BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-203

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF BCX7353 AS A PREVENTATIVE TREATMENT TO REDUCE THE FREQUENCY OF ATTACKS IN SUBJECTS WITH HEREDITARY ANGIOEDEMA

EudraCT Number: 2016-001272-29

Version 5.0 : 05 July 2017

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

CONFIDENTIAL

Protocol Number:	BCX7353-203
Study Title:	A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema
IND Number:	N/A
EudraCT No.	2016-001272-29
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: (919) 226-5860 Cell: (773)304-8942 Email: sdobo@biocryst.com
Principal Investigator:	Dr. Emel Aygören-Pürsün University Hospital Frankfurt Goethe University (Universitätsklinikum Frankfurt Klinik für Kinder-und Jugendmedizin Angioödem-Ambulanz Theodor-Stern-Kai7 D-60596 Frankfurt, Germany Tel: +49-69-63016334 Email: Aygoeren-Puersuen@em.uni-frankfurt.de
Sponsor Project Manager:	Desiree Clemons Clinical Study Manager BioCryst Pharmaceuticals Office: + 1 919-226-5836 Email:dclemons@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: 25 March 2016 Version 1.1: 27 April 2016 (UK-Specific) Version 1.1 (also effective for Switzerland): 15 July 2016 Version 2.0: 23 September 2016 Version 3.0: 30 December 2016 Version 4.0: 21 March 2017 (Non-Substantial) Version 5.0: 05 July 2017

1.1. Protocol Approval Signature Page

Protocol No: BCX7353-203

Protocol Title: A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema

Date: Version 5.0: 05 July 2017

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

William Sheridan JUL 5, 2017

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

06 July 2017

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

1.2. Clinical Study Protocol Agreement

Protocol No: BCX7353-203

Protocol Title: A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics, of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema

Date: Version 5.0: 05 July 2017

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:
(+)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride

Title of Study:
A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema

Study Number: BCX7353-203

EudraCT Number: 2016-001272-29

Study center(s): Multiple centers in Europe, Australia and Canada

Principal Investigator: Dr. Emel Aygören-Pürsün

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: June 2016 Estimated date last subject completed: March 2018	2

Objectives:

Primary:

- To evaluate the efficacy of once-daily prophylactic BCX7353 at up to 5 dose levels as measured by the number of attacks of hereditary angioedema (HAE) observed in patients with HAE enrolled in each treatment group

Secondary:

- To evaluate the safety and tolerability of BCX7353 over 28 days in subjects with HAE
- To describe the pharmacokinetic (PK) profile of daily BCX7353 in subjects with HAE
- To characterize the anticipated pharmacodynamic (PD) effects of BCX7353 in subjects with HAE
- To characterize the dose-response relationship of BCX7353 in subjects with HAE
- To evaluate effects of BCX7353 on quality of life

Primary Endpoint:

- Number of confirmed HAE attacks

Methodology:

Randomization

Up to 36 subjects with Type 1 or 2 HAE who meet all eligibility criteria are planned to be enrolled in Part 1 of the study and will be randomized in a 1:1 ratio (placebo : active) to receive one of the following treatments:

- Part 1, Treatment Group 1: placebo once per day (QD) orally for 28 days
- Part 1, Treatment Group 2: 350 mg BCX7353 QD orally for 28 days

After 24 subjects have completed through Day 28, there will be an administrative interim analysis of the accrued efficacy data by the Sponsor. If it is desired to more fully characterize the treatment effect of study drug (BCX7353 or placebo) or to verify assumptions made for sizing this proof-of-concept study, additional subjects will be enrolled to complete Part 1 (up to 36). Enrollment into Part 1 will continue until either a decision is made to halt enrollment in favor of opening Part 2 or enrollment reaches 36 subjects in Part 1.

In Part 2, approximately 14 subjects with Type 1 or Type 2 HAE who meet all eligibility criteria are planned to be randomized in a 1:3:3 (placebo:active:active) ratio into 1 of the following 3 treatment groups:

- Part 2, Treatment Group 1: placebo QD orally for 28 days
- Part 2, Treatment Group 2: 125 mg BCX7353 QD orally for 28 days
- Part 2, Treatment Group 3: 250 mg BCX7353 QD orally for 28 days

If tolerability issues prevent full enrollment of Part 1 as described, future subjects randomized to active study drug in Part 1 may receive 250 mg orally once daily for 28 days. In this case, any dose level changes warranted for Part 2 will be instituted via protocol amendment.

Following completion of enrolment in Part 2, Part 3 of the study may be initiated:

In Part 3, approximately 20 subjects with Type 1 or Type 2 HAE who meet all eligibility criteria are planned to be randomized in a 1:3:3:3 (placebo: active: active: active) ratio into 1 of the following 4 treatment groups:

- Part 3, Treatment Group 1: placebo QD orally for 28 days
- Part 3, Treatment Group 2: 125 mg BCX7353 QD orally for 28 days
- Part 3, Treatment Group 3: 250 mg BCX7353 QD orally for 28 days
- Part 3, Treatment Group 4: 62.5 mg BCX7353 QD orally for 28 days

Following completion of enrollment in Part 3, Part 4 of the study may be initiated in order to more fully define the dose-response relationship. The decision to enroll Part 4, including the doses selected for Part 4, will be based on PK, safety, and efficacy results through Part 3 of the study.

If Part 4 is initiated, should the 62.5 mg and 125 mg BCX7353 dose groups in Part 3 be less efficacious than higher doses of BCX7353, approximately 14 subjects in Part 4 will be randomized in a 1: 6 (placebo:active) ratio into 1 of the following 2 treatment groups:

- Part 4, Treatment Group 1: placebo QD orally for 28 days
- Part 4, Treatment Group 2: 175 mg BCX7353 QD orally for 28 days

Alternatively, if Part 4 is initiated, should efficacy at the 62.5 mg BCX7353 dose group not be ruled out after analysis of Part 3 data, approximately 20 subjects in Part 4 will be randomized into 1 of the following 3 treatment groups as follows:

- Part 4, Treatment Group 1: placebo QD orally for 28 days (n = 2)
- Part 4, Treatment Group 2: 175 mg BCX7353 QD orally for 28 days (n = 12)
- Part 4, Treatment Group 3: 62.5 mg BCX7353 QD orally for 28 days (n = 6)

Study Conduct Overview

Following an up to 21-day screening period, eligible subjects, who have had entry criteria confirmed by the Sponsor, will be dosed on Day 1. Subsequent clinic visits will be held on Days 7, 14, 21 and 29, At the Day 14 visit, subjects will also have serial blood samples drawn immediately prior to and after the dose, including a visit on Day 15 for collection of a 24-hour postdose PK sample. A follow-up visit will be performed on Day 44.

Subjects will record the occurrence and details of all angioedema attacks at least once daily beginning from the date of screening until the follow-up visit. On Days 1 through 28, subjects will also record the time of day that the study drug (BCX7353 or placebo) was taken and the number of capsules of study drug taken at each dose. Subject-reported study drug administration and HAE attacks will be captured in a diary.

During the study, each subject will continue to use their prescribed acute attack medication to treat any attacks, under the medical management plan advised by their physician. All participants must have access to effective, approved acute treatments for attacks of angioedema as part of their routine medical care.

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Subjects will only participate in one part of the study.

All subjects who successfully complete treatment in the study will be offered the opportunity to participate in a future long-term study of BCX7353 where locally approved, provided that development of BCX7353 continues.

Number of subjects (planned):

Approximately 58 to approximately 90 subjects are planned to be enrolled and randomized in this study.

Main 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 as documented at any time in the medical records or at the screening visit by a low C1 INH functional level (Type 2) or a low C1 INH antigenic level (Type 1).
4. All subjects must have a documented HAE attack rate of at least 2 HAE attacks per month for 3 consecutive months (defined as 93 days) within the 6 months prior to the screening visit.

5. Access to and ability to use 1 or more acute medications approved by the relevant competent authority for the treatment of attacks of HAE (icatibant, plasma-derived C1INH, or recombinant C1INH).
6. Female and male subjects must agree to the contraception requirements and must meet the inclusion criteria regarding contraception, and contraception of female partners and sperm donation (as applicable), as outlined in Section 8.2.1.
7. Any concomitant medication 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.
8. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures for the duration of the study. The subject must demonstrate adequate compliance with all study procedures required from the screening visit through randomization, including diary recording of HAE attacks beginning at the screening visit.

Criteria for exclusion:

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject of participating in the study.
2. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
3. Use of C1 INH, androgens, or tranexamic acid for prophylaxis of HAE attacks within the 7 days prior to the screening visit or initiation during the study. Androgen use is not permitted at any time during the study. Use of a C1 INH therapy for treatment of attacks is not excluded at any time.
4. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a QTcF > 470 msec, a PR > 220 msec, 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 cardiovascular abnormality.
6. Known family history of sudden death from causes other than HAE.
7. History of or current implanted defibrillator or pacemaker.
8. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the Investigator, is clinically significant and relevant for this study. A calculated creatinine clearance of ≤ 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.

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

Investigational product, dosage and mode of administration:

BCX7353 hydroxypropyl methylcellulose (HPMC) opaque capsules for oral administration.

Part 1 and Part 2: The following doses will be administered orally once daily as 3 capsules (each capsule filled with drug substance to correspond to one-third of the total dose): BCX7353 350 mg (Part 1), BCX7353 250 mg (Part 2) and BCX7353 125 mg (Part 2).

Part 3: The following doses will be administered orally once daily as 2 capsules (each capsule filled with drug substance to correspond to one-half of the total dose): BCX7353 250 mg, BCX7353 125 mg, BCX7353 62.5 mg

Part 4: BCX7353 will be administered orally once daily as 2 capsules (each capsule filled with drug substance to correspond to one-half of the total dose) per dose: BCX7353 175 mg. Depending on the results through Part 3, a daily BCX7353 dose of 62.5 mg may also be administered.

Duration of treatment:

Subjects will receive 28 days of dosing with either BCX7353 or placebo.

Reference therapy, dosage and mode of administration:

Matched placebo capsules for oral administration. Placebo will be HPMC capsules to match active treatment.

Criteria for evaluation:

Efficacy: Efficacy will be evaluated by the number and rate of angioedema attacks and related details (eg, timing, duration of symptoms, anatomical location, treatment used), the number of subjects who are attack free, the number of attack free days, attack severity, and discontinuations due to lack of efficacy. All attacks will be reviewed and either confirmed or rejected for inclusion in the primary analysis dataset by an expert adjudication panel.

Safety: Safety will be evaluated by adverse events (AEs), laboratory analyses [clinical chemistry, hematology, coagulation, urinalysis, creatine kinase-MB (CK-MB), troponin I and T, neutrophil gelatinase-associated lipocalin (NGAL)], vital signs, electrocardiograms (ECGs), physical examinations and pulmonary diffusion (D_LCO) assessments. Relationships between safety assessment findings and HLA typing results may be examined.

Pharmacokinetics: Plasma samples for steady-state BCX7353 concentrations will enable calculation of standard noncompartmental pharmacokinetic parameters.

Pharmacodynamics: Pharmacodynamics will be evaluated by ex-vivo plasma kallikrein inhibition, cleaved high molecular weight kininogen, and C1 INH functional level. Additional exploratory assays to elucidate PD properties of BCX7353 may also be conducted on plasma samples drawn for PD analyses.

Quality of Life: Composite scores and domain scores of the disease-specific Angioedema Quality of Life questionnaire (AE-QoL) and Depression, Anxiety, Stress Scales (DASS) questionnaire.

Statistical methods:

Efficacy Analyses:

Subjects will be randomized initially 1:1 to the 350mg BCX7353 and placebo groups. An interim review will be performed by the Sponsor after the first 24 subjects complete the study. The number of dose groups and treatment allocations may be adjusted based on the interim review of the first 24 subjects completed.

Efficacy endpoints will be summarized and listed for each treatment group; Treatment Group 1 (placebo) will be pooled across all study parts for the final analyses. In Part 2 and Part 3, Treatment Groups 2 (125 mg BCX7353) and 3 (250 mg BCX7353) will each be pooled for the final analyses. Similarly, Treatment Groups 4 and 3 (62.5 mg BCX7353) in Parts 3 and 4, respectively, will be pooled for the final analysis if a 62.5 mg dose is administered in Part 4 of the study. The between-treatment comparisons (active vs placebo and between active dose groups) for continuous efficacy variables will be performed using an analysis of variance (ANOVA) or analysis of covariance (ANCOVA) model including the qualifying attack rate as a covariate in the model. The between treatment comparisons for the proportion of subjects who are attack free will be compared using a Fisher's exact test.

Safety Analyses: Treatment Group 1 from all study parts (placebo) will be pooled for the final safety analyses. In Part 2 and Part 3, Treatment Groups 2 (125mg BCX7353) and 3 (250 mg BCX7353) will each be pooled for the final analyses. Similarly, Treatment Groups 4 and 3 (62.5 mg BCX7353) in Parts 3 and 4, respectively, will be pooled for the final analysis if a 62.5 mg dose is administered in Part 4 of the study.

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. D_LCO results will be summarized and presented as change from baseline in mL/min.

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.

Pharmacokinetic Analyses:

Plasma pharmacokinetic parameters for each subject will be estimated over the sampling interval using non-compartmental analysis (WinNonlin, Pharsight Corp). Parameters will be summarized by treatment, dose and study day using descriptive statistics.

Dose proportionality will be performed using a power model and an ANOVA model based on dose normalized PK parameters. Additional analyses may be conducted as appropriate.

Pharmacodynamic Analyses:

On–treatment plasma kallikrein inhibition will be expressed as percent inhibition compared to subject baseline activity. All PD data will be summarized by subject, treatment, day, and time (plasma kallikrein inhibition only). Descriptive statistics will be reported. Mean and individual PD vs. time

profiles will be plotted by treatment group.

Exposure-response analyses of the relationships between efficacy endpoints or PD markers and BCX7353 plasma concentrations will be explored using model-based techniques as applicable.

Quality of Life Analyses:

The change from baseline in the domain scores of the AE-QoL and the DASS as well as the composite score of each instrument will be compared between the treatment and placebo groups. Individual items will be plotted to understand their contribution to the domain sub-scores.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and specialist terms

Abbreviation	Explanation
AAS	angioedema activity score
ABW	actual body weight
ADR	adverse drug reaction
AE	adverse event
AE-QOL	Angioedema Quality of Life questionnaire
ALT	alanine aminotransferase
ANOVA	analysis of variance
AR	adverse reaction
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	di-docosahexaenoyl (22:6)- Bis(mono)acylglycerol phosphate
BQL	below the quantification limit
C1 INH	C1 esterase inhibitor
CI	confidence interval
C_{last}	last measurable concentration of drug
CK-MB	creatine kinase-MB
CLcr	creatinine clearance
CL/F	apparent oral clearance after administration of the drug
C_{max}	maximum plasma concentration of the drug
CNS	central nervous system
CPK	creatine phosphokinase

Abbreviation	Explanation
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)
CV	coefficient of variation
CYP	cytochrome P450
DASS	Depression, Anxiety, Stress Scales
DDI	drug-drug interaction
D_LCO	pulmonary diffusion testing
DMC	Data monitoring committee
DMID	Division of Microbiology and Infectious Diseases
EC_{50}	Half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulation hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GPCR	G-protein-coupled receptor
HAE	hereditary angioedema
HBV	hepatitis B virus
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
HLA	Human leukocyte antigen
HPMC	hydroxypropyl methylcellulose
IB	Investigator's brochure
IC_{50}	50% inhibitory concentration

Abbreviation	Explanation
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine system
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
MedDRA	Medical Dictionary for Regulatory Activities
NGAL	neutrophil gelatinase–associated lipocalin
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PBMC	peripheral blood mononuclear cells
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Principal Investigator
PK	pharmacokinetic
PKK	prekallikrein
PLD	phospholipidosis
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

Abbreviation	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	system order class
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
ULN	Upper limit of normal
US	United States
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 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, 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 HAE attacks in the European Union (EU). In the United States (US), Berinert® and Ruconest® are licensed for this indication. 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). Administration of ecallantide is associated with an approximately 4% rate of anaphylaxis.

Icatibant (Firazyr®) is also an 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 the EU and the US, licensed therapy for prevention of HAE attacks is limited to a purified plasma-derived C1 INH (Cinryze®) administered intravenously every 3 to 4 days (STN125267). Oral attenuated androgens such as danazol are also licensed for prevention of HAE attacks in some countries. While administration of androgens is convenient, unacceptable adverse effects (including androgenic hormonal effects [masculinization], intracranial hypertension and risk of hepatocellular adenoma/carcinoma) and contraindications (including pregnancy) limit their clinical use (Maurer and Magerl 2011, Cicardi, Bork et al. 2012).

A Phase 2, double-blind, placebo-controlled study (Study BCX4161-203 [OPuS-1]) in subjects with HAE confirmed that inhibition of plasma kallikrein by an oral prophylactic treatment can significantly reduce attack rates. In that study, subjects with high attack rates (>1 week) were treated with avoralstat (BCX4161), a potent, small-molecule inhibitor of human plasma kallikrein discovered at BioCryst Pharmaceuticals, Inc (BioCryst). Overall, avoralstat was shown to be efficacious, reducing attacks in most subjects (88%), irrespective of the attack definition (subject-reported, adjudicated and treated) and was generally safe and well-tolerated.

In a subsequent Phase 3, 12-week, parallel-group study of avoralstat (OPuS-2) as prophylaxis against HAE attacks, avoralstat did not reduce the rate of attacks relative to placebo treatment. The failure of this study to demonstrate a treatment difference is likely related to: the limiting physicochemical and pharmacokinetic properties of avoralstat (low solubility and half-life); difficulty in adhering to an administration schedule requiring dosing on an empty stomach three times per day; and inhibition of plasma kallikrein that was neither maximal nor sustained across a dosing interval. Further investigations of either novel oral kallikrein inhibitors that do not suffer from those limitations, or novel avoralstat formulations that overcome the limitations of the formulation studied to date, are warranted.

