j]		X[j]	X[j]
ECG[k]	X	X		X		X		X	X
Vital signs[l]	X	X		X		X		X	X
Diary dispensing/ instruction/review/ collection[m]	X	X	X	X	X	X	X	X	X
Diary completion	◄	———	———	———	———	———	———	———	
Concomitant medications	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X
Study drug dispensing/accountability and reconstitution instruction[n]		X		X		X		X	X
TSQM[o]		X		X		X		X	

a Signing of informed consent may occur in advance of the screening visit, which is defined as the visit where site-conducted screening procedures are performed. Informed consent for the observational substudy may be obtained at the follow-up visit or earlier.

b *Screening telephone contact*: Subjects are instructed to contact the site as soon as they become aware of the onset of symptoms of pain or swelling associated with an HAE attack during the screening period. The on-call Investigator (or designee) will review the subject's symptoms by phone and confirm the date of the call. The Investigator may fill out a form to document the conversation. Approximately 4 hours after the initial call, the subject will again contact the on-call Investigator as is expected during the study.
Attack 1, 2, 3 contact: Subjects are instructed to contact the on-call Investigator (or designee) as soon as they become aware of the onset of symptoms of pain or swelling associated with a potentially protocol-qualified HAE attack. The on-call Investigator (or designee) will review the subject's symptoms by phone and confirm that they constitute an acute attack that qualifies for treatment with study drug, including ensuring that the subject is in an environment that he/she deems suitable for completion of the timed diary. The Investigator will fill out a form to document the conversation. Following treatment of the attack, the subject will again contact the on-call Investigator (or the Investigator will contact the subject) at least 4 hours after treatment with study drug to review the subject's response to treatment and to confirm adequate documentation of the attack in the Diary. The on-call Investigator (or designee) will call

the subject if the subject has not contacted the on-call Investigator (or designee) within 4-5 hours of the initial phone call. A follow-up visit to the clinic will be scheduled. Sites must attempt to contact subjects every 7 days from the last clinic visit to inquire about the occurrence of an attack.

c Clinic visits are scheduled for Screening, Baseline and 10 to 14 days following the first and second attack treated with study drug. The Post-Attack 3 visit suffices as the end of study visit and will be held approximately 16 days after the third attack. Study drug cannot be authorized for administration for at least 14 days from a previously treated attack.

d Weight only.

e Analytes to be measured can be found in Table 6.

f Follicle-stimulating hormone will be measured in women declaring themselves postmenopausal ≤ 2 years.

g A serum pregnancy test will be administered to women of childbearing potential or who are postmenopausal ≤ 2 years at screening; all other pregnancy tests performed during the study may be urine pregnancy tests (for women of childbearing potential only).

h Safety laboratory parameters and urinalysis testing as described in Table 6.

i Randomization to a treatment sequence should occur prior to or during the Baseline visit, following confirmation of eligibility and Sponsor approval.

j Post-baseline, physical examinations will be targeted to reported signs and symptoms.

k ECGs will be captured as single assessments. Any scheduled blood draws should occur after obtaining the ECG. Subjects should rest quietly for 10 minutes in a supine position prior to ECGs being performed.

l Vital signs include measurement of heart rate, blood pressure and temperature.

m Diaries will be dispensed at Screening, Baseline, and Post-Attack Visits 1 and 2. The Investigator (or designee) will provide diary instruction at Screening and will review diary entries on an ongoing basis. During each visit, any issues warranting diary re-education must occur on an as-needed basis. The completed diary will be collected at Baseline and Post-attack Visits 1 to 3. For subjects participating in the observational substudy, a diary will be dispensed at the Post-Attack 3 visit.

n Subject will be dispensed study drug for self-administration at Baseline, Post-Attack 1 visit and the Post-Attack 2 visit. Reconstitution and dosing instructions will be reviewed with the subject. Accountability will be conducted at the Post-Attack visits.

o At baseline, the TSQM will be completed in reference to the subject's currently used acute attack medication prescribed/authorized by their HAE treater; at each subsequent study visit, the TSQM will be completed in reference to the attack previously treated with study drug.

Table 5. Schedule of Assessments for Optional Observational Substudy

	Post-Attack 3 Visit	Week 4 of Observational Period[a]	Week 8 of Observational Period[a]	Week 12 of Observational Period[a]
Informed consent[b]	X			
Telephone contact[c]		X	X	X
Clinic visits	X			
Diary dispensing/instruction/review/collection[d]	X	X	X	X
Diary completion		◄———	———	———►
AE assessment	X	X[e]	X[e]	X[e]

a The 12-week observational period begins from dispensation of HAE diary for recording of all attacks after completion of the Post-Attack 3 visit.
b Signing of informed consent for the optional observational study may occur at the Post-Attack 3 visit or any time prior to this visit. Subjects will be asked to participate in the substudy following completion of Post-Attack 3 visit if approved by the Sponsor.
c During the substudy, subjects will be primarily contacted via telephone; however, a clinic visit is allowed to replace the telephone contact if warranted.
d Diaries to record details of all HAE attacks occurring after the Post-Attack 3 visit will be dispensed at the Post-Attack 3 visit and as needed thereafter. Completed diaries will be collected from the subject (in-person or via post) approximately every 4 weeks. The Investigator (or designee) will provide diary instruction at the Post-Attack 3 visit and will review diary entries upon collection for correct completion and follow-up with the subject as needed.
e Only AEs assessed as possibly, probably or definitely related to the previously taken study drug administered will be recorded.

10.3. Study Visits

10.3.1. Screening

Prospective subjects should be screened within 35 days prior to baseline.

Written informed consent 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 are performed.