BCX7353 is a potent, synthetic, second-generation small molecule inhibitor of plasma kallikrein discovered at BioCryst whose pharmacokinetic (PK) profile is superior to avoralstat's. Chronic inhibition of kallikrein with an orally bioavailable small molecule such as BCX7353 is expected to have significant benefits for patients with HAE by reducing the frequency of attacks or even completely eliminating the occurrence of attacks and improving quality of life.

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). The Guidance to Investigators section of the IB provides clinical context for the findings and relevance to dosing subjects in clinical protocols of BCX7353.

Nonclinical studies have demonstrated potent and specific inhibition of plasma kallikrein, high bioavailability after oral dosing with the potential for once-daily dosing, and a tolerability and safety profile that supports continued clinical development with appropriate safety monitoring.

5.2.1. Nonclinical Pharmacology

BCX7353 is a potent and highly specific inhibitor of human plasma kallikrein activity.

BCX7353 shows subnanomolar potency in isolated enzyme assays against the intended target, human plasma kallikrein, with an inhibition constant (K_i) of 0.44 nM; the 50% inhibitory concentration (IC_{50}) of BCX7353 against plasma kallikrein is 0.88 nM.

BCX7353 also inhibits kallikrein activity in activated human plasma from normal subjects, with a mean half-maximal effective concentration (EC_{50}) value of 5.83 nM, and in activated plasma from 14 subjects diagnosed with HAE, with mean (± standard error [SE]) EC_{50} value of 15.9 ± 0.57 nM. Similarly, BCX7353 is a potent inhibitor of HK/PKK-dependent BK production on human umbilical vein endothelial cells, with a mean (± SE) EC_{50} of 5.56 ± 1.2 nM.

The IC_{50} of BCX7353 against a range of other serine proteases varies from approximately 4,500-fold to more than 56,000-fold greater than for plasma kallikrein.

5.2.2. Safety Pharmacology

A battery of in vitro and in vivo (rat and cynomolgus monkey) safety pharmacology studies were conducted to evaluate BCX7353, and included studies as outlined in the International Conference of Harmonization (ICH) guidance S7A.

BCX7353 has very low affinity for G-protein coupled receptors (GPCRs), with K_i of > 3 μM for 100 of 103 target GPCRs; for the cannabinoid CB_1, melanocortin MC_5, and somatostatin SST_1 receptors, affinity of BCX7353 was 1.56, 1.92, and 2.09 μM, respectively. These K_i values are at least 3,545 higher than for plasma kallikrein, therefore there is low concern for interactions with these GPCRs.

In vitro, BCX7353 inhibits the human ether-à-go-go-related gene (hERG) channel, with an IC_{50} value of 0.29 μM. However, there was no demonstrable increase in action potential duration in rabbit cardiac Purkinje fibers at 100 μM, more than 500 times the hERG IC_{50}. Additional studies of calcium and sodium channels showed mixed effects. In conscious monkeys, a single dose of 15 mg/kg or repeated doses of 30 mg/kg daily for 28 days had no adverse effects on the cardiovascular system. Doses > 30 mg/kg increased the duration of electrocardiogram (ECG) intervals including the QTc interval, but these effects were not considered adverse as the maximum increase was 10% versus the pretest group mean.

Central nervous system (CNS) and respiratory safety pharmacology studies in the rat indicate that BCX7353 has a low potential to affect either the respiratory system or the CNS. The no-observed-effect-level (NOEL) in both studies was 450 mg/kg.

5.2.3. Nonclinical Pharmacokinetics

Following a single oral dose of [^{14}C]BCX7353 in rats, approximately 90% of the administered radioactive dose was recovered within the 168 hour time course of the study. A large component of the dose was recovered in the urine (41.1%). Recovery in feces was 44.7%. The excretion of radioactivity via the bile accounted for approximately half of the excretion in feces. Metabolic evaluations showed that, in the rat, BCX7353 is subject to metabolic oxidative deamination, oxidation, and/or conjugation of cyclopropanecarboxylic acid. The estimated oral bioavailability of BCX7353 was 62%.

After [^{14}C]BCX7353 oral administration to monkeys, 24.1% of the radioactivity was recovered in the urine. The majority of the dose was recovered in feces, 59.6%. The metabolic profile in monkeys was similar to rats with a number of metabolic products in plasma, urine, and feces, suggesting that BCX7353 is subject to metabolic oxidative deamination and oxidation processes, and/or conjugation of cyclopropanecarboxylic acid. The estimated oral bioavailability was 52%.

The IC_{50} of BCX7353 for inhibition of P450 cytochromes is < 1 µM for cytochrome P450 (CYP) 2C9 and CYP2C19, and is < 3 µM for CYP2D6 and CYP3A. The time-dependent inhibition screen with BCX7353 suggests it may irreversibly inhibit CYP3A, but not CYP2C9 or CYP2C19. Irreversible inhibition typically requires resynthesis of the CYP enzyme to return full functionality. CYP3A metabolizes over 50% of known marketed drugs.

Based upon (1) the measured systemic levels achieved in Study BCX7353-101, (2) the likely gastrointestinal (intraluminal) levels after oral dosing, (3) the in vitro inhibition potential outlined above, and (4) the recommendations provided in the Food and Drug Administration (FDA) drug interaction guidance (FDA 2012), there is a potential for a drug-drug interaction (DDI) with drugs that are affected by CYP3A, CYP2C9, CYP2C19 and CYP2D6. Therefore, an initial clinical DDI study is planned to quantify the DDI potential of BCX7353 at clinically relevant doses.

In human liver S9 fractions with and without cofactors the percent substrate loss was 12%, and in vitro half-life (min) was > 60 min. Substrate loss of approximately 10% was observed in incubations of BCX7353 with recombinant CYP enzymes in the absence of cofactors (ie, nonspecific loss due to routes other than CYP metabolism). Incubation with recombinant human CYP3A4 showed 22.4% loss of BCX7353. Other recombinant human CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) resulted in a loss of 15% or less. Thus the net loss of BCX7353 due to CYP metabolism was low over a 120 minute period, approximately 5 to 12%.

BCX7353 inhibited p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), MATE1, and MATE2-K with calculated IC_{50} values of 0.550 µM, 13.8 µM, 3.98 µM, and 5.19 µM, respectively. There was less than 50% inhibition of the OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 in the presence of BCX7353. Of the transporters that BCX7353 inhibits, P-gp and BCRP are widely distributed throughout the body, and contribute to efflux of substrates in the intestine which can limit absorption, enhance biliary and urinary excretion of substrates, and limit brain penetration. Since, in vitro, BCX7353 is a substrate as well as an inhibitor of the transport proteins P-gp and BCRP, albeit at high micromolar inhibitory concentrations for the latter, medications that rely upon the BCRP or p-gp transport proteins or medications known to clinically induce or inhibit transport proteins will be excluded from clinical trials, based on

decision tree calculations outlined in the draft FDA Drug Interaction Guidance (2012). The MATE1 and MATE2-K transporters are largely expressed in the kidney proximal tubules, and enhance urinary excretion of substrates. Unbound systemic concentrations of BCX7353 are well below the concentrations required for MATE1 and MATE2-K inhibition, which suggests limited potential for an interaction with the transporters. Additionally, as data on the MATE transporters emerges, there has been limited guidance with regards to evaluation of whether in vitro inhibition data is indicative of a potential clinical interaction.

In efflux experiments, BCX7353 was found to be a substrate of P-gp and BCRP. BCX7353 was not appreciably transported by OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

5.2.4. Nonclinical Toxicology

BCX7353 was not mutagenic in bacteria AMES assay and did not induce chromosomal aberrations in human peripheral blood lymphocytes cells. There was also no evidence of clastogenic activity in vivo as assessed in the micronucleus assay. Thus, BCX7353 has a low concern for genotoxicity.

The phototoxicity potential of BCX7353 was assessed in BALB/c 3T3 mouse fibroblasts and it was found that BCX7353 has no phototoxic potential.

In rats and cynomolgus monkeys, the effects of repeated oral doses for durations of 28 days and 13 weeks have been investigated, in accordance with the Organisation for Economic Co-operation and Development Test Guidelines and Principles of Good Laboratory Practice (GLP).

Rats were dosed once-a-day for 28-days at dose levels of 5, 10, 25, and 75 mg/kg/day. With the exception of the highest dose, administration of BCX7353 was well-tolerated. Administration of 75 mg/kg caused mortality, weight loss, reduced weight gain and decreased food consumption. Before their deaths, most of these animals were reported to have audible, shallow or difficult breathing. Evidence of inflammation, and changes secondary to hepatocellular and myocyte damage were observed mostly at 75 mg/kg/day in both sexes. These microscopic effects in liver and muscle correlated with increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST). At ≥ 25 mg/kg/day there was minimal to mild bile duct degeneration/necrosis in males and females without changes in liver transaminases. Minimal to mild tubular regeneration and minimal to mild tubular vacuolation were present in the kidneys of males and females at 75 mg/kg/day. Vacuolation was characterized by microvesiculation of the cytoplasm of tubular epithelial cells of the cortex. In addition, tubular regeneration and vacuolation were present in the kidneys and myofiber degeneration/necrosis were present in multiple tissues including the heart, skeletal muscle, tongue, larynx, esophagus, and the glandular stomach of males and females at 75 mg/kg/day. Minimal to mild vacuolation was present in multiple tissues including the choroid plexus of the brain, the pituitary gland, pancreas, parotid salivary gland, and the adrenal cortex at ≥25 mg/kg/day. At 75 mg/kg/day, minimal to severe generalized lymphoid depletion was present in the thymus and spleen. All of these effects showed evidence of partial or full reversibility during a 2-week recovery period.

Due to the adversity of effects at 25 mg/kg/day in the bile duct, the no observed adverse effect level (NOAEL) after dosing BCX7353 for 28 days in rats was considered to be 10 mg/kg/day. At

this dose level, the combined male and female mean C_{max} and AUC_{0-24} values on Day 28 were 186 ng/mL and 2,230 ng•hr/mL, respectively.

In the 13-week study, once daily oral gavage administration of BCX7353 to Wistar Han rats was well tolerated for 91 days at dose levels of 0, 2.5, 7.5, and 20 mg/kg/day. No BCX7353-related morbidity, clinical observations, body weight changes, food consumption differences, ophthalmic findings, or clinical pathology findings were observed at any dose level. At 7.5 and 20 mg/kg/day, BCX7353 induced a dose-related increase in the putative phospholipidosis biomarker BMP in the urine of male and female rats. Liver weights were increased and bile duct hypertrophy was noted in the liver of males and females at 20 mg/kg/day. Bile duct hyperplasia was present in females at 20 mg/kg/day, and vacuolated hepatic macrophages were present in males and females at 20 mg/kg/day. By electron microscopy, myelinosomes were observed within the cytoplasm of Kupffer cells. These liver findings were not considered adverse due to the minimal to mild degree of change, the lack of clinical pathology findings, and since no findings were present after recovery.

Therefore, the NOAEL after dosing BCX7353 by oral gavage for 91 days in rats is considered to be 20 mg/kg/day. At this NOAEL, the combined male and female mean C_{max} and $AUC0_{-24hr}$ values on Day 90 were 567 ng/mL and 11,200 ng•hr/mL respectively.

Oral dosing of 10, 30 and 100 mg/kg/day to cynomolgus monkeys for 28-days was well tolerated with the exception of emesis at 100 mg/kg/day. At the highest dose there were also mild increases of platelets, mild decreases in albumin and mild increases in globulin, mild increases in phosphorus in females and a mild glucosuria in males. Mild to moderate increases of ALT at 30 and 100 mg/kg/day were noted, and AST was increased at 100 mg/kg/day. Increases in liver transaminases correlated to microscopic changes in the liver. Elevated AST could also be related to skeletal muscle degeneration observed microscopically.

There were microscopic changes in several organs and tissues. In the liver of males there were large hepatocytes with foamy to large cytoplasmic vacuoles and hyperplasia of oval cells at 100 mg/kg/day. There were an increased number of necrotic hepatocytes at 30 and 100 mg/kg/day. In females there was increased vacuolation consistent with increased glycogen at all dose levels. The kidney of male monkeys was a target organ at 30 and 100 mg/kg, as there was degeneration/regeneration of tubules, characterized by vacuolated cytoplasm and regenerated tubular epithelial cells. In the kidney of females there were basophilic tubules, casts and inflammation. There were increased numbers of cellular infiltrates at 30 and 100 mg/kg/day in both sexes which correlated with an increased kidney weight at 100 mg/kg/day. In the small intestines, villi were expanded by foamy, pigmented macrophages. Minimal infiltrates were observed in the duodenum of males and females at 100 mg/kg/day. Minimal to mild infiltrates in the jejunum were observed in males at 30 and 100 mg/kg/day and females at 100 mg/kg/day. Minimal to mild infiltrates in the ileum were observed in males and females at 30 and 100 mg/kg/day. Skeletal muscle (rectus femoris, tongue and larynx) showed evidence of degeneration and/or regeneration of the myofibers in males and females at 100 mg/kg/day and in males at 10 mg/kg/day. These effects at 30 and 100 mg/kg/day were considered adverse. These microscopic changes in the different tissues and organs all showed partial reversibility following a 3-week recovery, and there were no residual effects considered adverse. Due to the adversity of effects at 30 mg/kg/day in liver the NOAEL was considered to be 10 mg/kg/day and the

associated plasma exposures (C_{max} and AUC_{0-24}) values on Day 28 were 84 ng/mL and 1,350 ng•hr/mL, respectively.

In the 13-week study, administration of BCX7353 was well tolerated when given daily to cynomolgus monkeys by oral gavage for 91 days at dose levels of 0, 2.5, 7.5, and 20 mg/kg/day. The only test article related findings were increases in ALT in both sexes at 20 mg/kg/day, and increases in the putative phospholipidosis biomarker BMP in the urine of male and female monkeys at 7.5 and 20 mg/kg/day, without any microscopic correlate. The increases in ALT were noted at day 28 and were partially resolved by the end of dosing and fully resolved at the end of recovery. BMP increases showed evidence of resolution by the end of the recovery period. Since there were no microscopic findings to correlate with ALT or BMP increases, they were not considered adverse.

Therefore, the NOAEL after oral gavage dosing BCX7353 in primates when given for 91 days is 20 mg/kg/day, the highest dose level administered. At 20 mg/kg/day, the combined male and female mean C_{max} and AUC_{0-24hr} values on Day 91 were 192 ng/mL and 3,350 ng•hr/mL respectively.

Definitive embryo-fetal development studies were conducted in pregnant Sprague Dawley rats and New Zealand White rabbits. In rats there was no evidence of embryo-fetal mortality, fetotoxicity, or dysmorphogenesis at any dose level. Adverse maternal toxicity was observed at 75 mg/kg/day. Based on these results, the NOAEL for maternal toxicity was 25 mg/kg/day and the NOAEL for embryo-fetal development was 75 mg/kg/day. In rabbits there was no evidence of embryo-fetal mortality, fetal growth effect, or dysmorphogenesis at any dose level. There was no evidence of maternal toxicity at 50 mg/kg/day and no effect on embryo-fetal development at $\leq$100 mg/kg/day.

5.3. Clinical Findings for BCX7353

Two clinical studies of BCX7353 have been completed (Study BCX7353-101 and Study BCX7353-102). Brief summaries are provided below.

5.3.1. Study BCX7353-101

Study BCX7353-101 was a 3-part, Phase 1, double-blind, placebo-controlled dose-ranging study of BCX7353 conducted in healthy subjects. Part 1 of the study assessed the safety, PK, and pharmacodynamics (PD) of a single ascending dose of BCX7353 (10 mg, 30 mg, 100 mg, 250 mg, 500 mg, or 1000 mg), and included a food-effect assessment in the 250-mg cohort. Part 2 of the study assessed the safety, PK, and PD of multiple ascending doses of BCX7353 given over 7 days. In Part 2, study doses of 125 mg once daily (QD) × 7 days, 250 mg QD × 7 days, 500 mg QD × 7 days, and 350 mg QD × 14 days BCX7353 were evaluated. 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. Preliminary data are available for all parts of the study.

Overall, in Parts 1, 2, and 3 a total of 96 subjects were treated with single doses of BCX7353 up to 1000 mg, or multiple doses up to 500 mg for 7 days, or 350 mg for 14 days. Oral administration of BCX7353 was generally well tolerated with no treatment-emergent serious adverse events (TESAEs). Most treatment-emergent adverse events (TEAE) were Grade 1 in

severity; following single doses, 2 subjects in the 100-mg dose group (Part 1) experienced Grade 2 AEs (nausea and vomiting in 1 subject and seasonal allergy in the other subject) and in the multiple ascending dose cohorts 4 subjects (Part 2) and 1 subject (Part 3) experienced a Grade 2 TEAE and 1 subject (Part 2) a Grade 3 TEAE.

The Grade 3 event occurred in the 500-mg group and was a cutaneous rash with no mucosal involvement, no desquamation, or constitutional symptoms or laboratory abnormalities. This event was consistent with a Type IV hypersensitivity reaction, and resolved following treatment with oral and topical steroids. In the 500-mg group (Part 2), 1 subject experienced a Grade 2 headache, and 1 subject experienced Grade 2 upper abdominal pain upper and diarrhea (2 TEAEs) which led to the subject's discontinuation from study drug dosing. Additionally, Grade 2 syncope was experienced by 1 subject in the 250-mg group and Grade 2 upper abdominal pain in 1 subject in the 350-mg group. The Grade 2 upper abdominal pain led to the subject's discontinuation. In Part 3 following multiple dosing with 250 mg BCX7353, 1 subject experienced a Grade 2 maculo-papular rash. In Parts 1 and 2, the most commonly reported TEAEs were gastrointestinal disorders (eg, nausea and diarrhea) and nervous system disorders (eg, headaches). There was no apparent dose response with regards to any individual AE; however, more gastrointestinal adverse events (AEs) were reported in the higher dose cohorts. In Part 3, the most commonly reported TEAE was medical device site reaction (eg, skin irritation from the ECG electrode site). The next most frequently reported TEAE was a rash-like reaction in 3 subjects; however, only 1 was considered related to IMP. Across all parts of the study, there were no trends in laboratory abnormalities and the only Grade 3 or 4 laboratory abnormalities in BCX7353-treated subjects were 2 Grade 3 lipase values in the 350-mg group (Part 2) 3 days after discontinuing treatment that normalized or improved the following day. No significant increase of > 60 msec in QTcF was observed across dose groups and 1 subject in the 350 mg dose group (Part 2) had a single treatment emergent QTcF > 450 msec 3 days after discontinuing treatment (ie, 455 msec). Across all cohorts and treatments, no subject had a clinically significant ECG abnormality. With the exception of 1 subject with a >20% decrease in pulmonary diffusion testing (D_LCO) result, no other clinically significant changes in D_LCO results were noted from baseline to end of dosing in the multiple day cohorts. In addition, no differences were seen comparing changes in D_LCO in BCX7353-treated with placebo-treated subjects.

In Western subjects (Parts 1 and 2) following single oral doses of BCX7353 up to 1000 mg and multiple oral doses of up to 500 mg QD administered under fasting conditions, C_{max} was reached approximately 2 to 5 hours after dosing. There was a prolonged absorption phase followed by a distribution/elimination phase. A second "peak" occurred around 5 hours after dosing, after the time of a meal. The double-hump PK profiles suggest that BCX7353 may undergo enterohepatic recirculation. BCX7353 plasma concentrations then declined biphasically. The effective half-life of BCX7353 was calculated to be 41 to 75 hours, based upon the 3.0- to 5.1-fold increase in exposure with 7 to 14 days of BCX7353 dosing. Across Part 2 cohorts, analysis of trough values indicated that steady-state conditions were achieved from 6 to 12 days post first dose.

In Part 1, examination of point estimates for dose-normalized 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; point estimates and associated 95% confidence interval (CI) ranges suggest reasonable dose-proportionality with doses between 250 mg and 500 mg for C_{max}. In Part 2 cohorts dosed for 7 days, there was a slightly greater than dose proportional increase in exposure

(AUC_{tau} and C_{max}) over the 125-mg to 500-mg dose range. With 4-fold increases in dose, there was a 5.1 and 5.3-fold increase in the geometric mean values for AUC_{tau} and C_{max}, respectively.

After a high-fat breakfast, there was no significant effect on AUC_{0-24}; the geometric mean value (coefficient of variation [CV]%) for AUC_{0-24} was 995 (25) ng•hr/mL under fasting conditions compared with 944 (28) ng•hr/mL under fed conditions. Also, no effect was observed on the geometric mean C_{max} values. Given that there was no appreciable difference in the PK with or without a high-fat meal, the recommendation in future clinical studies will be to administer BCX7353 with food. Administration with food may mitigate any potential for gastrointestinal AEs.

BCX7353 concentration-time profile following single and multiple dose administration in Japanese subjects (Part 3) was similar to those observed in the Western subjects (Parts 1 and 2). Maximal plasma BCX7353 concentrations were achieved at approximately 2 to 6 hours postdose. The second peak observed during absorption occurs after the administration of a meal. BCX7353 plasma concentrations then declined bi-exponentially with a geometric mean terminal elimination half-life of 73 hours following repeated dosing at 250 mg QD. After repeated dosing, the geometric mean accumulation ratio in AUC_{tau} was approximately 4-fold, which is consistent with the observed long half-lives. In comparison to Western subjects dosed 250 mg for 7 days, the plasma exposure appeared to be slightly higher in Japanese subjects who received the same oral administration of BCX7353 (geometric mean AUC_{tau} of 4180 vs 3710 ng•hr/mL and geometric mean C_{max} of 261 vs 217 ng/mL).

The effect of BCX7353 on the target enzyme, plasma kallikrein, was evaluated by comparing specific amidolytic activity in plasma samples taken after drug administration to baseline samples. A rapid and substantial inhibition of plasma kallikrein activity was observed following single 250 mg or higher doses of BCX7353. The response was generally dose dependent with a more sustained effect observed over the 24-hour period with the 500-mg and 1000-mg single doses.

Oral administration of multiple doses of BCX7353 at 125 mg QD for 7 days imparted measureable plasma kallikrein inhibition through a dosing interval, achieving mean maximal reductions of approximately 70% around the time of T_{max}. Higher doses of BCX7353 (250 mg QD or higher) provided more potent inhibition that was more consistently sustained through a dosing interval, achieving approximately 90% inhibition across an interval on average. Similar levels of kallikrein inhibition were observed in Japanese subjects (Part 3) as compared to Western subjects (Parts 1 and 2) given comparable doses. Potent kallikrein inhibition of approximately 90% was consistently sustained throughout the dosing interval after administration of BCX7353 at 250 mg QD. The BCX7353 concentration and kallikrein inhibition relationship was well-described by a sigmoidal E_{max} model; drug effect on the target enzyme was highly correlated with exposure ($r = 0.921$ for Parts 1, 2, and 3 combined).

5.3.2. Study BCX7353-102

Study BCX7353-102 evaluated the effect of multiple oral doses of BCX7353 on hepatic and intestinal CYP3A4 (intravenous [IV] and oral [PO] midazolam, respectively), CYP2C9 (tolbutamide), CYP2C19 (omeprazole) and CYP2D6 (dextromethorphan) enzyme activity using probe substrate drugs in healthy subjects.

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 was increased, indicating that metabolism was inhibited. Based on the draft 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

Interim efficacy, safety, PK, PD, and PK/PD results are available for Parts 1 and 2 of this ongoing proof-of-concept Phase 2 study in subjects with HAE. As of the cut-off date of 19 May 2017, 51 subjects with HAE were randomized and had received up to 28 days of treatment with BCX7353 once daily; 18 subjects received BCX7353 350 mg, 6 subjects received BCX7353 250 mg, and 7 subjects received BCX7353 125 mg. In addition, 20 subjects with HAE had received placebo. Part 3 of the study is currently ongoing.

5.3.3.1. Interim Safety Results

Overall, once daily dosing of BCX7353 up to 350 mg for 28 days was well tolerated. There were no SAEs reported in Parts 1 or 2 of the study, no Grade 4 TEAEs, and no TEAEs leading to death. The majority of TEAEs were Grade 1 in severity. Three subjects experienced 7 Grade 3 TEAEs, all in the 350-mg dose arm: constipation, abdominal pain, nausea, vomiting, alanine aminotransferase (ALT) elevation, gastrointestinal infection and migraine. Three subjects discontinued study drug due to an AE, all in the 350-mg dose arm: Grade 3 abdominal pain and vomiting, Grade 1 liver disorder, and Grade 3 ALT elevation.

Gastrointestinal-related AEs (primarily mild in severity) were reported more frequently in the 350-mg arm suggesting a dose response. Some GI events, namely nausea and abdominal pain, are also hallmarks of abdominal HAE attacks which were reported more commonly in the 350-mg dose arm (see Section 5.3.3.3 below). It is possible that subjects may have mis-attributed GI TEAEs as abdominal attacks. The incidence of GI events as well as abdominal attacks decreased in the 2 lower dose cohorts compared to the 350-mg dose cohort.

In addition, liver transaminase elevations were noted primarily in the 350-mg dose arm, but may have been confounded by both baseline elevated ALT and AST as well as a much higher rate of past and/or recent androgen use, neither of which were controlled for in the study. No drug rashes were reported in HAE patients as of the interim cutoff. No QTcF increase from baseline or absolute QTcF interval was considered clinically significant, and no TEAEs of arrhythmia were reported.

5.3.3.2. Interim Pharmacokinetic, Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Results

In subjects with HAE, the exposure of BCX7353 was consistent with that observed in healthy subjects. There was a greater than dose proportional increase in exposure (AUC_{tau} and C_{max}) over the 125-mg to 350-mg dose range, with an approximate 4-fold increase in exposure with a 2.8-fold increase in dose. The greater than proportional increase in exposure was observed from 125-mg to 250-mg, while the increase in exposure over the 250-mg to 350-mg dose range was proportional to the increase in dose. Trough concentrations collected on Days 14, 15, 28 and 29 indicated that steady state was reached by Day 14 in subjects at all dose levels. The geometric mean 24-hour concentrations (C_{tau}) were maintained at levels at or above a target therapeutic concentration range of 41 ng/mL to 71 ng/mL, estimated to be approximately 4-to 8-fold the EC_{50} required for plasma kallikrein inhibition.

Exposure of BCX7353 in subjects with HAE was overall consistent with the exposure observed in healthy subjects. BCX7353 exposure following administration of a 350-mg dose for at least 14 days in subjects with HAE was 0.98-fold the AUC_{tau} observed in healthy subjects following administration for 14 days. Despite differences in dose proportionality seen over the multiple dose range in healthy subjects and patients, exposure following either a 125-mg or 250-mg dose for at least 14 days in Study BCX7353-203 was 0.86-fold and 1.15-fold the AUC_{tau}, respectively, that was observed following administration of the same doses for 7 days to healthy subjects, when subjects were likely at or approaching steady state.

Exposure-response analyses of the relationship between kallikrein inhibition and BCX7353 plasma concentrations was evaluated in an exploratory ex-vivo kallikrein inhibition assay by comparing specific amidolytic activity in plasma samples taken after drug administration to that in baseline samples. BCX7353 showed potent inhibition of plasma kallikrein. Following at least 14 days of administration of the 250-mg and 350-mg doses, plasma kallikrein inhibition was maintained over the dosing interval, with maximal inhibition of approximately 90% occurring around the median T_{max} that were sustained above 75% for the 24-hour dosing period. The mean maximum kallikrein inhibition was observed around the median T_{max} with the 125-mg dose, and was approximately 60%, with mean kallikrein inhibition at 24 hours of approximately 40%. In general, kallikrein inhibition in subjects with HAE was consistent with the inhibition observed in Study BCX7353-101 in healthy subjects. A preliminary BCX7353 concentration and kallikrein inhibition relationship has been described by a sigmoidal E_{max} model with predicted EC_{50} values between 9.7 and 10.8 ng/mL. The drug effect on kallikrein inhibition was highly correlated with exposure ($r = 0.85$); inclusion of the 62.5 mg dose in Part 3 is expected to further refine the model by providing a greater number of concentrations in the linear range of the model.

5.3.3.3. Interim Efficacy Results

Interim results for the primary efficacy endpoint, number of confirmed HAE attacks, and the secondary efficacy endpoint of number of HAE attacks analyzed by anatomical location, are presented for Parts 1 and 2 as of the cut-off date of 19 May 2017.

Statistically significant and clinically meaningful reductions in the rate of attacks were observed in subjects treated with BCX7353 compared to placebo. Reductions in attack rates were observed at all doses tested, compared to placebo. In the Full Analysis Set (FAS) for the Entire Dosing Period (Days 1-28), the Least Squares Mean (LSM) attack rate for placebo was 0.898 per week,

and a reduction in the confirmed attack rate of 0.434 attacks/week (48.4%, $p < 0.001$) was observed for all BCX7353 doses combined compared to placebo. Reductions in confirmed attack rates by treatment group were: 350-mg dose group n = 18, 0.384 attacks/week, 42.8% reduction compared to placebo ($p = 0.007$); 250-mg dose group n = 6, 0.417 attacks/week, 46.4% reduction compared to placebo ($p = 0.039$); and 125-mg dose group n = 7, 0.579 attacks/week, 64.5% reduction compared to placebo ($p= 0.003$). Consistent results were observed in the Per Protocol (PP) population and during the Effective Dosing Period (Days 8-28), the duration at which study drug was at steady state.

A prespecified secondary endpoint analyzed the rate of confirmed attacks by anatomical location, specifically attacks that included abdominal symptoms versus attacks with only peripheral symptoms. This analysis identified a dose-ordered difference in attack rate by anatomical location. A differential response in attack rate reductions was observed for attacks with objective peripheral symptoms compared to attacks with abdominal symptoms, particularly at the two higher doses (250 mg and 350 mg).

In the FAS for the Entire Dosing Period, at the 350-mg dose a LSM reduction in peripheral attacks of 0.390 attacks/week (72.0%, $p = 0.002$) compared to placebo was observed, versus a 0.007 attacks/week (1.9%, $p = 0.947$) increase in abdominal attacks. At the 250-mg dose a reduction in peripheral attacks of 0.363 attacks/week (67.0%, $p = 0.045$) compared to placebo was observed, versus a 0.053 attacks/week (15.0%, $p = 0.704$) reduction in abdominal attacks, and at the 125-mg dose a reduction in peripheral attacks of 0.456 attacks/week (84.0%, $p = 0.008$) compared to placebo was observed, versus a 0.123 attacks/week (34.7%, $p = 0.354$) reduction in abdominal attacks. When reviewed in the context of reported TEAEs, the apparently poor response to treatment with BCX7353 in abdominal attacks may be due to a misattribution of GI-related side effects of the study drug as symptoms of an abdominal attack because of overlapping symptoms.

5.4. Rationale for Study

BCX7353 is a second-generation small molecule developed as an orally administered inhibitor of plasma kallikrein for the prevention of angioedema attacks in adult and adolescent patients with HAE Type I and II. 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 HAE attacks, and C1 INH treatments also target kallikrein. BCX7353 has activity against plasma kallikrein at low nM concentrations (see Section 5.2.1) that are attainable and sustained in humans following oral administration. As noted earlier (see Section 5.1), the plasma kallikrein inhibitor avoralstat was shown to be efficacious in the OPuS-1 study, reducing attacks in most subjects and was generally safe and well-tolerated. These data support further investigations of oral plasma kallikrein inhibitors as prophylactic interventions in patients with HAE.

Study BCX7353-203 is the initial proof-of-concept study of BCX7353 in adult subjects with HAE. This study is designed to evaluate the treatment effect of BCX7353 on HAE attacks over a 28-day period, relative to that on placebo treatment.. Multiple dose levels of BCX7353 will be evaluated.

5.4.1. Rationale for Study Drug Doses

5.4.1.1. Rationale for Target Concentrations Proposed as Efficacious

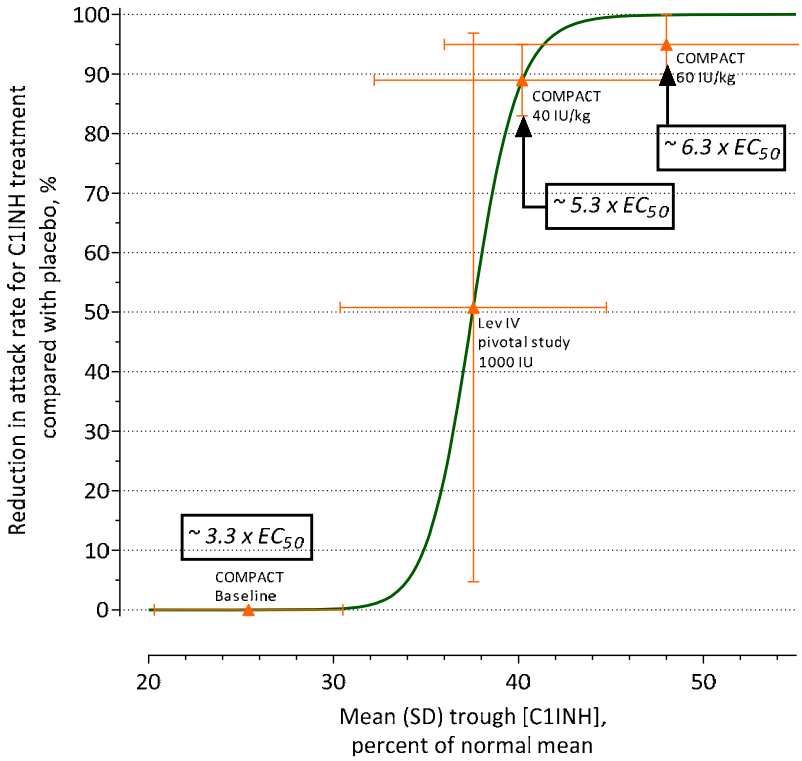
In healthy subjects in Study BCX7353-101, inhibition of plasma kallikrein was highly correlated with plasma BCX7353 concentrations (r = 0.92). Therefore, sustaining BCX7353 concentrations near or greater than a target level over a dosing interval is hypothesized to reduce attacks of HAE in subjects with little or no functional C1 INH, the endogenous inhibitor of kallikrein and ultimately, bradykinin production.

Trough concentrations expected to be efficacious were determined on the basis of C1 INH plasma concentrations in healthy subjects and HAE patients and the relative potency of C1 INH and BCX7353 against plasma kallikrein determined in vitro. The underlying hypothesis is that restoring normal levels of kallikrein inhibitory activity will restore a normal phenotype and eliminate angioedema attacks in patients with HAE.

The original rationale for the calculation of efficacious target concentrations for this protocol was as follows: 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 1680 nM; therefore, the LLN for C1 INH corresponds to a BCX7353 concentration of 125 nM, or 71 ng/mL (approximately 8 x EC_{50}). If the BCX7353 C_{tau} could be maintained above 71 ng/mL, total plasma kallikrein inhibitory activity would be in the normal range. This level of BCX7353 would be sufficient to replace normal function in HAE patients who have zero functional C1 INH. The average patient with HAE has functional C1 INH levels of about 30% of the normal mean (720 nM). In the average patient, the difference between this level and the LLN of C1 INH is 960 nM, which corresponds to about 73 nM or 41 ng/mL (approximately 4 x EC_{50}) of BCX7353. In summary, maintaining C_{tau} at either ≥ 41 ng/mL or ≥ 71 ng/mL (4 – 8 x EC_{50}) should restore the normal phenotype in the average HAE patient, and most HAE patients, respectively.