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

- Review of inclusion and exclusion criteria
- Review of HAE attack frequency documentation
- HAE, medical, and medication history
- Complete physical exam

- 12-lead ECG
- Height/weight/body mass index (BMI) estimation
- Vital signs (blood pressure, heart 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, C4 and C1 INH functional level, FSH (for women who declare that they have been postmenopausal ≤ 2 years)
- Urine collection for urinalysis and drugs of abuse screen
- Recording of AEs and concomitant medications
- Dispensing of HAE attack diary and any applicable subject instruction sheets
- Instructions on procedures to take during at least one HAE attack during the screening period: phoning the on-call Investigator (or designee) at the outset of HAE-associated pain or swelling, completing the diary, and placing a second call to the on-call Investigator (or designee) approximately four hours after the initial call.

All screening procedures are outlined in Table 4 and are described in Section 11.

A subject will be randomized to a treatment sequence at or prior to the Baseline visit. Subject randomization will occur after the subject has been fully determined to be eligible during screening (see Section 9.3.2).

If the Investigator has not received a call for an HAE attack through Day 35 of the screening period, the subject is considered a screening failure. If agreed by the Sponsor or designee, subjects having an attack late in the course of the screening period may prolong the screening period beyond 35 days to allow for randomization and shipment time of study drug to the clinical site, if applicable.

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 with the Sponsor. Any screening ECGs may be repeated if the results suggest operator or machine error. Retesting of specific laboratory tests within the screening period without entirely rescreening a subject is permitted.

A reason for screen failure will be recorded in the screening eCRF for all subjects who do not enter the study.

10.3.2. Baseline

Subjects who meet all study eligibility criteria, who agree to participate, have demonstrated competence in phoning an investigator for an HAE attack and completing an attack diary during the screening period and who are authorized for randomization by the Sponsor will be asked to return for a Baseline visit. Inclusion/ exclusion criteria will be reviewed to ensure continued subject eligibility. Subjects are asked to fast overnight for at least 8 hours prior to the blood draw for laboratory testing.

The following assessments will be completed:

- Review of inclusion and exclusion criteria
- Review of medical history
- Review of concomitant medications
- Administration of the TSQM (the TSQM will be completed in reference to the subject's currently used acute attack medication prescribed/authorized by their HAE treater)
- Weight
- Vital signs (heart rate, blood pressure and temperature)
- 12-lead ECG
- Complete physical exam
- Assessment of any AEs that occurred since the Screening visit
- Urine collection for urinalysis and urine pregnancy test for female subjects of child-bearing potential
- Blood collection for clinical chemistry, hematology, and coagulation
- Blood collection for C1 INH antigen level, C3, CK-MB, Troponin I, and Troponin T
- Study drug dispensing for treatment of an acute HAE attack by self-administration
- Instruction on reconstitution of study drug and administration
- Screening HAE diary collection and review
- HAE diary dispensing for recording Attack 1, daily HAE diary and any applicable subject instruction sheets
- Instructions on treatment of attacks by self-administration with study drug. Subjects should also be taught to record start and stop time and treatment of any additional HAE attacks that occur following the Baseline visit.

10.3.3. Telephone Contacts

Subjects will be instructed to contact site personnel at the first symptom of swelling or pain associated with a potentially protocol-qualified HAE attack, and if treated with study drug, at approximately 4 hours following treatment. If the subject has not contacted the on-call study Investigator (or designee) within 5 hours, the on-call Investigator will call the subject. The on-call Investigator (or designee) will review the treatment and progression of the HAE attack with the subject and document the conversation. Subjects who did not require standard of care at 4 hours will be reminded at the telephone call by the Investigator that they may use standard of care at any time point at their own discretion if not experiencing improvement or who are experiencing progression of the HAE attack. Subjects will also be reinstructed on diary completion. AEs and concomitant medications will also be collected by phone. Exceptions to the return phone call at 4 hours are discussed in Section 11.2.2.

The site staff will schedule a clinic visit within 10 to 14 days after the administration of study drug and remind the subject to bring their HAE attack diary and study drug containers to their next visit.

Sites must attempt to contact subjects approximately every 7 days from the last clinic visit (i.e., after the Baseline visit, Post-Attack 1 clinic visit, and Post-Attack 2 clinic visit) to inquire about the occurrence of an attack if the subject has not contacted the site during this time frame.

10.3.4. Clinic Visits Following Study Drug Administration

Subjects will return to the clinic following the administration of study drug to treat an acute attack. Subjects will attend a total of 3 on-study clinic visits: Post-Attack 1 clinic visit, Post-Attack 2 clinic visit, and Post-Attack 3 clinic visit. After Attack 1 and Attack 2, subjects will return to the clinic 10-14 days after administration of study drug. Subjects will not be authorized to treat a subsequent attack until at least 14 days have elapsed since the last study drug administration. After Attack 3, subjects will return to the clinic for a follow-up visit 16 days after their last use of study drug (visit window permissible up to 19 days).

The following assessments will be performed at each visit:

- Targeted physical examination
- Vital signs (blood pressure, heart rate and temperature)
- 12-lead ECG (including comparison of QTcF to Baseline value)
- Review of concomitant medications and AEs
- Administration of TSQM questionnaire (TSQM will be completed in reference to the attack previously treated with study drug)
- Blood collection for clinical chemistry, hematology and coagulation
- Blood collection for CK-MB, Troponin I and Troponin T
- Urine collection for urinalysis and urine pregnancy test for female subjects of child-bearing potential
- Study drug accountability
- Post-Attack 1 and 2 clinic visits only: dispense study drug
- Collection of subject-completed HAE attack diary and review
- Post-Attack 1 and 2 clinic visits only: HAE diary dispensing for recording Attacks 2 and 3, daily HAE diaries and any applicable subject instruction sheets
- Review/re-education, as applicable, of completion of HAE attack diary, dosing instructions, phone call(s) to investigators (Post-Attack 1 and 2 clinic visits only). Subjects should record start and stop time and treatment of any additional HAE attacks that occur prior to the Post-Attack 3 visit.
- Post Attack 3 visit, for those participating in the optional observational study:

- Signing of informed consent for participation in the optional observational study (consent may be signed prior to this visit)
- Instruct and dispense diary to record details of any HAE attacks that occur

10.3.5. Early Termination Visits

Subjects who discontinue treatment early (i.e., prior to the treatment of 3 acute attacks) must complete an early termination visit as outlined in Section 10.3.5.

Assessments to be performed at this visit are described in Section 11. In the event that there are clinically significant findings from safety assessments that are ongoing at the time of the visit, the subject will be followed at additional unscheduled study visits until the findings are resolved or stabilized at a new baseline.

The following assessments will be performed at the early termination visit:

- Subject weight
- Targeted physical examination
- Vital signs (blood pressure, heart rate and temperature)
- 12-lead ECG (including comparison of QTcF to Baseline value)
- Review of concomitant medications and AEs
- Blood collection for clinical chemistry, hematology, and coagulation
- Urine collection for urinalysis and urine pregnancy test for female subjects of child-bearing potential
- Blood collection for CK-MB, Troponin I and Troponin T
- Study drug accountability
- Review and collection of the diary

10.3.6. Optional Observational Substudy

Subjects who complete the study will be offered an opportunity to participate in an observational substudy at the Post Attack 3 visit. The subjects will provide consent and will record details of all HAE attacks into an HAE diary, dispensed at the Post-Attack 3 visit that occur for approximately 12 weeks.

The following assessments will be performed after the Post-Attack 3 visit:

- Week 4, 8, 12 of the observational period: phone call to discuss completion of the HAE attack diary, collection of completed diaries (in person or via mail) and whether additional diaries are needed. In addition, AEs assessed as possibly, probably or definitely related to study drug will also be collected
- Week 4, 8, 12: review of completed HAE diaries for correctness/completeness

11. ASSESSMENTS

The schedule of procedures/assessments to be conducted is outlined by study day in Table 4 with details on the conduct of the procedures/assessments provided below.

11.1. Investigator-Completed Assessments

Demographic information, including year of birth, sex, race or ethnicity, and medical history will be captured for each subject participating in the study at the Screening visit. Medical history and review of inclusion and exclusion criteria will also be rechecked at the Baseline visit.

Contraceptive methods enabling eligibility will be captured in source documentation at the screening visit.

11.1.1. HAE Medical and Medication History

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

11.1.2. Physical Examination

A full physical examination should be conducted at Screening and Baseline. All subsequent physical examinations may be targeted (i.e., symptom-driven). Genitourinary and breast examinations may be omitted when not required by normal site practice.

11.1.3. Weight/Body Mass Index

For determination of height and weight, subjects should be dressed, without shoes. Body mass index should be calculated using the following formula:

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

11.1.4. 12-lead Electrocardiograms

A standard bedside 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 must 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 postdose ECGs, change from baseline). For all ECGs, the clinical interpretation of the ECG should be recorded directly on a hard copy of the ECGs. Copies of the ECGs may be requested by the Sponsor.

All ECGs will be captured as single assessments.

An ECG should be repeated during the clinic visit if possible for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec for confirmation of the change.

11.1.5. Vital Signs

Blood pressure (systolic and diastolic) and heart 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 will also be obtained at all visits.

11.1.6. Clinical Laboratory Assessments

Blood and urine samples will be obtained per the schedule of events. Individual laboratory tests to be performed are provided in Table 6. Laboratory samples should be obtained in the fasted state.

Laboratory samples will be routinely analysed by a centralized laboratory with the exception of urine pregnancy tests which will be assessed locally at the site. A laboratory reference manual will be provided to the site detailing laboratory kit contents reordering instructions, 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 lab findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings in the opinion of the Investigator should be recorded as an AE and handled as described in Section 12.1.

Table 6. Clinical Laboratory Evaluations

Chemistry	**Hematology**
• Albumin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Bilirubin (total and direct) • Blood glucose (fasting) • Blood urea nitrogen (BUN) • Electrolytes (calcium, sodium, potassium, chloride, phosphorus) • Creatine kinase • Creatinine and calculated creatinine clearance • Gamma-glutamyltransferase (GGT) • Lactate dehydrogenase (LDH) • Total serum protein • Uric acid • Amylase *reflex to lipase for amylase > 2x ULN	• Hemoglobin • Hematocrit • Erythrocytes • MCH • MCHC • MCV • White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) • Platelets

	Pregnancy Test
	Serum (screening) and urine (other scheduled visits) βHCG for women of childbearing potential only
	Drug screen
Urinalysis	• Amphetamines • Barbiturates • Benzodiazepines • Cocaine • Opiates • Methamphetamine • Ecstasy
• Specific gravity • Blood • Bilirubin • Glucose • Leukocytes • Ketones • Nitrates • pH • Protein • Urobilinogen • Microalbumin to creatinine ratio • Microscopy if dipstick is abnormal	**Additional Tests**
Coagulation	• Follicle-stimulating hormone (FSH; screening) for women postmenopausal ≤ 2 years • Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody (screening) • Troponin I • Troponin T • CK-MB • C1 INH function • C4 • C1 INH antigen • C3
• Prothrombin time (PT) and international normalized ratio (INR) • Activated partial thromboplastin time (aPTT)	

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

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

11.1.7. Screening for Human Immunodeficiency Virus, Hepatitis B, and Hepatitis Serology

Blood samples will be collected at screening for serologic testing for evidence of HIV, chronic hepatitis B, and hepatitis C infection. Subjects with a positive Hepatitis C antibody but have no evidence for HCV RNA upon reflex testing are eligible for study participation.

11.1.8. Pregnancy Testing

Follicle stimulating hormone 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.

A serum pregnancy test will be administered to women of childbearing potential or who are postmenopausal ≤ 2 years at Screening; all other pregnancy tests performed during the study may be urine pregnancy tests (for women of childbearing potential only). A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test.