Since this protocol was initiated, newly available data suggest that a lower target concentration range of BCX7353 may be efficacious. Results of a Phase 3 blinded randomized 2-period cross-over study of a subcutaneous formulation of C1INH (CSL830) (COMPACT study) were recently reported. This study demonstrated an approximately 89-95% reduction in HAE attacks during the C1INH treatment period in patients with a qualifying minimum attack rate of at least 2 attacks per month at entry and an on-study attack rate of 3.6-4.0 attacks per month in the placebo period (Zuraw et al, 2016). An estimated exposure-response analysis of the mean trough C1INH level from this study indicated that the observed clinical responses correlated with C1INH trough levels of approximately 5.3 – 6.3 fold EC_{50} of C1INH on plasma kallikrein (210 nM) in the same assay as used to estimate the EC_{50} of BCX7353 on the same target enzyme Figure 1. Baseline mean levels of endogenous C1INH in this population were reported to be at approximately 25.4% of normal mean (~13.1 x EC_{50}), ie equivalent to approximately 3.3 x EC_{50}. Thus, high levels of efficacy were achieved in these severely affected HAE patients with the addition of exogenous C1INH equivalent to 2-3 x EC_{50} at trough. These data support a rationale that doses of BCX7353 resulting in a trough level of 2-3 x EC_{50} may also be efficacious, on a background mean level of endogenous C1INH of approximately 3.3 x EC_{50}.

Figure 1: Estimated exposure-response relationship for C1INH (CSL830 and Cinryze)



As outlined in Section 5.3.3, unblinded safety, PK, PD, and efficacy data are available through completion of dosing in Part 2 of the current study, including doses of 350 mg (n = 18), 250 mg (n = 6) and 125 mg (n = 7). HAE attack rates were reduced at all BCX7353 dose levels relative to placebo, with the greatest reduction observed at the 125 mg QD dose level. At all doses, the fold above EC_{50} was exceeded by greater than 2-3 x EC_{50} and the minimum target concentrations of 41 and 71 ng/mL were also consistently exceeded at doses ≥ 250 mg QD (Table 2). Taken together, this data suggests that lower target concentrations than originally anticipated (ie 4x EC_{50} or lower) may be efficacious. This trough concentration corresponded to kallikrein inhibition of approximately 40%. However, it should be noted that data at doses < 350 mg has been obtained from a very small population thus far; completion of Part 3 will approximately double the number of subjects receiving 125 and 250 mg and will provide efficacy and trough PK and PD data on a small number of subjects dosed 62.5 mg QD.

Table 2. Preliminary BCX7353 Trough Concentrations Obtained in Study BCX7353-203 Through Part 2 and Relationship to Pre-defined Target Concentrations Proposed as Efficacious

BCX7353 Dose	n	Mean (SD) trough [BCX7353] ng/mL	Mean (SD) trough EC_{50}, x-fold	Mean (SD) x-fold over target of 71 ng/mL at trough	Mean (SD) x-fold over target of 41 ng/mL at trough
350 mg	17	177 (58.84)	19.0 (7.04)	2.51 (0.874)	4.34 (1.51)
250 mg	6	132 (38.74)	14.2 (5.18)	1.90 (0.704)	3.29 (1.22)
125 mg	7	42.8 (16.52)	4.63 (2.00)	0.61 (0.234)	1.06 (0.406)

5.4.1.2. Rationale for Proposed Doses: Parts 1-3

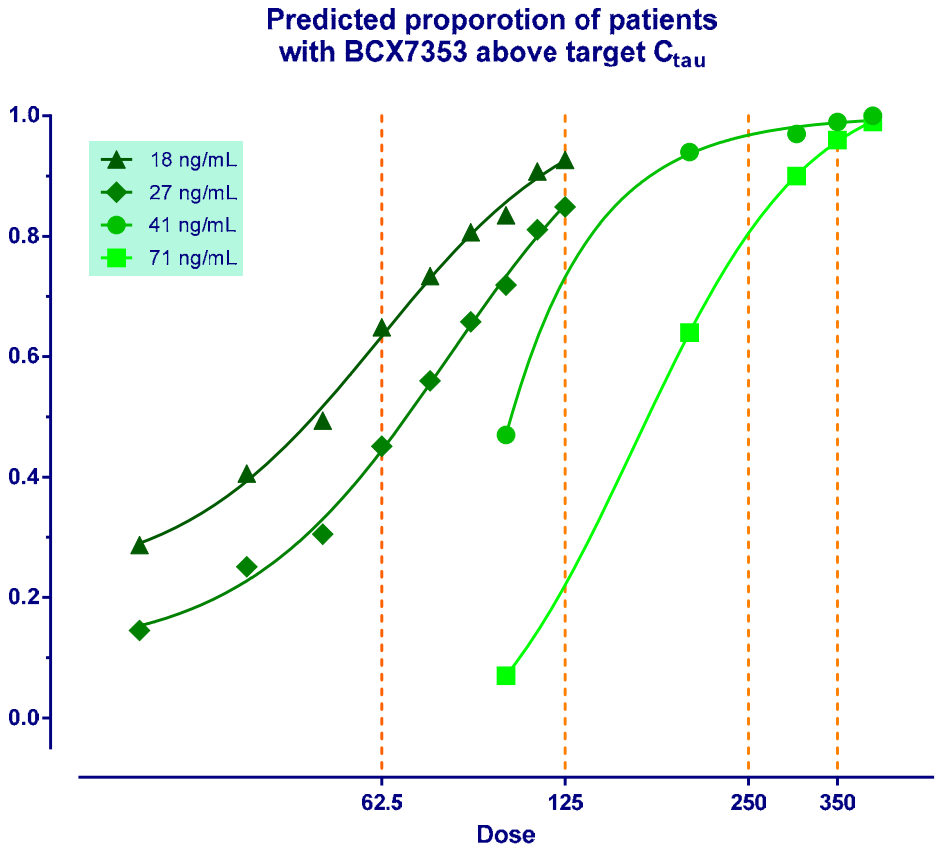
This dose ranging study will evaluate the safety and efficacy of daily BCX7353 doses of 62.5 mg, 125 mg, 250 mg, and 350 mg compared to placebo. The rationale for selection of these doses is based upon the safety observed in Study BCX7353-101 and the achievement of potentially efficacious BCX7353 plasma concentrations.

In Study BCX7353-101, dosing regimens of up to 500 mg BCX7353 QD for 7 days and 350 mg BCX7353 QD for 14 days were generally safe and well-tolerated. Gastrointestinal effects were reported more frequently at higher dose levels, although these events were predominantly mild and may be mitigated with concomitant food intake. No other dose-related safety concerns were noted, and the maximum tolerated dose was not reached in Study BCX7353-101, supporting selection of 350 mg to 500 mg BCX7353 QD as an upper dose to be considered for future clinical evaluation.

Using BCX7353 trough concentrations achieved in Part 2 of Study BCX7353-101, Monte-Carlo simulations were performed to estimate the percentage of clinical trial subjects who may meet or exceed the target trough concentrations equivalent to 4 and 8 x EC_{50} (41 ng/mL and 71 ng/mL). Linear regression parameter estimates obtained across dose ranges that produced relatively dose-proportional increases in exposure (125 mg to 250 mg and 250 to 500 mg) were used to interpolate trough estimates for putative doses in between those studied. Additional extrapolation for a dose range from 125 mg down to a dose of 25 mg was added to this analysis to estimate the percentage of clinical trial subjects who may meet or exceed the target trough concentrations equivalent to 2 and 3 x EC_{50} (18 ng/mL and 27 ng/mL). Results of simulations with 1000 subjects per dose point (100 mg, 200 mg, 300 mg, and 400 mg QD, and 25 mg, 37.5 mg, 50 mg, 62.5 mg, 75 mg, 87.5 mg, 100 mg, 112.5 mg and 125 mg QD, symbols) are provided graphically in Figure 2, together with fitted dose-response regressions (lines). Daily doses of approximately 125 mg and greater should provide trough concentrations above 41 ng/mL in approximately 70% of patients and therefore, selection of daily doses of 125 mg or higher for evaluation in the current study are supported. However, if maintenance of 71 ng BCX7353/mL is required to prevent attacks, doses of approximately 300 mg QD and greater will provide those levels in ≥ 90% of patients and therefore, selection of a 350 mg daily dose for evaluation in the current study is supported. To ensure that a full dose response is evaluated in this Phase 2 dose ranging

study, addition of a lower, 62.5 mg dose, which should provide trough concentrations above 18 ng/mL in approximately 65% of patients, is deemed reasonable. Enrolment of additional subjects at doses of 250 mg and 125 mg per day in Part 3 will aid in a full characterization of the dose response to enable selection of doses for future studies (Figure 2).

Figure 2: Proportion of Simulated Clinical Trial Subjects Anticipated to Meet or Exceed Target Trough Concentrations



5.4.1.3. Rationale for Proposed Doses: Part 4

The results of Part 3 will provide robust safety and efficacy data at BCX7353 doses of 125 and 250 mg QD. Both dose levels have been well-tolerated to date during a 28-day dosing regimen. Current safety data suggest that gastrointestinal AEs and liver enzyme abnormalities are dose-related, with the 125-mg dose level currently not associated with either finding and the 350-mg dose level most associated with these findings.

At all dose levels assessed in Parts 1 and 2, HAE attack rates were significantly reduced relative to placebo, with the greatest overall reduction observed at 125 mg QD, corresponding to ~4-fold EC_{50} on plasma kallikrein and a mean of 42% kallikrein inhibition at the end of a dosing interval. A closer evaluation of the attacks reported by 18 subjects receiving 350mg BCX7353 revealed that BCX7353 had a high degree of efficacy on peripheral attacks, with no effect on abdominal attacks, potentially due to mis-attribution of abdominal TEAEs as attacks. A 250 mg QD dose

did provide proportionally less exposure than a 350 mg dose, however kallikrein inhibition was generally indistinguishable over a dosing interval.

Therefore, the optimal BCX7353 dose is predicted to be one in which GI TEAEs are reduced but where effective plasma concentrations and kallikrein inhibition are maintained to prevent true HAE attacks from occurring. Based on available data this is likely to be in the 125 to 250 mg QD dose range. Following completion of enrollment in Part 3, Part 4 may be initiated in order to fully define the dose-response relationship with a dose intermediate to 125 and 250 mg. The decision to enroll Part 4, including the doses selected for Part 4, will be based on the PK, safety and efficacy results through Part 3 of the study.

Part 4 will be implemented if the 62.5 mg dose is shown to be less efficacious than the higher doses and the 125 mg dose efficacy is not sustained through the completion of Part 3, in order to further define the dose-response relationship. A 175 mg dose is proposed for study in Part 4, based upon predictions for exposure and kallikrein inhibition that are intermediate between the 125 and 250 mg doses. Results of simulations based upon PK data at the 125 and 250 mg doses in the current study and in Study BCX7353-101, suggest that 93% of subjects dosed with 175 mg QD will have trough concentrations above 4 x EC_{50}, in contrast to 70% for a 125 mg dose. A 175 mg QD dose is also predicted to inhibit kallikrein by 62%, approximately midway between 125 mg (42%) and 250 mg QD (76%).

As discussed in Section 5.4.1.1, a dose < 125 mg BCX7353 QD may be efficacious based upon the HAE attack rate observed at this dose level in Part 2 and given that concentrations sufficient to block kallikrein through a dosing interval are greater than that now thought to be minimally efficacious (2 to 3 x EC_{50} [18 ng/mL and 27 ng/mL]). A 62.5 mg QD dose is the only dose < 125 mg QD being evaluated in the ongoing Part 3 of the study. It is unlikely that this dose will provide target BCX7353 concentrations in a significant proportion of subjects treated with this dose (see Figure 2). Nevertheless, this concentration and efficacy threshold has not yet been established and given that only 6 subjects will be dosed with 62.5 mg QD in Part 3, additional subjects may need to be dosed with 62.5 mg QD in Part 4 to elucidate the benefit: risk profile of this dose level.

If the interim review indicates that Part 4 is not needed, it will not be conducted.

5.4.2. Rationale for Study Design

This is a Phase 2a study designed to assess the safety, efficacy, and PK of BCX7353 for the prophylactic treatment of subjects with HAE over a 28-day treatment period.

A parallel group design was considered the most appropriate study design to evaluate BCX7353 relative to other doses of BCX7353 and relative to placebo because of its very long half-life. The terminal half-life of BCX7353 was estimated at approximately 60 hours at doses ranging from 100 mg to 1000 mg in the single ascending dose Part 1 of Study BCX7353-101. Given this long half-life it would be more difficult to minimize carry-over effects in a study utilizing a cross-over design.

Since Study BCX7353-203 is the initial proof-of-concept study of BCX7353 in adult subjects with HAE, enrollment of subjects known to the study investigators as having frequent HAE attacks allows evaluation of the BCX7353 treatment effect of the highest proposed clinical dose (350 mg) over a short period (28 days) relative to placebo. This will prudently establish proof-of-

concept and risk/benefit at the dose of BCX7353 modeled to provide the most complete plasma kallikrein suppression through a daily dosing interval, 350 mg QD. A tiered enrollment approach of analyzing data from the first 24 subjects completing either placebo or BCX7353 350 mg QD treatment prior to enrolling a maximum of 36 subjects will help to limit the number of subjects exposed to an investigational product that has undetermined efficacy. Additional BCX7353 doses down to 62.5 mg QD will be evaluated in subjects once the risk/benefit balance has been ascertained at this highest dose.

5.4.3. Study Population Rationale

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 PK differences.

Although there is no evidence of feto-toxicity with BCX7353, pregnant women will be excluded from participation. BCX7353 is early in clinical development and the benefit/risk profile has not been characterized in the general HAE population to allow pregnant women to receive BCX7353. Additionally, any female subject who becomes pregnant during the course of the study will be immediately removed from study drug and followed through the end of the pregnancy.

Women of childbearing potential may be enrolled in this trial only if they agree to utilize at least an acceptable effective contraceptive method. The specific types of allowable acceptable effective contraception outlined in Section 8.2.1 are in accordance with the Clinical Trial Facilitation Group (CTFG) *Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials* document.

The allowance of an acceptable effective contraception method in this trial is based on the completion and outcome of nonclinical studies in accordance with the general recommendations of the ICH M3(R2) guideline that “all female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential not using highly effective birth control or whose pregnancy status is unknown.” The completed studies for BCX7353 include a standard battery of genotoxicity testing, 13-week repeat dose toxicity studies in two species, embryofetal development studies in two species, and a fertility and early embryonic development study in rats. As described, the results from all studies indicates no risk to the unborn, thus supporting the option for highly effective or acceptable effective methods of contraception to be used during BCX7353 clinical trials.

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.

5.4.3.1. Rationale for Allowance and Restriction of Concomitant Medications for HAE

While there are approved therapies in the US and EU for prophylaxis against HAE attacks, including C1 INH infused intravenously, consensus recommendations do not exist for either a standard of care for prophylactic treatment or a definition of indications for prophylaxis. A recent guideline published on the management of HAE by the US HAE Association Medical Advisory board suggests that decisions on when to use prophylaxis should be individualized:

> *'The decision about when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient. Decisions regarding which patients should be considered for long-term prophylaxis should take into account attack frequency, attack severity, comorbid conditions, access to emergent treatment, and patient experience and preference.'(Zuraw, Banerji et al. 2013)*

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

5.4.4. BCX7353 Risk/Benefit Analysis

5.4.4.1. Risks for Potential Severe Adverse Reactions

Given that BCX7353 is a small molecule kallikrein inhibitor with a completed Phase 1 single and multiple dose study, there is an acceptably low risk of severe adverse reactions. Potential risks are outlined below.

5.4.4.2. Risks of Potential Adverse Events with BCX7353

The 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 for 13 weeks, there were no adverse effects noted. In rats dosed at 20 mg/kg/day for 13 weeks, 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, particularly at higher doses. In addition, delayed hypersensitivity drug rash was reported.

Liver: At 20 mg/kg/day of BCX7353 dosed to rats for 13 weeks, bile duct hypertrophy, hyperplasia, and vacuolated macrophages were present in the liver with evidence of 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 AST and 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 (ALP) 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 Phase 1 study. In the 50 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.

In the ongoing study, two of the first 23 subjects treated in Part 1 (350 mg BCX7353) experienced a treatment-emergent Grade 3 (one subject) or Grade 4 (one subject) lab abnormality in GGT, along with lower Grade increases in AST, ALT and ALP.
The first subject is a 64 year old man with a medical history of hypertension, depression, right bundle branch block, and erectile dysfunction. Concomitant medications included tadalafil and escitalopram. One week prior to starting blinded study drug he stopped his calcium channel blocker and switched to irbesartan/HCTZ for blood pressure control. He was on danazol until approximately 40 days prior to starting study drug. He developed a Grade 1 gastroenteritis (symptoms of vomiting and diarrhea: possibly related) on Day 10. The study drug was interrupted. He restarted study drug on Day 18 with a reoccurrence of vomiting and diarrhea 5 hours post dose. Labs on Day 14 demonstrated Grade 3 GGT, Grade 2 ALT, Grade 1 ALP and normal AST and bilirubin. He was taken off study drug on Day 18. Since then, he has done well with normal LFTs on Day 29 with the exception of a Grade 1 GGT.

The second subject is a 51 year old woman with a medical history of active colitis treated with mesalamine. She had no recent use of androgens. She did well during the study and had no reported AEs, although she complained of fatigue at the Day 29 visit. At baseline, she had Grade 1 ALT, GGT and Direct bilirubin elevations. Her AST and ALP were normal. Her LFTs were stable at the Day 14 visit. At the Day 29 visit, her lab results demonstrated a Grade 4 GGT, Grade 3 ALT and Grade 1 AST and ALP. Since then, she has done well and her follow-up labs have all normalized with the exception of a Grade 3 GGT.

Additionally, no significant laboratory abnormalities or significant liver transaminase elevations were observed in Part 2 (250 mg BCX7353 and 125 mg BCX7353), except for a single subject randomized to BCX7353 250 mg. The subject was a 60 year-old woman who had a baseline

ALT of 97 IU/L (Grade 2 [2.9 X ULN]) and AST 46 IU/L (G1 [1.4 X ULN]). She experienced nausea and lethargy during the first week of dosing. Her ALT rose to 116 IU/L (G3 [3.5 X ULN]) and AST to 61 IU/L (G1 [1.8 X ULN]) at week 7. The investigator continued her on study drug and her AEs resolved and LFTs remained elevated but stable. Two weeks after study drug was completed, she still had an ALT of 107 IU/L (G3[3.2 X ULN]). Several weeks later, her ALT and AST were normal.