11.1.9. C1 INH Testing

C1 INH functional level and C4 will be measured at screening to establish the laboratory diagnosis of HAE Type 1 or 2. These tests should be drawn at least 3 days after a previous dose of C1 INH.

Should C4 be normal, as is the case in a small percentage of subjects with HAE, C4 may be drawn during an attack or the SERPING-1 gene may be analyzed and the subject confirmed eligible if a known mutation associated with HAE Types 1 or 2 is identified.

C1 INH antigen level will be drawn for demography on enrolled subjects at the Baseline visit.

11.1.10. Other Laboratory Assessments

Troponin I, Troponin T and CK-MB will be measured in this study at all time points beginning at Baseline (i.e., Post-Attack 1, 2, and 3 clinic visits and early termination visit [if applicable]). C3 levels will be taken at Baseline on all subjects and will only be drawn on-study if required for AE assessment (see Section 11.1.11).

11.1.11. Rash Assessment

Because of the potential for a study drug-related rash (see Section 5.3), 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.

Subjects should be medically evaluated within 24 to 36 hours of awareness of any treatment-emergent rash, regardless of grade or causality, and the site must inform the Sponsor medical monitor at the time the rash is diagnosed via the Event of Special Interest Form (Section 12.1.5.1). In the event the site is notified of a rash on the weekend or holiday, the medical evaluation and Sponsor notification can be performed on the next working day.

The following assessments must be completed for all subjects with a rash, regardless of causality, as soon as logistically possible:

- Full dermatological exam to include the anatomical location(s) of the rash, vital signs, and mucosal examination. The notes documenting the examination should include detailed description of the rash, presence or absence of blistering and if present, its extent and presence or absence of mucosal involvement and if present, its extent and any other associated abnormal physical findings.

- High resolution photographs taken to provide both detail regarding the rash and details regarding the extent of the rash. Cameras must be able to provide clear images taken in close proximity to the skin. The picture should include a ruler (centimeter) for scale. Every attempt to protect subject anonymity should be made.
- All detailed clinical information regarding the rash, examination, clinical and laboratory assessments, treatment and interpretation of the event needs to be reported on an SAE/Event of Special Interest Report form as per Section 12.1.5.1.

The following assessments must be completed for all subjects with a rash assessed as possibly, probably, or definitely related to study drug by the Investigator as soon as logistically possible:

- Blood taken for clinical chemistry, hematology including differential, and C3 level. Table 6 outlines the clinical chemistry and hematology analytes to be assessed.
- Urine sent to local laboratory for urine eosinophils (if evaluation is available locally)
- Subjects will also be requested 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 1-3 months after occurrence of the rash. Information on PBMC collection, processing and shipment will be communicated to sites prior to sample collection.

11.2. Subject-Completed Assessments

11.2.1. Treatment Satisfaction Questionnaire

To assess treatment satisfaction of the medication a TSQM will be administered once at Baseline and at each clinic visit following treatment of an acute attack with study drug. At Baseline, the TSQM will be completed in reference to the subject's currently used acute attack medication prescribed/authorized by their HAE treater; at each subsequent study visit, the TSQM will be completed in reference to the attack previously treated with study drug

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.

11.2.2. HAE Attack Diaries and Phone Calls

11.2.2.1. Screening through Post-Attack 3 Visit

The Sponsor will supply an attack diary for subject documentation of one HAE attack occurring during the screening period and for each of 3 study-drug treated attacks. To ensure compliance with on-study requirements in treating an appropriate attack with study drug after the Baseline visit, subjects will be required to complete timed attack details of at least 1 HAE attack during the screening period after approval of the on-call Investigator (or designee). Subjects will also be required to complete the details of three HAE attacks that are treated with study drug, each after approval from the on-call Investigator (or designee).

All attacks for which acute attack diaries are completed by the subject will be included in the eCRF.

Apart from the principal Investigator at each clinical site, the Sponsor will approve on-call study Investigators (or designees). Approval will be based upon demonstration that the proposed on-call Investigator (or designee) ordinarily has oversight of the care of HAE patients.

The diaries will be composed of a questionnaire and 3-component VAS on a 100 mm scale for abdominal pain, cutaneous pain, and cutaneous swelling. The questionnaire includes queries about symptom location, severity/limitation of activities and a global assessment that qualitatively compares HAE symptomatology against that experienced prior to study drug intake. The diaries will include questions/VAS to be completed prior to study drug administration and 1, 2, 3, 4, approximately 8 and at 24 hours post study drug intake (or post call for a screening attack). All medications used from the time of symptom onset through 24 hours postdose will also be captured in the diary, including standard of care treatment for acute attacks and any symptomatic treatments such as analgesics.

At the Screening, Baseline, and Post-Attack 1 and Post-Attack 2 visits, attack diaries will be dispensed and the subject will be instructed on completing the diary (written instructions may also be provided). In addition, subjects will be informed of what is expected regarding attacks likely to be approved for study drug treatment by the Investigator and also administration of standard of care rescue medication on a continuing basis.

At the Baseline and Post-Attack 1, 2, and 3 visits, sites must collect and review the diary for completeness and plausibility; any re-education required to ensure correct diary completion will be performed. Study staff are not permitted to make any entries into the diary regarding HAE attack information.

Diary instruction will include demonstration on how to properly complete the VAS, review of all questions for understanding, and those questions that allow more than one response. Subjects must be instructed to complete all questions unless medically prevented from doing so or the subject is sleeping after a treated attack, and the importance of completing the diary at the scheduled time points must be stressed.

Following the Baseline visit and prior to the Post-Attack 3 visit, subjects will be asked to record the start and stop time of all HAE attacks that occur and any standard of care administration.

11.2.2.1.1. Documented Screening Attack

The documented screening attack is intended as a practice for on-study requirements in the identification, approval, and documentation of an HAE attack treated with study drug. As such, the steps required in identifying, approving and documenting the attack should be as close to as would be expected or required after the Baseline visit. All steps must take place (initial call for HAE symptom review, HAE attack diary documentation, return call) to assess a subject's understanding and compliance with the study requirements. The Investigator (or designee) may request that the subject complete more than one documented screening attack if he or she is not satisfied that the subject has demonstrated compliance with the procedures required for treating and documenting attacks.

At the first symptom of swelling or pain associated with at least one HAE attack occurring during the Screening period, the subject will phone their on-call study Investigator (or designee) who will review the subject's symptoms by phone. It is preferable that the subject call the Investigator within one hour of symptoms and that the attack is one that is protocol-qualified

on-study (see Section 11.2.2.1.2). Subjects will not be asked to avoid standard of care attack treatment for four hours from the phone call.

During the documented Screening HAE attack, subjects will record the occurrence and details of the HAE attack in the diary immediately after the call to the Investigator as well as any medications used since the onset of symptoms. Subjects will fill out the diary questionnaire and a 3-component VAS at 1, 2, 3, 4, approximately 8 and at 24 hours after the phone call. Any questions regarding study drug administration may be left blank.

The subject will be asked to phone the on-call study Investigator (or designee) at least 4 hours after the phone call to review diary completion. The on-call study Investigator will call the subject if they have not heard from the subject within 5 hours of their initial phone call.

An exception to the requirement of a phone call follow-up at 4 hours may be made if the 4 hour timepoint occurs during the typical period of sleep and the subject is asleep at 4 hours post-study medication. In this case, the subject will be required to call the on-call Investigator (or designee) upon waking. The on-call Investigator (or designee) and subject may agree at the initial attack approval phone call that the subject will try to rest to avoid an Investigator call 5 hours later. For subjects who were sleeping during diary-required timepoints after the phone call, only the 4 hour timepoint in the diary questionnaire is required to be completed at the time they awake and any medications taken.

The on-call Investigator (or designee) will document the details of both calls.

11.2.2.1.2. On-Study Attacks

After the Baseline and Attack 1 and 2 visits, the subject will phone their on-call study Investigator (or designee) at the first symptom of swelling or pain associated with a potentially protocol-qualified HAE attack. The Investigator (or designee) will review the subject's symptoms and confirm that they constitute an acute attack that qualifies for treatment with study drug, including ensuring that the subject is in an environment that he/she deems suitable for completion of the timed diary.

Protocol-qualified attacks approved for treatment must meet all of the following:

- have pain and/or swelling associated with an HAE attack reported as a symptom
- subject has contacted Investigator within approximately 1 hour of onset time of HAE pain and/or swelling
- not involve HAE pain or swelling in the throat or mouth. Such attacks should be treated using the subject's standard of care acute attack treatment (e.g., C1 INH, icatibant).
- not be an abdominal attack that has already resulted in vomiting. Such attacks should be treated using the subject's standard of care acute attack treatment (e.g., C1 INH, icatibant).
- have an identifiable onset time, with the exception that abdominal attacks with an onset during sleep may be permitted for study drug treatment. Onset time for approved abdominal attacks will be time the subject woke up with symptoms.

Peripheral attacks starting with an onset during sleep are not to be authorized for study drug treatment.

- occur during an HAE symptom-free period as follows:
  - if the previous HAE attack was treated with a bradykinin B2 receptor antagonist (i.e. Firazyr) OR treated with human recombinant C1 INH (i.e. Ruconest) OR any non-targeted therapy (i.e. pain medication, anti-spasmodic, anti-emetic, tranexamic acid) OR was not treated with any medication: new attack can be treated with IMP if has been 48 hours since the complete resolution of all symptoms of the previous HAE attack AND the Investigator believes it is a new (de novo) attack.

    OR

  - if the previous HAE attack was treated with plasma-derived purified C1 INH (i.e. Berinert or Cinryze) OR plasma preparation (fresh frozen or solvent detergent plasma): new attack can be treated with IMP if it has been 96 hours since the complete resolution of all symptoms of the previous HAE attack
- occur at least 96 hours after complete recovery from a procedure or injury
- occur at least 14 days from a previous dose of study drug

Following confirmation by the Investigator that an attack may be treated with study drug, subjects should reconstitute and take study drug almost immediately (within 5 minutes) following the approval phone call, with the goal for subjects to take study drug within or approximately one hour of the onset of symptoms. Subjects will be asked to avoid food for at least one hour after taking study drug and will be asked to withhold standard of care attack treatment for four hours from administration of study drug (see Section 9.2). If symptoms are progressing rapidly or if intraoral symptoms occur, subjects may treat the attack with their standard of care attack medication prior to 4 hours.

The subject will be asked to phone the on-call study Investigator (or designee) at least 4 hours after taking study medication (or earlier if they have any concerns over the course of their symptoms) to review their response to study drug and diary completion, unless they are sleeping. The on-call study Investigator will call the subject if they have not heard from the subject within 5 hours of their initial phone call. Subjects who did not require standard of care at 4 hours will be reminded at the telephone call by the Investigator that they may use standard of care at any time point at their own discretion if not experiencing improvement or who are experiencing progression of the HAE attack.

An exception to the requirement of a phone call follow-up at 4 hours may be made if the 4 hour timepoint occurs during the typical period of sleep and the subject is asleep at 4 hours post-study medication. In this case, the subject will be required to call the on-call Investigator (or designee) upon waking. The on-call Investigator (or designee) and subject may agree at the initial attack approval phone call that the subject will try to rest to avoid an Investigator call 5 hours later.

Subjects will record the occurrence and details of the HAE attack immediately prior to treating the approved HAE attack with study drug. Subjects will also fill out the diary questionnaire and a 3-component VAS at 1, 2, 3, 4, approximately 8 and at 24 hours after record of study drug

administration. All medications taken after study drug administration through 24 hours will also be captured. For subjects who were sleeping during these timepoints after administration of study drug, subjects are only required to fill out the 4 hour timepoint in the diary questionnaire and any medications taken at the time they awake.