After a DMC review of blinded data on December 13, 2016, triggered as per criteria listed in Section 12.2, the DMC recommended the study dosing continue unchanged but that liver enzymes be monitored on a weekly basis while subjects are on study drug. Therefore, the frequency of monitoring of liver function has been changed from every 2 weeks to weekly in this study. This additional safety monitoring was instituted by a memo from the Sponsor to all sites on December 16, 2016, and was formalized in Protocol Amendment 2, (Version 3.0).

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. 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 trial, no clinically significant abnormalities of renal function, as measured by serum creatinine and creatinine clearance (CL_{cr}) 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, CL_{cr}, and NGAL will be regularly monitored in this study.

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 trial neither AST nor creatine phosphokinase (CPK) demonstrated any clinically significant elevations. In addition, no subjects have experienced any AEs of potential muscular injury.

Given the preclinical data, AST and CPK will be regularly monitored in this study.

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 were 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 in vitro, BCX7353 inhibited the hERG channel inhibition, although the cardiac action potential was not prolonged. Since hERG inhibition has been associated with Torsades de pointes, ECGs will be performed until the effects in humans are better characterized.

There was no evidence of foamy or vacuolated cells in the heart in either the rat or the monkey.

Cardiac monitoring in the Phase 1 study did not demonstrate any arrhythmias or ischemia. Although there were some subjects with a QTcF interval increase between 30 and 60 msec, none of these subjects had an absolute QTcF > 450 msec and all subjects had transient value(s) which returned to <30 msec increase on the same day or the following day.

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 (upper limit of normal [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 creatine kinase (CK-MB) elevations, and had no ECG evidence of ischemia.

Six subjects treated with BCX7353 in the Phase 1 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 6 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 discharge from the Phase 1 unit. 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.

This study will exclude subjects with evidence of cardiac disease as indicated by medical history, family history of sudden death or abnormal screening ECG. Monitoring with ECG, troponin and CK-MB will be regularly monitored in this study.

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 study, no clinically significant changes in any hematologic parameter or lymphoid tissue were noted. No organomegaly and no lymphadnopathy were noted on physical exam. Complete blood counts and general physical examinations will be regularly monitored in this study.

Presumed Phospholipidosis: In the 28 day studies in both rats and monkeys, there were foamy macrophages and vacuolated infiltrates found in multiple organs and various tissues, presumed to be signs of PLD. Vacuolated macrophages were noted in the liver, lungs, duodenum, jejunum, ileum, cecum, nonglandular stomach, mandibular lymph node, mesenteric lymph node, spleen,

and ovaries of rats. Vacuolation was present in the choroid plexus, the pituitary gland, the adrenal cortex, pancreas acinar cells and ductal cells of the parotid salivary gland in rats. In monkeys, foamy cells were noted in the liver, lymphoid tissue and small intestines. In most tissues, these infiltrates did not appear to be adverse and there were no clinical or blood chemistry findings that correlated. However, the infiltrates in the intestinal villi, which were not considered adverse in rats, caused significant villous thickening in monkeys at 100 mg/kg/day that appeared to correlate to possible malabsorption, manifested as decreased weight and low body nutrients. Importantly, the PLD was 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 there was no physical correlate as there were no microscopic abnormalities and no foamy macrophages or vacuolated cellular infiltrates. Increased urinary levels of BMP, an investigational biomarker for PLD, were demonstrated in both rats and monkeys dosed with BCX7353 for 13 weeks.

PLD is not adverse in and of itself and there are approved products that cause this phenomenon without any associated toxicity. It currently cannot be directly measured in an effective and noninvasive way and there are no validated biomarkers in humans (Chatman, Morton et al. 2009). Since PLD is not a toxic manifestation and cannot be easily measured in humans, end organ toxicity is monitored. PLD may manifest by expanding the thickness of intestinal absorption and pulmonary diffusion tissues. This may result in various clinical findings, such as possible decreased nutrient absorption when PLD is present in intestinal villi.

In the Phase 1 trial, there were no events suggesting PLD in either the intestines or lungs. No clinically significant changes in weight or evidence of malabsorption occurred. In addition, D_LCO was performed as an experimental marker of foamy macrophage deposition in the lung. Except for a single subject in the 125-mg dose group who had a 22% decrease from baseline, no other clinically significant changes were noted from baseline to end of dosing in the multiple-day cohorts. This subject had no signs or symptoms suggestive of a diffusion deficit. In addition, no differences were seen comparing changes in D_LCO in BCX7353-treated with placebo-treated subjects.

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. In addition, monitoring with D_LCO will be employed as an experimental marker to gauge lung foamy macrophages.

Gastrointestinal symptoms: Gastrointestinal symptoms, primarily mild, were noted in all cohorts in the Phase 1 study 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, 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. PK analyses of both 250 mg doses administered in Part 1 of Study BCX7353-101 demonstrated no impact on drug exposure from

taking BCX7353 with food. Therefore, in order to help mitigate any gastrointestinal effects, particularly upper abdominal effects, BCX7353 should be taken with food.

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. In addition, human leukocyte antigen (HLA) typing of all future enrolled subjects in multiple dose trials is being undertaken to understand whether any specific HLA genotypes play a role in the development of cutaneous hypersensitivity and could be used to identify patients at higher risk.

5.4.5. Benefits of Trial Participation

Study subjects will receive regular medical care for the duration of the study. Subjects may experience a reduction in the number of attacks while receiving active study drug for 28 days, although subjects will not know if they are receiving BCX7353 or placebo.

Participation in this study will not exclude study subjects from being able to participate in longer term open-label studies of BCX7353, if further development of the drug is warranted. 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. Even findings in animals such as PLD that are not directly monitorable will be followed by robust assessment of organ health and function. Although there may be no direct benefit to any individual subject, the information obtained from this trial will support the development of BCX7353 for HAE, a serious, debilitating and potentially 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 once-daily prophylactic BCX7353 at up to 5 dose levels, as measured by the number of attacks of HAE observed in patients with HAE enrolled in each treatment group

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of BCX7353 over 28 days in subjects with HAE
- To describe the PK profile of daily BCX7353 in subjects with HAE
- To characterize the anticipated PD effects of BCX7353 in subjects with HAE
- To characterize the dose-response relationship of BCX7353 in subjects with HAE
- To evaluate effects of BCX7353 on quality of life

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan: Description

This is a Phase 2, randomized, double-blind, placebo-controlled parallel-group, dose-response study to evaluate the safety, tolerability, PK, PD, and efficacy of BCX7353 in subjects with HAE. HAE patients with a documented recent history of frequent 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 HAE are planned to be enrolled in Part 1 of the study and will be randomized 1:1 (placebo: active) to receive one of the following treatments:

- Part 1, Treatment Group 1: placebo QD orally for 28 days
- Part 1, Treatment Group 2: 350 mg BCX7353 QD orally for 28 days

After 24 subjects have completed through the Day 28 dose, there will be an administrative interim analysis of the accrued efficacy data by the Sponsor. If it is desired to more fully characterize the treatment effect of BCX7353 relative to placebo or to verify assumptions made for sizing this proof-of-concept study, additional subjects will be enrolled to complete Part 1 (up to 36). Enrollment into Part 1 will continue until either a decision is made to halt enrollment in favor of opening Part 2 or enrollment reaches 36 subjects in Part 1. Additionally, upon completion of Part 1 (36 subjects dosed), enrollment into Part 2 of the study may immediately commence.

In Part 2, approximately 14 subjects who meet all eligibility criteria are planned to be randomized in a 1:3:3 (placebo:active:active) ratio into 1 of the following 3 treatment groups:

- Part 2, Treatment Group 1: placebo QD orally for 28 days
- Part 2, Treatment Group 2: 125 mg BCX7353 QD orally for 28 days
- Part 2, Treatment Group 3: 250 mg BCX7353 QD orally for 28 days

If tolerability issues prevent full enrollment of Part 1 as described or study drug is poorly tolerated due to gastrointestinal effects, future subjects randomized to active study drug in Part 1 may receive 250 mg orally once daily for 28 days. In this case, any dose level changes warranted for Part 2 will be instituted via protocol amendment.

Following completion of enrolment in Part 2, Part 3 of the study may be initiated:

In Part 3, approximately 20 subjects who meet all eligibility criteria are planned to be randomized in a 1:3:3:3 (placebo:active:active:active) ratio into 1 of the following 4 treatment groups:

- Part 3, Treatment Group 1: placebo QD orally for 28 days
- Part 3, Treatment Group 2: 125 mg BCX7353 QD orally for 28 days
- Part 3, Treatment Group 3: 250 mg BCX7353 QD orally for 28 days
- Part 3, Treatment Group 4: 62.5 mg BCX7353 QD orally for 28 days

Following completion of enrollment in Part 3, Part 4 of the study may be initiated in order to more fully define the dose-response relationship. The decision to enroll Part 4, including the doses selected for study, will be based on results through Part 3 of the study.

Should the 62.5 mg and 125 mg BCX7353 dose groups in Part 3 be less efficacious than higher doses of BCX7353 and Part 4 is initiated, approximately 14 subjects in Part 4 will be randomized in a 1:6 ratio into 1 of the following 2 treatment groups:

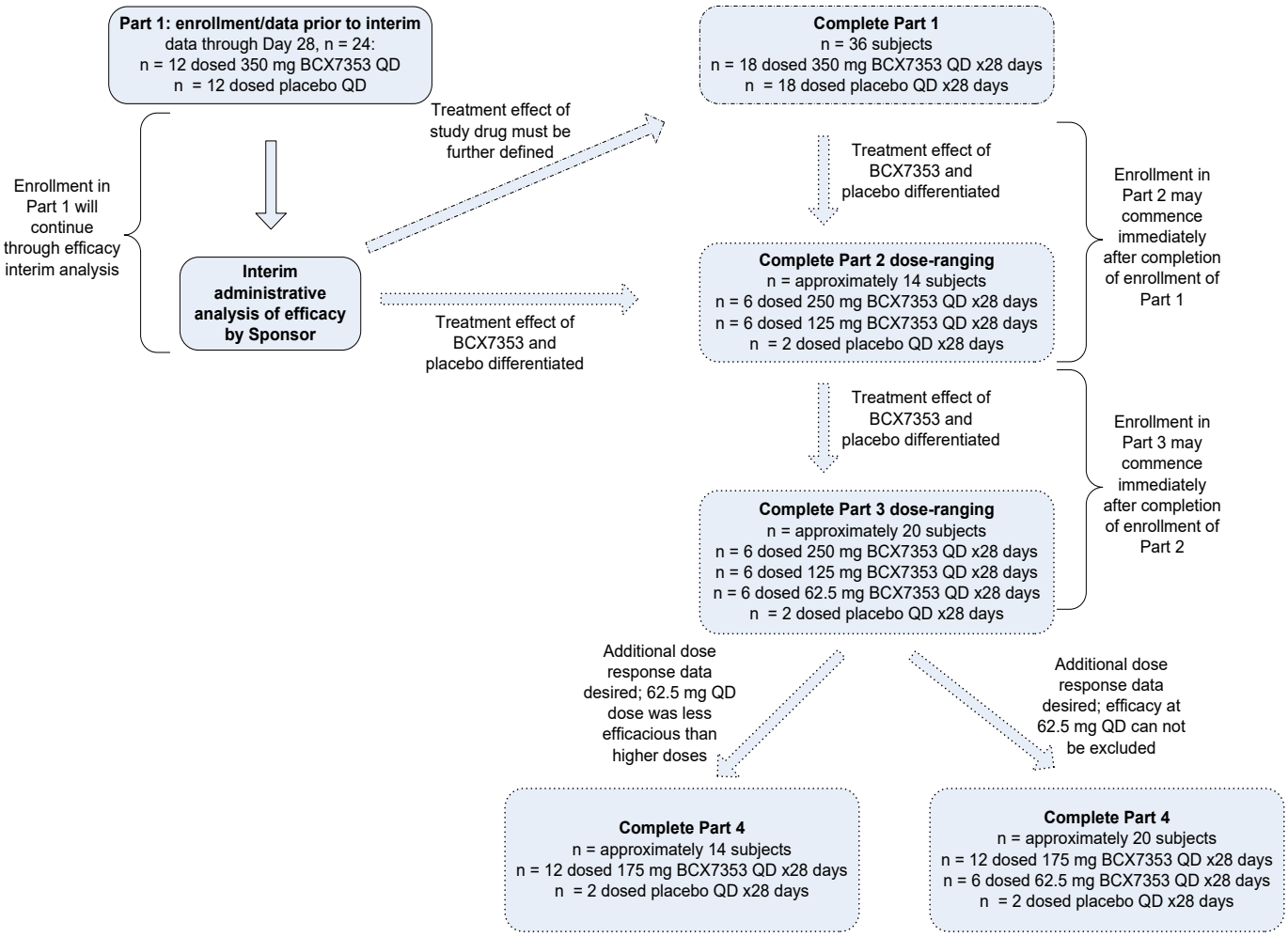
- Part 4, Treatment Group 1: placebo QD orally for 28 days (n=2)
- Part 4, Treatment Group 2: 175 mg BCX7353 QD orally for 28 days (n=12)

Alternatively, should the 62.5 mg BCX7353 dose group not be shown to be less efficacious after analysis of Part 3 data and Part 4 is initiated, approximately 20 subjects in Part 4 will be randomized in a 1:6:3 (placebo:active:active) ratio into 1 of the following 3 treatment groups as follows:

- Part 4, Treatment Group 1: placebo QD orally for 28 days (n = 2)
- Part 4, Treatment Group 2: 175 mg BCX7353 QD orally for 28 days (n = 12)
- Part 4, Treatment Group 3: 62.5 mg BCX7353 QD orally for 28 days (n = 6)

The overall study design is presented in Figure 3; Figure 4 depicts the schema for conduct of each study part.

Figure 3: Study BCX7353-203 Study Design



Following an up to 21-day screening period, eligible subjects, who have had entry criteria confirmed by the Sponsor, will be dosed on Day 1. Subsequent study visits will be held on Days 7, 14, 21 and 29. At the Day 14 visit, subjects will also have serial blood samples drawn immediately prior to and after the dose, including a visit on Day 15 for collection of a 24-hour postdose PK sample. A follow-up visit will be performed on Day 44.

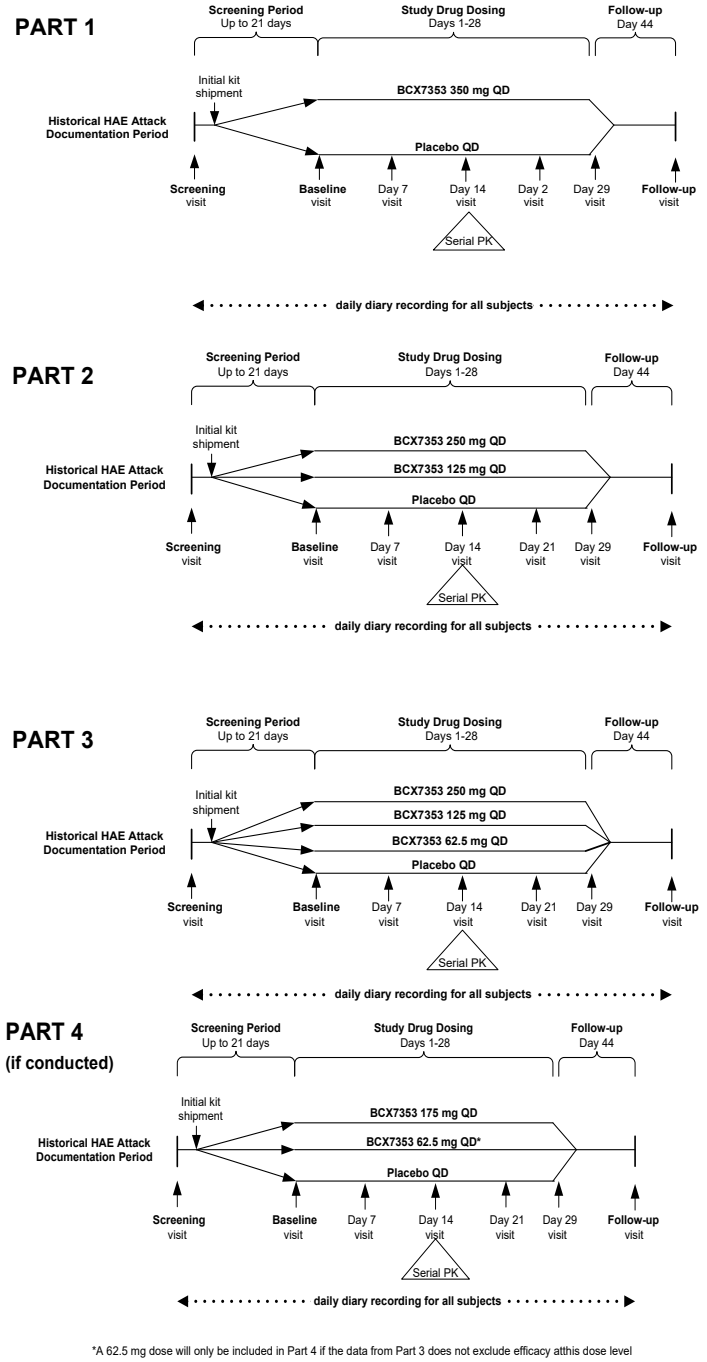
Subjects will record the occurrence and details of all angioedema attacks at least once daily beginning from the date of screening until the follow-up visit. On Days 1 through 28, subjects will also record the time of day the study drug (BCX7353 or placebo) was taken and the number of capsules of study drug taken at each dose. Subject-reported study drug administration and HAE attacks will be captured in a diary.