The on-call Investigator will document the details of both calls involving approval of and follow-up after study drug treatment. If duplicate data is collected on this form and in the HAE diary, the HAE diary will always be source documentation. In the event that a diary field is empty when reviewed subsequently at the Post-Attack 1, 2, or 3 visit, the details of the Investigator form may serve as source documentation.

11.2.2.2. Optional Observational Substudy

Subjects who complete randomized dosing and who provide consent will be offered an opportunity to participate in an observational substudy. Consenting subjects will be provided an HAE attack diary at the Post-Attack 3 visit and will record details of all HAE attacks that occur for approximately 12 weeks. Resupply of diaries will be provided as needed. Completed diaries should be returned to the site, in person or via mail, approximately every 4 weeks.

Subjects will be provided further instruction on completing the diaries at home for any attacks that occur for subsequent 12 weeks. Subjects will record the occurrence and details of each HAE attack in the diary, beginning from the time of onset of pain or swelling associated with an HAE attack. Subjects will fill out the diary questionnaire and a 3-component VAS at 1, 2, 3, 4, approximately 8 and at 24 hours after the attack started, as well as any medications used since the onset of symptoms.

During Weeks 4, 8, 12 of the observational period, the Investigator (or designee) will phone the subject to discuss completion of the HAE attack diary, collection of completed diaries and whether additional diaries are needed. In addition, AEs assessed as possibly, probably or definitely related to study drug will also be collected. After receipt of the Week 4, 8, 12 diaries, the Investigator (or designee) will review completed HAE diaries for correctness/completeness.

12. ASSESSMENT OF SAFETY

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. Full details on recording and reporting AEs are provided in Section 12.1.2.

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/ IMP 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 (e.g, requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be AEs.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 12.1), 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

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, unless they meet the criteria for a SAE. HAE attacks and associated symptoms will be recorded in the subject's diary. The events that may trigger a HAE attack such as an infection or trauma are considered AEs and should be reported as such.

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.

Adverse events are designated as “nonserious” or “serious.”

12.1.1.2. Serious Adverse Event

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

- Death
- Is life-threatening (subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (i.e., 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.

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 12.2.2). 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.

BioCryst also considers abortions, whether elective or spontaneous, fetal demise, and still births as SAEs.

12.1.1.3. Adverse Events of Special Interest

For this protocol, nonserious treatment-emergent rashes will be considered events of special interest. This event in and of itself will not be considered serious unless it meets the criteria above. Events of rash regardless of severity or suspected relationship to study drug/IMP must be reported to the Sponsor Medical Monitor as described in Section 12.1.5.1. Management of rash possibly, probably or definitely suspected to be related to study drug/IMP, 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 until the post –attack 3 visit of the study drug phase. All AEs and SAEs are to be reported on the AE CRF. For subjects who continue in the optional observational substudy, **only** those AEs deemed possibly, probably or definitely related to the previously taken study drug need to be recorded on the AE CRF. These AEs will be recorded in the same manner and include the same information as AEs during the study phase.

AEs should be documented on eCRFs 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 in the main study, 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/IMP (see Section 12.1.3 for AE grading). For all Grade 3 and 4 events or events deemed possibly, probably or definitely related to use of study drug/IMP, 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 fax or email, and entering the event onto the AE eCRF 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/IMP in clinical trial.

12.1.3. Definition of Severity

All AEs will be assessed (graded) for severity and classified using the Division of Microbiology and Infectious Diseases (DMID) criteria for grading AEs (see Appendix 15.1). 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.

12.1.4. Definition of Relationship to Study Drug (Investigational Medicinal Product)

The Investigator or medically qualified designee must review each AE and make the determination of relationship to study drug/IMP 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/IMP 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/IMP 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 study drug/IMP administration, abates upon discontinuation of the study drug/IMP, 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/IMP administration, follows a known or suspected response pattern to the study drug/IMP, is confirmed by improvement upon stopping the study drug/IMP (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 or fax using the SAE/Event of Special Interest report form within 24 hours of the Investigator's awareness of the SAE. In addition, all SAEs must be recorded on the AE eCRF 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 or fax numbers:

Sylvia Dobo, MD, Medical Monitor

Cell number (24 hours) +1 773-304-8942

Email: safety@biocryst.com; sdobo@biocryst.com

Safety Fax: +1 919-226-5888

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

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

Investigators or designees at each site are responsible for retaining copies of all suspected unexpected severe adverse reaction (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 IEC and central IRBs.

BioCryst shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to all competent authorities, and to the IECs, and central IRBs, in any case no later than 7 calendar days after knowledge by BioCryst of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned and to the IECs/IRBs concerned as soon as possible but in no case later than 15 calendar days of first knowledge by BioCryst. BioCryst or designee shall also inform all Investigators.

12.1.5.1. Reporting Events of Special Interest

Although not an SAE, all events of treatment-emergent rash regardless of severity or relationship to study drug/IMP must be reported by phone or email to the Sponsor Medical Monitor and in writing via email or fax using the SAE/Event of Special Interest report form within 24 hours of the Investigator's assessment of the event. In addition, the event must be recorded on the AE eCRF in real time. All additional follow-up evaluations of the event must be reported to BioCryst or its designee on the form as soon as they are available. The SAE/Event of Special Interest report form should be sent to the following email addresses or fax numbers:

Sylvia Dobo, MD, Medical Monitor

Cell number (24 hours) +1 773-304-8942

Email: safety@biocryst.com; sdobo@biocryst.com

Safety Fax: +1 919-226-5888

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 event. In addition, the report form will allow a full clinical description and information regarding the evaluation that cannot be reported in the EDC.