During the study, each subject will continue to use their prescribed acute attack medication to treat any attacks, under the medical management plan advised by their physician. All participants must have access to effective, approved treatments for attacks of angioedema as part of their routine medical care.

Subject will only participate in one part of the study.

All subjects who successfully complete treatment in the study will be offered the opportunity to participate in a future long-term study of BCX7353 where locally approved, provided that development of BCX7353 continues.

Figure 4: Study Schema—Parts 1, 2, 3 and 4



*A 62.5 mg dose will only be included in Part 4 if the data from Part 3 does not exclude efficacy atthis dose level

7.2. Endpoints

7.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the number of confirmed HAE attacks during the treatment period in the Full Analysis Set (FAS) population. The number of HAE attacks will be analyzed by treatment group using appropriate descriptive statistics as follows: weekly attack rate, counts

of attacks, proportion of subjects with no attacks, and number of attack-free days. The relative change in attack rate from placebo will also be calculated for each active arm. The FAS includes all randomized subjects who receive at least 1 dose of study drug and have post baseline HAE attack data.

To ensure that consistent, objective assessments are used in accepting subject-reported attack data, a panel of expert physicians in the treatment of HAE patients will adjudicate all subject-reported attacks prior to their inclusion in primary efficacy analyses. The adjudication will be based upon all data provided by the subjects in their study diaries that document reported HAE attacks. A separate charter will describe membership, roles, and processes to be followed by the adjudication panel.

7.2.2. Secondary Efficacy Endpoints

Secondary endpoints will include the following:

- Number of attacks requiring attack medication
- Duration of attacks
- Severity of attacks
- Attack onset relative to the time of last dose of study drug
- Discontinuations due to lack of efficacy
- Symptoms and anatomical locations of attacks
- Number of emergency room visits and/or hospitalizations

7.2.3. Safety Endpoints

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

7.2.4. Other Secondary Endpoints

Other secondary endpoints will include quality of life scales, as measured by the Angioedema Quality of life (AE-QoL) (Weller, Groffik et al. 2012) and Depression, Anxiety, Stress Scales (DASS) (Crawford and Henry 2013). In addition, serial PK parameters and PD endpoints will be reported.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

Approximately 58 to 90 subjects are planned to be randomized and enrolled in this study: up to 36 subjects in Part 1 (350 mg or placebo) and approximately 14 subjects in Part 2, approximately 20 subjects in Part 3, and approximately 14 or 20 subjects in Part 4 (number predicated on results from 62.5 mg BCX7353 Treatment Group in Part 3). In the event that the active study drug dose is modified in Part 1 to 250 mg, up to 36 additional subjects may be enrolled into Part 1 (see Section 9.5.2) for a total of 126 subjects enrolled in this study (78 to 84 subjects receiving active study drug).

Subjects who withdraw from the study may be replaced at the Sponsor's discretion. Any subject that 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 as documented at any time in the medical records or at the screening visit by a low C1 INH functional level (Type 2) or a low C1 INH antigenic level (Type 1)
4. A documented HAE attack rate of at least 2 HAE attacks per month for 3 consecutive months (defined as 93 days) within the 6 months prior to the screening visit as documented in acceptable source records.

Source records of historical HAE attacks must exist (for all subjects) that permit a qualifying HAE attack rate to be calculated. 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.

NOTE: under no circumstances can the attack criterion threshold for enrollment be disclosed to any subject

5. Access to and ability to use 1 or more acute medications approved by the relevant competent authority for the treatment of attacks of HAE (icatibant, plasma-derived C1 INH or recombinant C1 INH).

6. 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 at least an acceptable effective contraceptive method during the study and for a duration of 30 days after last dose of study drug. One or more of the following methods are acceptable:
        - surgical sterilization (ie, bilateral tubal occlusion or vasectomy of male partner)
        - placement of an intrauterine device (IUD) or intrauterine system (IUS) (implanted any time prior to or during screening)
        - progesterone-only (implantable or injectable only) 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 at least an acceptable effective contraceptive method and (as proposed above) during study and for 30 days after the last dose of study drug.
    b. Be a woman of nonchildbearing potential (defined as postmenopausal for > 2 years or having 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."
7. Male subjects must comply with the following requirements during the study and for a duration of 90 days after last dose of study drug:
    a. Subjects with female partners of childbearing potential (defined as postmenopausal ≤ 2 years or a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) must agree to utilize at least 1 acceptably effective contraceptive method. At least 1 or more of the following methods are acceptable:
        - surgical sterilization (i.e., vasectomy or bilateral tubal occlusion of a female partner)
        - placement of an IUD or IUS
        - any form of hormonal contraception (oral, implantable, injectable, intravaginal, or transdermal)
        - use of a condom with or without spermicidal foam/gel/film/cream/suppository

- partner's use of an occlusive cap [diaphragm, or cervical/vault caps] with spermicidal (foam/gel/film/cream/suppository)

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

c. Male subjects who exclusively have male partners must consent to using a condom during intercourse throughout the duration of the study.

d. Must abstain from sperm donation during the study and for a period of 90 days after last dose of study drug.

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

8.2.2. Exclusion Criteria

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

1. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject of participating in the study.
2. Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.
3. Use of C1 INH, androgens, or tranexamic acid for prophylaxis of HAE attacks within the 7 days prior to the screening visit or initiation during the study. Androgen use is not permitted at any time during the study. Use of a C1 INH therapy for treatment of attacks is not excluded at any time.
4. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a QTcF > 470 msec, a PR > 220 msec, 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 cardiovascular abnormality.
6. Known family history of sudden death from causes other than HAE.
7. History of or current implanted defibrillator or pacemaker.

8. Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the Investigator, is clinically significant and relevant for this study. A calculated CL_{cr} (see Section 11.1.6) 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.

8.3. Subject Withdrawal Criteria

8.3.1. Subject Discontinuation from Study

Participation in the study is strictly voluntary. The only reason permitted for withdrawal from the study is a subject's withdrawal of consent to contribute additional study information. 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 must be recorded in the subject's medical records (source documents) and also in the electronic case report form (eCRF). If the reason for subject withdrawal is not known, the subject must be contacted to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 12.

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 may 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 all regularly scheduled visits and procedures outlined in Table 3.

- Emergence of any laboratory abnormality or adverse event 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
- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree

- Subject noncompliance with study drug or to the protocol
- 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)

8.3.2.1. Discontinuation Due to QT Prolongation

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

- The subject has a QTcF > 500 msec

  or

- The subject has a QTcF increase of more than 60 msec (confirmed by repeat ECG) from the mean QTcF value obtained from triplicate ECGs obtained predose on Day 1.

8.3.2.2. Discontinuation Due to Rash

Subjects who experience a Grade 2 or Grade 3 rash thought to be due to study drug will be discontinued from study drug and treated according to best medical practice. This may vary depending on the type of rash or reaction noted. All subjects with a suspected drug rash should undergo specific rash evaluation as described in Section 11.1.12.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

BCX7353 is an oral small molecule inhibitor of plasma kallikrein. All subjects will receive 28 days of BCX7353 capsules or matching placebo for oral administration at one of the following doses:

- BCX7353 placebo QD orally (Parts 1, 2, 3 and 4)
- BCX7353 350 mg QD orally (Part 1)
- BCX7353 250 mg QD orally (Parts 2 and 3)
- BCX7353 175 mg QD orally (Part 4, if conducted)
- BCX7353 125 mg QD orally (Parts 2 and 3)
- BCX7353 62.5 mg QD orally (Part 3; Part 4 if conducted)

The study drug in this study consists of BCX7353 and placebo capsules. The active ingredient for this study is BCX7353, supplied by BioCryst. BCX7353 is a white to tan powder.

The BCX7353 capsules will be provided as hydroxypropyl methylcellulose (HPMC), size 00, opaque capsules. In Parts 1 and 2, capsules will be filled with drug substance to correspond to one-third of the total daily assigned treatment dose. Three capsules of BCX7353 will be administered orally QD for 28 days. In Parts 3 and 4, capsules will be filled with drug substance to correspond to one-half of the total daily assigned treatment dose. Two capsules of BCX7353 will be administered orally QD for 28 days.

The matching placebo will also be provided as HPMC, size 00, opaque capsules to match the BCX7353 capsules. The matching placebo will contain microcrystalline cellulose. Three capsules (Parts 1 and 2) or two capsules (Parts 3 and 4) of matching placebo will be administered orally QD for 28 days.

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.

Parts 1 and 2: The study drug will be packaged in bottles of 27 capsules per bottle and each kit will contain 2 bottles of study drug.

Parts 3 and 4: The study drug will be packaged in bottles of 32 capsules per bottle and each kit will contain 1 bottle of study drug.

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

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

Further details on the study drug will be provided in the study drug manual.

9.3. Blinding and Randomization

9.3.1. Blinding

This is a double-blind study. As such, study drug assignment will be blinded to the Investigator, study staff, study subjects, and clinical research organization (CRO) staff. Sponsor employee(s) will also be blinded to the treatment allocation of individual subjects, with the exception of Sponsor staff responsible for managing clinical supplies. Employees who are not blinded to drug assignment will have no access to any other subject-level information for the duration of the study.

In order to make informed decisions about the conduct of the study after 24 subjects complete dosing in Part 1, Sponsor employees not regularly interacting with site staff may be unblinded at the time that the data package is available for review at the administrative interim analysis. Likewise, Sponsor employees may be unblinded at any time after the administrative interim during completion of Part 1 to enable decisions about initiation of or continued enrollment into Part 2.

9.3.2. Randomization

Up to 36 subjects will be randomized in Part 1 in 1:1 (placebo:active) ratio to one of the following treatments:

- Part 1, Treatment Group 1: placebo QD orally for 28 days
- Part 1, Treatment Group 2: 350 mg BCX7353 QD orally for 28 days

In Part 2, approximately 14 subjects are planned to be randomized in a 1:3:3 (placebo:active:active) ratio into 1 of the following 3 treatment groups:

- Part 2, Treatment Group 1: placebo QD orally for 28 days
- Part 2, Treatment Group 2: 125 mg BCX7353 QD orally for 28 days
- Part 2, Treatment Group 3: 250 mg BCX7353 QD orally for 28 days

In Part 3, approximately 20 subjects are planned to be randomized in a 1:3:3:3 (placebo: active: active: active) ratio into 1 of the following 4 treatment groups:

- Part 3, Treatment Group 1: placebo QD orally for 28 days
- Part 3, Treatment Group 2: 125 mg BCX7353 QD orally for 28 days
- Part 3, Treatment Group 3: 250 mg BCX7353 QD orally for 28 days
- Part 3, Treatment Group 4: 62.5 mg BCX7353 QD orally for 28 days

In Part 4, if conducted, approximately 14 subjects are planned to be randomized in a 1:6 (placebo:active) ratio into 1 of the following 2 treatment groups:

- Part 4, Treatment Group 1: placebo QD orally for 28 days
- Part 4, Treatment Group 2: 175mg BCX7353 QD orally for 28 days

OR the Alternative Part 4, if conducted, approximately 20 subjects are planned to be randomized in a 1:6:3 (placebo:active:active) ration into 1 of the following 3 treatment groups:

- Part 4, Treatment Group 1: placebo QD orally for 28 days
- Part 4, Treatment Group 2: 175mg BCX7353 QD orally for 28 days
- Part 4, Treatment Group 3: 62.5mg BCX7353 QD orally for 28 days

In all study parts, randomization will proceed in accordance with a computer-generated randomization schedule prepared by a nonstudy statistician.

A subject will be randomized by the Sponsor or designee during the screening period. Subject randomization will occur only after:

- Entry of the following data into the eCRF: qualifying historical HAE attack data, concomitant and past medications, historical C1 INH functional and antigenic assay results (if available), and the data collected on the HAE medication and medication history form.

  AND

- Sponsor review of eligibility of potential subjects based upon the entered eCRF data and any subsequent follow-up necessary with the Investigator or clinical site.

Subject randomization will trigger shipment of a study drug kit (used for 14 days) to the site. Specific details of the randomization and kit shipment processes will be communicated to the sites.

A study drug kit will contain sufficient treatment for 14 days (including overage to cover the visit window) and each subject will initially be assigned a drug kit to cover the first 14 days of treatment. Each subject will be assigned a total of 2 drug kits.

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

9.4. Study Drug (Investigational Medicinal Product) Administration and Treatment Compliance

Subjects will take all study drug doses at home with the exception of study drug that will be administered under Investigator (or designee) supervision during scheduled on-treatment clinic visits on Days 1, 14 and 15 (and Day 28 if applicable). Subjects will be instructed to take 3 capsules (Parts 1 and 2) or 2 capsules (Parts 3 and 4) of study drug orally QD in the morning for 28 days. Subjects will be instructed to take study drug with food, or within 30 minutes after consuming food. On Days 1, 14 and 29, subjects should fast for 8 hours prior to their blood draw for laboratory testing.

The first dose of study drug will be administered in the clinic on Day 1. For study Days 14 and 15, subjects should be instructed to refrain from taking study drug prior to their visit to obtain a trough and/or serial blood draws at steady state.

On in-clinic dosing days (Days 1, 14 and 15), subjects will be required to consume food within 30 minutes prior to dosing (but after any blood draws for safety laboratory testing); the requirements for type and amount of food is to be provided to the subject (e.g., number of

servings of protein, carbohydrate, and/or fat) will be communicated in a separate document. On all other days, subjects should take the study drug in the morning with food (or within 30 minutes after consuming food). It is recommended that the study drug be administered with food in order to help minimize gastrointestinal effects. If gastrointestinal-related symptoms are noted as an AE, the site should query the subject and record whether the drug is being taken as instructed (i.e., with food).

Subjects will be instructed to maintain approximately the same daily dosing interval between study drug doses. If a subject forgets to take the study drug at the correct time, the dose may be taken later in the day; however, no more than 1 dose of BCX7353 should be taken on any calendar day. The subject should resume the standing regular dosing schedule on the next day.

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

Subjects will be instructed to bring all drug kits (including both unused and used kit bottles) and diaries with them for each study visit. Accountability and adherence will be reviewed at each clinic visit.

9.5. Study Drug Dose Modification

9.5.1. Subject-Level Dose Modification

Subjects should be instructed to take the study drug dose and regimen as indicated by the protocol. No dose reductions are allowed on a subject-level basis. Temporary treatment interruptions may be permissible on a case-by-case basis in consultation with the Sponsor (see Section 12.1.8).

9.5.2. Part-Level Dose Modification

If the prevalence of gastrointestinal effects prevents full enrollment of Part 1 or study drug is poorly tolerated due to gastrointestinal effects, the Sponsor may reduce the Part 1 dose of BCX7353 to 250 mg QD for all future subjects randomized to active drug. Poor tolerability may be defined as prevalent mild events that affect quality of life. The data monitoring committee (DMC) will be convened to review gastrointestinal effects meeting the criteria outlined in Section 12.2.

A decision to reduce the Part 1 active dose to 250 mg QD will be communicated in writing to all sites with a date of implementation for newly enrolled subjects. Subjects in the 28-day treatment period at the time of implementation will continue on the study drug they received beginning on Day 1. Up to 36 subjects may be treated at 250 mg or placebo QD (1:1 ratio) in Part 1, regardless of the number of subjects previously randomized to 350 mg or placebo QD in Part 1.

Any dose level changes warranted for Parts 2, 3 or 4 will be instituted via protocol amendment.

9.6. Study Drug (Investigational Medicinal Product) Accountability

Accountability of returned drug kits will be performed by site personnel at study visits on Days 14 and 29. Returned drug kits must be retained and reviewed during monitoring visits by the clinical research associate (CRA, Section 14.2).

The Investigator/pharmacist must maintain accurate records of the disposition of all IMPs received from the Sponsor, issued to the subject (including date), and any drug accidentally destroyed. The Sponsor will supply a specific drug accountability form. At the end of the study, information describing study drug supplies (e.g., kit numbers) 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 or at other times as agreed by all involved parties, all medication not dispensed or administered will be collected with supervision of the CRA and returned to the Sponsor (or designee) or destroyed on site as dictated by the appropriate Standard Operating Procedure at the participating institution.

9.7. Concomitant Medications

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

Any concomitant medication not listed as prohibited 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 60 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

The following medications are prohibited in advance of screening through completion of the study given the potential for modulation of HAE attacks and/or exacerbation of HAE:

1. Use of C1 INH, androgens, or tranexamic acid for prophylaxis of HAE attacks within the 7 days prior to the screening visit or initiation during the study. Androgen use is not permitted at any time during the study. Use of a C1 INH therapy for treatment of attacks is not excluded at any time.
2. Use of an estrogen-containing hormonal contraceptive within 60 days of the screening visit or initiation during the study.
3. Initiation of a progesterone-containing hormonal contraceptive within 60 days of the screening visit or initiation during the study. Progesterone eluding IUDs may be placed at any time. Conversion from an oral progesterone contraceptive that inhibits ovulation to an injectable or implantable progesterone contraceptive is allowed up to 1 week prior to study drug initiation.
4. Use of an angiotensin-converting enzyme inhibitor at screening or initiation during the study.

The following are prohibited medications based upon nonclinical data generated with BCX7353:

1. Daily use of a medication that is clinically known to induce or inhibit drug transporters P-gp or BCRP 7 days prior to Day 1 or initiation during the study.

An updated list of such medications can be found at: http://dbts.ucsf.edu/fdatransportal/transporters/ABCB1/ and http://dbts.ucsf.edu/fdatransportal/transporters/ABCG2/; see *clinical drug-drug interactions, Interacting Drug* column.

2. Daily use of a medication that primarily relies upon BCRP or P-gp transport proteins for systemic disposition 7 days prior to Day 1 or initiation during the study.

   An updated list of such medications can be found at: http://dbts.ucsf.edu/fdatransportal/transporters/ABCB1/ and http://dbts.ucsf.edu/fdatransportal/transporters/ABCG2/; see *clinical drug-drug interactions*, *Affected Drug* column.

3. Use of a medication that is clinically known or possibly to prolong the QT interval 7 days prior to Day 1 or initiation during the study.