The follow-up report should contain information about the clinical course, medical evaluation, photographs, biopsy, and laboratory results.

12.1.6. Pregnancy

Any female subject who becomes pregnant during the course of the study should have study drug/IMP 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 study partners 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

It is the responsibility of the Sponsor to notify the competent authority of any serious breach 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. Emergency Procedures

Access to study drug/IMP assignment will be available immediately if the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety. In addition, the blind may be broken 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 unblinding of the subject; however, the final decision to break the treatment code in emergency situations resides solely with the Investigator. Detailed instructions for immediate unblinding in the interactive web response system used by the site to randomize a subject will be provided.

12.2. Toxicity Management

The Investigator (or qualified designee) will grade clinically significant events and laboratory abnormalities (if considered AEs) 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/IMP discontinuation, unless such a delay is not consistent with good medical practice.

In the event that 2 subjects experience similar Grade 3 or 4 treatment-emergent laboratory abnormality or AE that is suspected to be IMP related as determined by the Investigator and not otherwise physiologically explained, a DMC meeting will be immediately convened by the Sponsor. 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

Management of rash should be based on best medical practice and address the subject's presentation. If a subject experiences a Grade 3 or4 rash suspected to be due to study drug/IMP, the subject should have study drug/IMP stopped as per Section 8.3.2.2.

In the event that 2 subjects experience a rash that is suspected to be study drug/IMP related as determined by the Investigator and not otherwise physiologically explained, a DMC meeting will be convened by the Sponsor. 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.

Special evaluation of drug rash is required as per Section 12.1.1.3 and special reporting is described in Section 12.1.5.1.

12.2.2. Overdose

To date there is no experience with overdose of oral BCX7353. Only one dose of study drug is provided to each subject at a time, so overdose is not of concern in the study. The maximum dose to be administered in the current study is 750 mg. Single doses of up to 1000 mg, 7 days of

dosing up to 500 mg/day, and 14 days of dosing with 350 mg/day revealed no clinically significant safety concerns in healthy subjects in Study BCX7353-101.

12.3. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will review safety data on an as needed basis. The DMC will be convened upon meeting the criteria listed in Section 12.2 or at other times as requested. A separate DMC charter, maintained in the trial master file, will describe membership, roles, timing of DMC review, and responsibilities of the DMC members.

13. STATISTICS

13.1. Sample Size Considerations

Given the exploratory nature of this study, the sample size was not chosen based on statistical considerations, but rather to provide preliminary safety and efficacy data on BCX7353 in subjects with HAE when treated in accordance with this study.

13.2. Hypothesis Testing

An analysis may be conducted during Part 1, using the Heybittle-Peto boundary for significance, to determine whether there is a clinically important treatment effect with BCX7353. The endpoint for this analysis is the proportion of subject attacks with a stable or improved VAS at 4 hours postdose in the full analysis set. The null hypothesis evaluated (H_0) is that the proportion of subject attacks treated with BCX7353 with stable or improved VAS at 4 hours postdose is the same as proportion of subject attacks treated with placebo with stable or improved VAS at 4 hours postdose (i.e., no treatment difference). The alternative hypothesis (H_1) is that the proportion of subject attacks treated with BCX7353 with stable or improved VAS at 4 hours postdose is greater than the proportion of subject attacks treated with placebo with stable or improved VAS at 4 hours postdose (i.e., treatment difference).

13.3. Statistical Methods

A detailed statistical analysis plan (SAP) will be developed and finalized prior to database lock. The SAP will describe the methods of analyses/summaries, including all endpoints, time points, populations, missing data, etc. Any deviation from the analyses outlined in the SAP will be described in the final clinical study report.

13.3.1. Analysis Populations

The analysis populations are defined below.

13.3.1.1. Full Analysis Set

The Full Analysis Set (FAS) population will include all subjects/subject attacks treated. Subjects/subject attacks will be analyzed according to the treatment randomized. The FAS population will be the primary population for efficacy analyses.

13.3.1.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study drug. Subjects will be analyzed according to the treatment received. This population will be used for all analyses of accountability, demographics, and safety.

13.3.2. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race or ethnicity, height at screening, weight at screening, and BMI at screening will be summarized by treatment sequence using descriptive statistics.

Disease and treatment characteristics including years since initial diagnosis of HAE, number of days since last HAE attack, documented attack frequency, and pattern of on-demand therapy will be summarized by treatment sequence using descriptive statistics.

Subject disposition will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation also will be presented. A tabulation of the number of subjects exposed to study drug will be presented.

13.3.3. Analysis of Efficacy Variables

As this is the first study of BCX7353 in the treatment of acute attacks, the analysis of attack resolution will be described in a number of ways which will be fully detailed in the SAP. The endpoint that may be utilized to first examine efficacy is the proportion of subject attacks with a stable or improved VAS at 4 hours postdose in the full analysis set. The number and proportion of subject attacks with a stable or improved VAS at 4 hours postdose will be summarized by treatment group. Attacks that require standard of care medication prior to the 4 hour time point will be considered as failure (i.e., not having a stable or improved VAS at 4 hours postdose). To assess treatment differences, a logistic mixed effect model including treatment, period and sequence as fixed effects, and subject within sequence as a random effect will be utilized. Other binary endpoints will be analyzed in a similar manner.

The 3-symptom composite VAS and its associated changes from baseline will be summarized for each attack by time point and treatment group. Treatment differences in the change from baseline values at each time point will be assessed with a mixed effect linear model with factors for treatment, period, sequence, and baseline value as fixed effects, and subject within sequence as a random effect. Analyses of other continuous variables will be analyzed in a similar manner.

The time to use of standard of care medication will be estimated using the method of Kaplan-Meier. For each attack, subjects who do not use standard of care medication will be censored at the end of the attack observation period (i.e., 24 hours). Treatment differences will be assessed using an appropriate proportional hazards model. Analyses of other type to event variables will be analyzed in a similar manner.