   Medications falling into the *drugs with a known risk of torsades de pointes*, *drugs with a possible risk of torsades de pointes* are listed at: https://www.crediblemeds.org/index.php/?cID=328 (please note this website requires registration)

4. Daily use of a medication that primarily relies upon (ie is a substrate for) CYP2C9, CYP2C19, CYP2D6 and CYP3A4 for metabolism 7 days prior to Day 1 or initiation during the study.

   A list of medications can be found at: http://medicine.iupui.edu/clinpharm/ddis/clinical-table; see *substrate* columns for the previously named CYPs. Please also note that desogestrel is a CYP2C substrate. Subjects who take a desogestrel-based contraceptive at screening may switch to an injectable or implantable progesterone-only contraceptive at any time prior to randomization.

   A drug interaction study designed to elucidate the clinical relevance of the nonclinical CYP2C9, CYP2C19, CYP2D6 and CYP3A4 inhibition data with BCX7353 is imminently planned for dosing. If the results of this study indicate that one or more CYP enzymes are not clinically inhibited by BCX7353, the medications metabolized by the unaffected CYP will no longer be prohibited for use on study. A memo outlining the findings and impact on prohibited medications will be sent to each study Investigator.

In addition, current participation in any other investigational drug study or having received another investigational drug within 30 days of the screening visit is prohibited.

9.7.2. Other Restrictions

Subjects will abstain from all bergamottin containing fruits and fruit juices (e.g., Seville oranges, grapefruit, grapefruit juice, pomelos, marmalade) from 7 days prior to Day 1 through the last follow-up visit.

10. STUDY CONDUCT

10.1. Overview

This is a randomized, placebo-controlled study. A subject's participation in this study is expected to be up to 65 days (inclusive of the screening and follow-up periods). Each eligible subject who consents to participate in the study will receive either 28 days of BCX7353 or placebo. All subjects will undergo a screening period of up to 21 days and a 16-day follow up period. During the 28-day dosing period, all subjects will be required to attend 6 visits: Day 1, Day 14 (safety, PK, and PD assessments), Day 7 and 21 (liver function assessment, AE, concomitant medication and diary compliance assessments), Day 15 (24-hour PK visit), and a final visit on the day following cessation of dosing, Day 29. All subjects will return for a follow-up visit on Day 44.

10.2. Schedule of Assessments

The schedule of assessments for this study is summarized in Table 3.

Table 3: Schedule of Assessments for Study BCX7353-203

Assessment	Screening	Baseline Day 1[u]							Follow-up (or Early Term [ET])
	Day –21 to –1	Day 1 Pre-Dose	Day 1 Post-dose	Day 7 ± 1 days	Day 14 ± 2 days	Day 15[t] Pre-dose	Day 21 ± 1 days	Day 29 + 1 day	Day 44 + 7 days
Informed consent[a]	X								
Clinic visit[b]	X	X		X	X	X	X	X	X
Inclusion/ Exclusion criteria & prohibited medications	X	X							
Medical history	X	X							
HAE medical and medication history	X								
Height/Weight/BMI	X	X[d]			X[d]			X[d]	X[d]
Drugs of abuse screen[e]	X								
HIV/HCV/ HBV serology	X								
C1 INH antigenic and/or functional level[f]	X	X						X	
Physical examination[g]	X	X[g]			X[g]			X[g]	X[g]
12-lead ECG[h]	X	X			X			X	X
Vital signs[i]	X	X			X			X	X
Pregnancy test[j]	X	X			X			X	X
FSH[k]	X								
D_LCO	X							X[l]	
Chemistry, hematology and coagulation laboratory evaluations[e]	X	X			X			X	X
Liver Function Test[e]				X			X		
Troponin I & Troponin T		X			X			X	X

Assessment	Screening	Baseline Day 1[u]							Follow-up (or Early Term [ET])
	Day −21 to −1	**Day 1 Pre-Dose**	**Day 1 Post-dose**	**Day 7** ± 1 days	**Day 14** ± 2 days	**Day 15[t] Pre-dose**	**Day 21** ± 1 days	**Day 29** + 1 day	**Day 44** + 7 days
C3		X							
HLA typing[m]		X							
Optional sample for possible exploratory pharmacogenomic testing[v]		X							
NGAL		X			X			X	X
CK-MB		X			X			X	X
Urinalysis[e]	X	X			X			X	X
Attack frequency confirmation	X								
Sponsor approval and randomization[n]	X								
HAE attack and dosing diary instruction/review/collection[o]	X	X	X	X	X	X	X	X	X
Diary completion[p]	←								→
AE-QoL and DASS		X			X[x]			X	
Plasma for PK analysis[q]		X			X[t]	X[t]		X	
Plasma for kallikrein inhibition[q]		X			X[t]	X[t]		X	
Plasma for additional PD analysis[r]		X			X			X	
Concomitant medications	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X
study drug accountability/dispensing			X		X[w]			X	X (ET)
study drug dosing[s]			←				→		

a Signing of the main informed consent may occur in advance of the screening visit, which is defined as the visit where site-conducted screening procedures are performed. Subjects will also be asked to sign a separate consent form permitting collection of a blood sample at baseline for possible exploratory pharmacogenomic analysis (this consent form may be signed at any time during the study prior to drawing the sample).

b Clinic visits are scheduled for screening and Days 1, 7, 14, 21, 29, and 44. Additionally, a Day 15 visit for a 24-hour PK and PD sample post 14 dose will occur. If the subject is unable to provide serial PK samples on Day 14, steady state PK samples may be obtained on Day 28, with a 24-hour PK sample drawn at the scheduled visit on Day 29. d Weight only.

e Analytes to be measured can be found in Table 4. Subjects are required to fast overnight for at least 8 hours prior to blood draw on Days 1, 14, and 29.

f If no prior laboratory results confirming HAE diagnosis are available at screening, C1 INH level and function will be drawn. At baseline (Day 1) and Day 29, all subjects will have a sample for C1 INH function drawn.

g Physical examinations conducted after the screening visit will be targeted to reported signs and symptoms. A complete physical examination will be performed at screening only.

h Bedside 12-lead ECGs will be conducted in triplicate predose on Day 1; all other 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.

i Vital signs include measurement of heart rate, blood pressure and temperature. Temperature will be measured only at screening and on Day 1.

j 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).

k FSH will be measured in women declaring themselves postmenopausal ≤ 2 years.

l If the site cannot perform D_LCO onsite, the Day 29 sample may also be assessed any time from Day 24 to Day 32.

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

n Subjects will be randomized by the Sponsor on or after the screening visit and is contingent upon review of screening visit data entered into the eCRF subsequent questions the Sponsor may have (see Section 9.3.2). Randomization will trigger shipment of a kit of study drug for the first 14 days and an automatic resupply to arrive on-site at approximately study Day 10 after entry into the eCRF system that the subject has had a Day 1 visit. More details on randomization and kit shipment will be provided to the site.

o The Investigator (or designee) will provide a diary for collection of HAE attacks (screening through follow-up) and study drug dosing (Days 1-28) at screening, Day 1, Day 14 and Day 29. Diaries will be collected on Day 1 (screening diary), Day 14, Day 29 and follow-up. At each visit and phone call, the Investigator (or designee) will review proper recording of attacks and dosing (as applicable) in the diary.

p At any time the diary is in a subject's possession, they will enter HAE attacks and relevant details and dosing information (as applicable) at least once per day.

q On Day 14, a blood sample for plasma PK and plasma kallikrein analysis will be drawn prior to dosing (< 5 min) and at 1, 2, 3, 4, 5, 6, 8, and 24 hours postdose (i.e., on Day 15); Day 29 will be trough samples. If the subject is unable to provide serial PK samples on Day 14, steady state PK samples may be obtained on Day 28, with a 24-hour PK sample drawn at the scheduled visit on Day 29. In this case, trough PK samples will be drawn on Day 14. If the subject has a Day 29 visit for the 24-hour PK sampling, concomitant medications and AEs should also be assessed at the visit. Within 6 hours postdose, an acceptable window around each PK draw is ± 10 minutes. After 6 hours, an acceptable window is ± 20 minutes. Plasma PK and plasma kallikrein samples will be collected prior to in clinic dosing on Day 1 and Day 14. The Day 29 samples will be collected approximately 24 hours post-last dose.

r A sample for possible exploratory analysis used to elucidate PD properties of BCX7353 will be drawn.

s Subjects will take their study drug in the clinic on Day 1, Day 14 and Day 15 (Day 28 if subjects must complete serial PK on the last dose). Subjects will take all other doses at home as instructed. The last day of study drug dosing is Day 28.

t Subjects unable to undergo the serial PK blood draw on study Day 14 will only have a predose or trough blood sample drawn; a steady-state serial PK blood collection will then be obtained on Day 28 with a 24-hour blood draw conducted at the scheduled visit on Day 29. In the event the serial PK is not conducted on Day 14, the Day 15 visit is not required.

u If the site is unable to conduct all procedures for an individual subject at Baseline on Day 1 because of logistical reasons, refer to Section 10.3.2 for procedures that may be conducted on Day −1.

v A blood sample for possible exploratory pharmacogenomic testing will be drawn at the Baseline/Day 1 sample only if consent is obtained for this optional testing; if a blood sample is not obtained at Baseline, the sample may be drawn at any time during the study following consent obtained from the subject.
w Study drug may be dispensed to the subject on Day 15 after in-clinic dosing in lieu of dispensing on Day 14 if preferred.
x The AE-QoL questionnaire will not be administered at the Day 14 visit.

10.3. Study Visits

10.3.1. Screening

Prospective subjects should be screened within 21 days prior to Day 1. 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 and prohibited medications
- Review of HAE attack frequency documentation
- HAE medical and medication history
- Medical history
- Complete physical exam
- 12-lead ECG
- Height/weight/BMI estimation
- Vital signs (blood pressure, heart rate and temperature)
- Serum pregnancy test for female subjects of child-bearing potential
- Blood collection for clinical chemistry, hematology, coagulation, HBV/HIV/HCV serology, C1 INH level and function (if no historical results), FSH (for women who declare that they have been post-menopausal ≤ 2 years)
- D_LCO testing (either at the screening visit or during the screening period [See Section 11.1.11])
- Urine collection for urinalysis and drugs of abuse screen
- Recording of adverse events and concomitant medications
- HAE attack diary provision and instruction
- Signing of informed consent for collection of optional sample for possible exploratory pharmacogenomic analysis (baseline blood draw)

In the case of time limitations for conduct of the screening visit, a site is permitted to perform screening assessments over more than one screening visit.

A subject will be randomized during the screening period by the Sponsor (or designee). Subject randomization will occur only after entry of the required data obtained during the screening period into the eCRF (see Section 9.3.2) and any discussion the Sponsor feels is necessary with

the Investigator to ensure suitability of the screened subject for the study. Subject randomization will trigger shipment of a study drug kit (for the first 14 days) to the site so the study drug is available on site for the Day 1 Baseline visit.

All screening procedures are outlined in Table 3 and are described in Section 11. Subjects will be given a subject HAE attack diary, and instructed how to record details of any angioedema attacks that occur (Section 11.2.2). Subjects will be asked to complete the diary once each day starting at the screening visit.

If a subject does not initiate treatment within the 21 day screening window, all or part of the screening procedures may be repeated if the subject's medical condition has changed, at the discretion of the Investigator, following discussion with the Sponsor.

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 that do not enter the study.

10.3.2. Baseline (Day 1)

Subjects that meet all study eligibility criteria, are approved by the Sponsor, and who agree to participate will be asked to return for a scheduled Day 1 visit. Inclusion/ Exclusion criteria will be reviewed to ensure continued subject eligibility. Subjects should fast overnight for at least 8 hours prior to the blood draw for the laboratory testing.

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

- Review of inclusion and exclusion criteria and prohibited medications
- Review of medical history
- Review and collection of diary entries during screening and further diary instruction
- Review of concomitant medications
- Administration of the AE-QoL and DASS questionnaires
- Weight
- Vital signs (heart rate, blood pressure, and temperature)
- 12-lead ECG (in triplicate)
- Targeted physical exam
- Assessment of any AEs that have 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 C3, Troponin I and Troponin T, NGAL, and CK-MB and HLA typing
- Optional blood collection for possible exploratory pharmacogenomic analysis (if consent was signed)
- Plasma sample for additional PD analyses for possible exploratory analyses used to elucidate PD properties of BCX7353
- Blood collection for C1 INH functional level
- Subjects will consume food within 30 minutes prior to first dose (specifications as to type and amount of food is to be served will be communicated to each site in a separate document)
- Predose blood samples for PK and plasma kallikrein inhibition testing

The first dose of study drug will be administered and the following assessments will then be completed:

- Dispensation of new HAE attack and dosing diaries and diary entry of dosing administration
- Dispense study drug for Days 1 through the Day 14 visit
- Review of concomitant medications and AEs

Prior to discharge from the clinic the subject will be reminded to complete the Diary once each day for dosing and any HAE attacks that occur.

If the site is unable to conduct all of the procedures for an individual subject at Baseline on Day 1 because of logistical reasons, the following procedures may be conducted on Day −1: review of inclusion and exclusion criteria, medical history, diary, and concomitant medications; administration of the AE-QoL and DASS questionnaires; weight, vital signs (heart rate, blood pressure, and temperature), and a 12-lead ECG (in triplicate) recording; conducting a targeted physical exam; assessment of any AEs that have 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, coagulation, C3, Troponin I and Troponin T, NGAL, CK-MB, and HLA typing; sample for optional possible exploratory pharmacogenomic analysis; plasma sample for additional PD analyses (e.g., a sample for possible exploratory analyses used to elucidate PD properties of BCX7353) and blood collection for C1 INH levels.

10.3.3. Study Day 7 Visit

Subjects are required to visit the clinic for the following assessments on Day 7 (± 1 day):

- Blood collection for liver function tests
- Review of concomitant medications and AEs
- Review of HAE attack and dosing diary completion and study drug compliance

10.3.4. Study Day 14 Visit

Subjects will return to the clinic during Week 2 (Study Day 14 ± 2 days). Subjects will be instructed not to take their dose of study medication before the study visit. Subjects should arrive in the clinic in a fasted state (8 hours from last ingestion of food).

The following assessments will be performed:

- Subject weight
- Targeted physical examination
- Vital signs (blood pressure and heart rate)
- 12-lead ECG (including review of QTcF to Baseline value)
- Review of concomitant medications and AEs
- Administration of the DASS questionnaires
- 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 Troponin I and Troponin T, NGAL, and CK-MB
- Plasma sample for additional PD analyses for possible exploratory analyses used to elucidate PD properties of BCX7353
- Subjects will consume food within 30 minutes prior to dosing (specifications as to what and how much food is to be served [e.g., servings of protein, carbohydrate, and/or fat] will be communicated to each site in a separate document)
- Collection and review of completed HAE attack and dosing diaries
- Predose blood samples for PK (i.e., trough PK sample) and plasma kallikrein inhibition testing

The last dose of study drug from the first assigned kit will be administered and the following assessments will then be completed:

- Serial blood samples drawn for PK analysis and for plasma kallikrein inhibition as outlined in Section 11.1.13 and Section 11.1.14.
- Dispensation of new HAE attack and dosing diaries
- Recording of study drug dosing time in the diary
- Study drug accountability and new study drug kit dispensing (unless held for Day 15 dispensation)
- Any further instruction on HAE attack and dosing diary completion and study drug compliance

10.3.5. Study Day 15

If the subject underwent serial PK blood draws on Day 14, the subject will return to the clinic to have blood drawn for a PK analysis sample and a plasma kallikrein inhibition sample 24 hours after the initial dose on Day 14. The subject will be instructed not to take their study drug prior to the blood draw. Subjects will consume food within 30 minutes prior to dosing (specifications as to what and how much food is to be served [e.g., servings of protein, carbohydrate, and/or fat] will be communicated to each site in a separate document). Study drug will be administered in-clinic; study drug dosing time will be recorded in the diary for Day 15 while the subject is in-clinic. If preferred by the subject and/or site, the new study drug kit assigned on Day 14 may be dispensed to the subject after dosing on Day 15. Review of concomitant medications and AEs will be performed. Subjects will also be reinstructed on HAE attack and dosing diary completion and study drug compliance. Concomitant medication, AE and diary review may take place post-dose if desired by the site.

10.3.6. Study Day 21 Visit

Subjects are required to visit the clinic for the following assessments on Day 21 (± 1 day):

- Blood collection for liver function tests
- Review of concomitant medications and AEs
- Review of HAE attack and dosing diary completion and study drug compliance

10.3.7. Study Day 29 Visit

Subjects who were unable to complete their steady state PK sampling at the Day 14 visit will undergo serial PK and PD assessments around the last dose (Day 28) visit with a 24-hour PK collection at the scheduled visit on Day 29; blood samples will be obtained as outlined in Section 11.1.13 and Section 11.1.14. AEs and conmeds will be collected and diary completion will be supervised should this visit occur.

Subjects will return to the clinic on Day 29 (+ 1 day), timed preferably to capture a trough PK sample approximately 24 hours post-last dose. Subjects should arrive in the clinic in a fasted state (at least 8 hours from last ingestion of food).

The following assessments will be performed:

- Blood samples for PK and plasma kallikrein inhibition testing
- Subject weight
- Targeted physical examination
- Vital signs (blood pressure and heart rate)
- 12-lead ECG
- Review of concomitant medications and AEs
- Collection and review of completed HAE attack and dosing diaries and dispensation of new diaries to be completed during follow-up
- Administration of AE-QoL and DASS questionnaires

- D_LCO testing*
- 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 Troponin I and Troponin T, NGAL, and CK-MB
- Plasma sample for additional PD analyses for possible exploratory analyses used to elucidate PD properties of BCX7353
- Blood collection for C1 INH functional level
- Study drug collection and accountability

*Note: If D_LCO testing cannot be conducted on site, the Day 29 D_LCO test may be assessed any time from Day 24 to Day 32.