Location of attacks, duration of attacks, and number of acute HAE medications administered will be summarized for each treatment group.

13.3.4. Analysis of Safety Variables

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. Any event reported on the subject's study record that occurs on or after the initiation of study drug within a given treatment period is defined as treatment emergent. Additionally, it is assumed that an AE that is reported to have started on the day of subject dosing to treat an attack without an associated onset time may have occurred after the initiation of study drug. Hence, AEs occurring on the day of subject dosing to treat an attack with no associated onset time will be assumed to be treatment emergent. AEs will be attributed to the corresponding treatment assignment of the corresponding treatment period. The occurrence of treatment-emergent AEs will be summarized by treatment group using MedDRA preferred terms, system organ classifications, and severity. Separate summaries of treatment-

emergent SAEs and AEs considered to be related to study drug will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries of vital signs, weight, ECG parameters, and clinical laboratory results will be presented separately for each treatment group. Laboratory abnormalities will be graded according to the DMID Adult Toxicity Table (Publish Date: Draft, November 2007, see Appendix 15.1). Any graded abnormality that occurs following the initiation of study drug and represents at least 1-grade increase from the baseline assessment for a given treatment period is defined as treatment emergent. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized by treatment group.

Clinically significant abnormal morphological ECG findings will be summarized by treatment group.

Physical examination results will be presented in listings.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary. These data will be summarized by treatment group.

13.3.5. Subject Satisfaction Analyses

The change from baseline in the TSQM global satisfaction score as well as effectiveness, side effects, and convenience subscales will be summarized. Data will be listed, summarized, and appropriately tested for differences between active treatment and placebo and between active and current acute therapy utilized at baseline.

13.3.6. Interim Monitoring and Statistical Stopping Rules

The study's design is intended to identify the dose or doses of BCX7353 shows an efficacy benefit over placebo. Dosing in the study will commence at the 750 mg dose level and lower doses (500 mg and 250 mg) will be evaluated in successive parts of the study.

After 12 subjects have completed Part 1 of the study, the proportion of subject attacks with a stable or improved VAS at 4 hours postdose may be estimated for BCX7353 750 mg and placebo by the study statistician using the analysis method described in Section 13.3.3. A test of no treatment difference is considered statistically significant with $p < 0.001$ (i.e., Haybittle-Peto boundary is crossed). Treatment differences may also be assessed using available data in Parts 1, 2 and 3 in order to plan for future studies.

14. STUDY ADMINISTRATION

14.1. Regulatory and Ethical Considerations

14.1.1. Regulatory Authority Approvals

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH E6); EMA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki. In addition, the study will be conducted in compliance with all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

14.1.2. Institutional Review Board and Ethics Committee Approvals

Before initiation of the study at an investigational site, the protocol, the ICF, the subject information sheet (if applicable), and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study must be obtained before the study center can be initiated or the study drug 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 substantial modification of the protocol, the ICF, the written information provided to subjects, and/or other procedures. After the protocol has been submitted, any amendment must be agreed by the Investigator after discussion with the Sponsor and will be formally documented. All substantial amendments will be submitted for an opinion as required by current regulations.

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 to be completed once the last subject completes their 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

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 policy.

If an ICF is updated as a result of a substantial protocol amendment, the new IRB/IEC-approved versions will be used to re-consent currently enrolled subjects and must be provided to additional subjects prior to their entry into the study.

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. Payment to Subjects

Reasonable compensation to study subjects may be provided if approved by the IRB/IEC responsible for the study at the Investigator's site.

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 the eCRF is 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 Investigator and their relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.3. Quality Assurance

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

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

14.4. Study Termination and Site Closure

Formal stopping rules for individual subjectsare listed below and also defined in Section 8.3.2.

- Intercurrent illness or emergence of a new illness/medical condition that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Subsequent determination that inclusion/exclusion criteria were not met
- Emergence of any laboratory abnormality or AE that in the judgment of the Investigator compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest due to an altered risk/benefit profile
- Subject noncompliance with study drug or to the protocol
- Discontinuation at the request of the Sponsor, competent authorities in the Member State(s) concerned, or the institutional review board (IRB)/independent ethics committee (IEC)
- A subject has a QTcF > 500 msec (confirmed on repeat testing)
- A subject has a QTcF increase of more than 60 msec (confirmed by repeat ECG) from the value obtained predose at the baseline visit
- A subject has a study drug related Grade 3 or 4 rash as described by the DMID criteria "Skin-mucocutaneous"

Overall, the Sponsor may suspend enrollment into the study, suspend treatment of ongoing subjects, or terminate the study to ensure that subjects' safety and welfare are protected.

The entire study, or individual sites, will be terminated for any of the following reasons:

- Request of a Competent Authority
- Recommendation of the independent DMC
- Inaccurate or incomplete data recording
- Non-compliance with study protocol

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

14.5. Records Retention

To enable evaluations and/or audits from regulatory authorities or BioCryst, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and medical/hospital records), all original signed ICFs, all eCRFs, and detailed records of study drug accountability and treatment disposition. The records should be

retained by the Investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

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

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

14.6. Confidentiality of Information

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

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

14.7. Study Publication

All data generated from this study are the property of BioCryst and shall be held in strict confidence along with all information furnished by BioCryst. Except as provided through written agreement between BioCryst, independent analysis and/or publication of these data by the Investigator or any member of his/her staff is not permitted without prior written consent of BioCryst. Such consent will not be withheld unreasonably. BioCryst is in agreement with the principle of full disclosure of clinical trial results.

15. REFERENCES

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APPENDICES

15.1. DMID Adult Toxicity Table (Publish Date: Draft November 2007)

https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf

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

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ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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CHEMISTRIES (continued)

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

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

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

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

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

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

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

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

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SKIN

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

SYSTEMIC

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