10.3.8. Follow-up/Early Termination Visits

Subjects who discontinue treatment early must continue to complete all regularly scheduled visits and procedures as outlined in Table 3. As indicated in Section 8.3.1, the only reason for withdrawal from the study is a subject's withdrawal of consent. A subject who withdraws consent prior to study completion will be requested to attend a termination visit to complete all end-of-study evaluations.

For all subjects who complete treatment the follow-up visit should be conducted on follow-up Day 44 (+ 7 days). Assessments to be performed at this visit are outlined in Table 3 and described in Section 11. In the event that there are clinically significant findings from safety assessments that are ongoing at follow-up Day 44, the subject will be followed at additional study visits until the findings are resolved or stabilized at a new baseline.

The following assessments will be performed at the follow-up or early termination visit:

- Subject weight
- Targeted physical examination
- Vital signs (blood pressure and heart rate)
- 12-lead ECG
- 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 Troponin I and Troponin T, NGAL, and CK-MB
- Study drug accountability (for subjects who discontinued treatment early)
- Review and collection of the attack diaries

11. ASSESSMENTS

The schedule of procedures/assessments to be conducted is outlined by study day in Table 3 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 and medication history will be captured for each subject participating in the study at the Screening visit. Medical history and review of inclusion and exclusion criteria and prohibited medications will also be rechecked before dosing on Day 1. Prior to dosing, laboratory samples should be obtained in the fasted state. Once blood samples are obtained, the investigator will need to ensure that the subject consumes food within 30 minutes prior to dosing and takes a PK sample where indicated within 5 minutes of dosing; all other assessments can occur in any order. After dosing PK sampling takes precedence and needs to be obtained at the specified time points as described in Section 11.1.13.

11.1.1. Physical Examination

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

11.1.2. HAE Medical and Medication History

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

11.1.3. 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.

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

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

11.1.5. 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 be obtained only at screening and Day 1 predose.

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 4. Subjects should fast overnight for at least 8 hours prior to the blood draw for the laboratory testing on Days 1, 14, and 29. An overnight fast is not required for the blood draws for laboratory testing on Days 7 and 21.

All laboratory samples will be analyzed 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 kit contents, reordering supplies, sample collection, handling, storage and shipment instructions. 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 4: **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, bicarbonate [CO2], phosphorus) • Lipid panel (total cholesterol, triglycerides) ***Baseline and Day 29 visit only* • Creatine kinase • Creatinine and calculated CL_{cr} • Gamma-glutamyltransferase (GGT) • Lactate dehydrogenase (LDH) • Total serum protein • Uric acid • Amylase (reflex lipase if amylase > 2 × ULN)	• Hemoglobin • Hematocrit • Erythrocytes • MCH • MCHC • MCV • White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) • Platelets
Urinalysis	**Pregnancy Test**
• Specific gravity • Blood • Bilirubin • Glucose • Leukocytes • Ketones • Nitrates • pH • Protein • Urobilinogen • Microalbumin to creatinine ratio • Reflex Microscopy if dipstick is abnormal	Serum (screening) and urine (other scheduled visits) βHCG for women of childbearing potential only
Coagulation	**Drug screen**
• Prothrombin time (PT) and international normalized ratio (INR) • Activated partial thromboplastin time (aPTT)	• Amphetamines • Barbiturates • Benzodiazepines • Cocaine • Opiates • Methamphetamine • Ecstasy
Liver Function Tests	**Additional Tests**
• ALP • ALT • AST • Bilirubin (total and direct) • GGT	• FSH for women postmenopausal ≤ 2 years • Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody; if HCV antibody positive, reflex to HCV RNA testing • Troponin I • Troponin T • Neutrophil gelatinase-associated lipocalin (NGAL) • CK-MB • C3 • HLA typing • Sample for possible exploratory pharmacogenomic analysis (optional) • C1 INH level and function

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

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

11.1.7. 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 chronic hepatitis C infection.

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

If laboratory results confirming HAE diagnosis are not historically available, additional testing to determine C1 INH levels and function will be performed from a sample drawn at screening.

C1 INH function will be measured from samples taken on all subjects at Day 1 and Day 29.

11.1.10. Other Laboratory Assessments

Troponin I, Troponin T, NGAL and CK-MB will be measured in this study at the following time points: Day 1, Day 14, Day 29, and follow-up/early termination. C3 level will be taken at Baseline only unless required for AE assessment (see Section 12.2.1).

11.1.11. Pulmonary Diffusion

Pulmonary diffusion testing, which can measure clinically significant thickening of the capillary alveolar space, will be required for all subjects. Testing will be conducted at the screening and Day 29 visits. If the site cannot perform this procedure onsite, an offsite provider may be used. The procedure will be done according to the specific protocol of the pulmonary lab performing the assessment. If the site cannot perform the D_LCO onsite, the screening assessment can occur anytime before baseline, and the Day 29 assessment may be assessed any time between Day 24 and Day 32.

Findings from the screening D_LCO will not be used to establish study eligibility. However, the results should be reviewed (with documentation of review) by the Investigator before dosing to ensure no underlying medical conditions, that, in the opinion of the Investigator, would interfere with the subject's safety or ability to participate in the study.

It is required that the same laboratory perform all D_LCO testing for an individual subject.

11.1.12. 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 a rash is diagnosed (Section 12.1.5.1). In the event the site is notified of a rash on the weekend, 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 assessed as possibly, probably or definitely related to study drug by the Investigator as soon as logistically possible:

- Full dermatological exam to include the scope of the rash (location), vital signs, and mucosal examination. The notes documenting the examination should include detailed description of the rash, presence or absence of 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.
- Blood taken for chemistry, hematology including differential, and C3 level
- Urine sent to local laboratory for urine eosinophils (if evaluation is available locally)
- 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.
- 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.

In addition, although not mandatory, it is requested that a biopsy of a fresh lesion both for diagnostic and scientific purposes be obtained in all subjects with a drug-related rash after obtaining specific informed consent for the biopsy. If the study site cannot perform a biopsy or any of the above mandatory assessments (i.e., photographs), then subjects should be referred to a physician who can perform the assessments/biopsy (i.e., a dermatologist). If a non-study physician performs any of the assessments or biopsy, a full written consultation should be obtained expeditiously consisting of their exam findings and assessment. Subjects undergoing a biopsy will provide appropriate consent for both the procedure and the reporting of the biopsy

results to BioCryst. Biopsies should be at least 3 mm minimum diameter and submitted to a local pathologist as per the local lab standard practices.

The time of each assessment described in this section, including any medications administered in the treatment of rash, must be denoted in the source records.

11.1.13. Pharmacokinetics

All plasma samples for determination of BCX7353 concentrations will be analyzed using a validated liquid chromatography-mass spectroscopy assay. Instructions for collection, processing, storage, and shipment of PK samples will be provided to the clinical site in the laboratory manual. Samples may also be analyzed on an exploratory basis for possible BCX7353-metabolites.

On Day 14 serial blood samples will be drawn for PK analysis predose and at the following time points: 1, 2, 3, 4, 5, 6, 8, and 24 hours postdose. For the 24 hour postdose samples, subjects will return to the clinic and have the blood sample drawn prior to dosing on Day 15. On Day 29, a trough PK blood sample will be drawn.

However, if the subject is unable to provide serial PK samples on Day 14, only the predose sample (i.e., trough PK sample) will be obtained on Day 14 and steady state serial PK samples will be obtained on Day 28, with a 24-hour PK sample drawn at the scheduled visit on Day 29.

Within 6 hours postdose, an acceptable window around each PK draw is ± 10 minutes. After 6 hours, an acceptable window is ± 20 minutes. Predose samples should be drawn within 5 minutes of the next scheduled dosing time.

Plasma BCX7353 PK parameters will be calculated as applicable, including the following: maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration versus time curve (AUC), and 24 hour half-life ($t_{1/2}$) in plasma.

Actual date and time of PK sample collection will be recorded in the eCRF. In addition, the site should verify that the time of last dose taken at home prior to the visit is documented in the diary.

The lab performing bioanalytical analysis will be provided the randomization scheme. Two samples will ordinarily be analyzed for subjects randomized to placebo: the 4 hour postdose sample on Day 14 and the trough at Day 29.

11.1.14. Pharmacodynamics

On Day 1 and Day 14 a plasma sample for plasma kallikrein analysis will be drawn prior to dosing and, on Day 14, at 1, 2, 3, 4, 5, 6, 8, and 24 hours postdose. The Sponsor may waive the participation in any or all serial PD sampling on a case by case basis. A sample for plasma kallikrein analysis will also be drawn on Day 29.

A plasma sample for possible exploratory analysis used to elucidate PD properties of BCX7353 will be drawn on Day 1, Day 14, and Day 29.

Instructions for collection, processing, storage and shipment of samples will be provided in a separate document.

11.1.15. HLA Typing

All subjects will have a blood sample drawn at Baseline/Day 1 (or any other time point on study if not obtained at Baseline) for HLA-typing. Samples will be sent to a central laboratory for analysis. The results will not be communicated back to the investigator or subjects because the results are not intended for diagnostic or prognostic purposes and will be used in a research related fashion only.

11.1.16. Possible Exploratory Pharmacogenomics Testing

All subjects who are willing to participate and sign a separate informed consent will have a blood sample drawn at Baseline / Day 1(or any other time point on study if not obtained at Baseline) for possible exploratory pharmacogenomics testing. Testing may be undertaken in one or more locus/loci if desired by the Sponsor to examine whether allelic variations account for efficacy or safety findings. Samples will be sent to a central laboratory for analysis and results will not be returned to sites.

11.2. Subject-Completed Assessments

11.2.1. Quality of Life Questionnaires

To assess quality of life, the AE-QoL and DASS questionnaires will be administered once at Baseline, Day 14 (DASS only) and at Day 29.

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 and Dosing Diaries

The Sponsor will supply paper diaries to all sites. Sites will dispense diaries to subjects at screening, Day 1, Day 14 and Day 29. Diaries will be collected on Day 1, Day 14, Day 29 and at follow-up.

At the Screening visit, subjects will be instructed how to complete the diary for an attack. While a subject has a diary in their possession, the subject will fill out the HAE attack diary daily, recalling whether symptoms of an HAE attack were experienced in the last 24 hours. Subjects must fill out the diary daily, regardless of the presence of HAE symptoms. If the subject does report an attack in their diary, additional details about the attack will be required, including location of the symptoms of the attack, severity, and treatment(s) administered and times of administration. During the treatment period, subjects will also record the time of day study drug was taken, and the number of capsules of study drug taken at each dose in the diary on a daily basis. Study drug doses administered in the clinic will be entered into the diary on site.

The Investigator (or designee) will proactively assess completion of the diary, during visits on Days 1, 7, 14, 21 and 29. While study staff are not permitted to make any entries into the diary, subjects may be asked to rectify incomplete diary entries made since the last visit/phone call based on outstanding questions a subject may have or incorrect assumptions/interpretation of diary questions.

Further training on completing the diary should be provided at each clinic visit or where required, during a telephone call.

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. Examples of such events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization.

In addition, the sponsor considers any abortions (elective or spontaneous), fetal demise, and still birth to be serious adverse events for reporting purposes (see Section 12.1.6).

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.

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. All AEs and SAEs are to be reported on the AE eCRF.

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, 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 be sent to the Sponsor within 24 hours 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 16.1). Any AEs not covered by the DMID criteria will be assessed and classified into 1 of 4 clearly defined categories as follows:

Mild: (Grade 1): Transient or mild symptoms; no limitation in activity; no intervention required. The AE does not interfere with the participant's normal functioning level. It may be an annoyance.

Moderate: (Grade 2): Symptom results in mild to moderate limitation in activity; no or minimal intervention required. The AE produces some impairment of functioning, but it is not hazardous to health. It is uncomfortable or an embarrassment.

Severe: (Grade 3): Symptom results in significant limitation in activity; medical intervention may be required. The AE produces significant impairment of functioning or incapacitation.

Life-threatening: (Grade 4): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required to prevent death, hospitalization or hospice care probable.

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 SUSAR reports (initial and follow-up) and other safety information (e.g., revised IB) in their files.

BioCryst or its designee will submit all SUSAR reports (initial and follow-up) or other safety information (e.g., 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 suspected 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 CRF in real time. All additional follow-up evaluations of the event must be reported to BioCryst or its designee as soon as they are available. The SAE/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. This also allows the independent DMC to review the emerging safety data in real time. In addition, the report form will allow a full clinical description and information regarding the evaluation that cannot be documented in the EDC due to free text limitations.

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 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 licensing 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. Treatment Interruptions

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

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

12.1.9. Emergency Procedures

Access to study drug/IMP assignment will be available if the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety, in case of a medical emergency, to meet regulatory reporting obligations, or if warranted during scheduled safety reviews. Where medically appropriate, the Investigator will contact the Sponsor Medical Monitor to discuss the situation which has arisen and resulted in the need for unblinding of the subject. The Sponsor Medical Monitor will not be involved in the decision to unblind.

Detailed instructions for unblinding will be provided in a separate communication to the sites.

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 abnormalities or AEs that are suspected to be drug 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 2 or higher 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 11.1.12 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. 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.

In the event that study personnel become aware of an overdose of study drug/IMP (> 3 capsules per calendar day) that is associated with an AE, both the overdose and the resultant event should be reported as AEs. Overdose without any symptoms (i.e., AEs) does not need to be reported as an AE. If overdose occurs with or without associated AEs, subjects should undergo clinical and laboratory monitoring as appropriate for their clinical condition and, if indicated, should receive clinically-indicated supportive therapy.

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

12.3. Data Monitoring Committee

An independent DMC will review safety data. The DMC will meet on a scheduled basis at least 3 times: once after every 12 enrolled subjects have completed 28 days of dosing through Part 3 of the study. The DMC will also be convened at any time 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 that the BCX7353 response rate is unknown, the sample size was kept flexible to cover a range of response options that would achieve 90% power with an alpha of 0.05. The study population is expected to have a mean baseline attack rate of 1 attack/week. The expected mean reduction in attack rate of 350 mg BCX7353 QD is at least 70%. The mean reduction in attack rate in the placebo group may be as high as 30%. Sample size sensitivity assessments provided in Table 5 and Table 6 are based on various BCX7353 and placebo responses and variability.

Table 5: Power assessment based on sample size and on-study attack rate

Placebo			BCX7353			
Mean	**SD**	**n**	**Mean**	**SD**	**N**	**Power**
0.7	0.45	12	0.3	0.3	12	68%
0.7	0.45	12	0.3	0.45	12	55%
0.7	0.45	18	0.3	0.3	18	86%
0.7	0.45	18	0.3	0.45	18	74%
0.8	0.45	12	0.3	0.3	12	86%
0.8	0.45	12	0.3	0.4	12	79%
0.8	0.45	12	0.3	0.5	12	69%
0.8	0.45	18	0.3	0.3	18	97%
0.8	0.45	18	0.3	0.4	18	93%
0.8	0.45	18	0.3	0.5	18	87%

Note: Calculations were based on a 2-sided test at significance level of 0.05 and rates and SD are expressed in units.

Table 6: Power assessment based on sample size and attack free proportion

Placebo		BCX7353				
N	**Attack Free**	**N**	**70% Attack Free**	**75% Attack Free**	**80% Attack Free**	**85% Attack Free**
12	15%	12	85%	91%	95%	98%
12	20%	12	76%	84%	91%	95%
12	25%	12	67%	76%	84%	91%
18	20%	18	90%	95%	98%	99%
18	25%	18	83%	90%	95%	98%
18	30%	18	73%	83%	90%	95%

Note: Calculations were based on a 2-sided test at significance level of 0.05.

13.2. Statistical Methods

Subjects will be randomized in Part 1 in a 1:1 ratio to the 350mg BCX7353 QD and placebo QD treatment groups, in a 3:3:1 ratio to the 125 mg QD, 250 mg QD and placebo QD treatment groups in Part 2in a 3:3:3:1 ratio to the 62.5 mg QD, 125 mg QD, 250 mg QD and placebo QD treatment groups in Part 3. Part 4, if conducted and if excluding a 62.5 mg dose, will have subjects randomized in a 1:6 ratio to the placebo QD and 175 mg QD treatment groups. Part 4, if conducted and if including a 62.5 mg dose, will have subjects randomized in a 1:6:3 ratio to the placebo QD, 175 mg QD, and 62.5 mg QD treatment groups. , Subjects randomized to the same treatment will be pooled across all study parts and Treatment Group 4 (62.5mg QD) will be pooled with Part 3 and 4, if conducted, for the final analyses of efficacy, safety, PD and PK/PD where applicable.

A detailed statistical analysis plan (SAP) will be developed and finalized prior to database lock at the conclusion of the study. 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.

13.2.1. Interim Analyses

There will be one planned administrative interim in Part 1 of the study, after 24 subjects complete through the Day 28 dose. Sponsor employees not interacting with the site will receive unblinded primary and secondary efficacy tables and statistical output, at a minimum. Ad hoc analyses to enable discernment of treatment differences between the study drugs may be requested. At the conclusion of the interim analysis, a decision will be made to either continue enrollment into Part 1 or to close Part 1 and initiate Part 2 (dose ranging). A continuation of Part 1 may include up to 12 additional subjects for a total of up to 36 subjects completing Part 1 of the study. Additional administrative interim analyses will be conducted after completion of Parts 2 and 3 to support decision making for future development of the drug.

13.2.2. Analysis Populations

The analysis populations are defined below.

13.2.2.1. Full Analysis Set

The FAS population will include all subjects who are randomized, receive at least 1 dose of study drug, and have post baseline HAE diary data recorded. Subjects will be analyzed according to the randomized treatment. The FAS population will be the population for efficacy analyses.

13.2.2.2. Safety Population

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

13.2.2.3. Pharmacokinetic Population

The PK population will include all subjects for whom PK parameters can be estimated. The PK population will be the primary population for the PK analysis.

13.2.2.4. Pharmacodynamic Populations

13.2.2.4.1. Plasma Kallikrein Inhibition

The PD population for plasma kallikrein inhibition will include all subjects for whom at least 1 pre- and postdose plasma kallikrein inhibition result can be estimated. This population will be used for all analyses of plasma kallikrein inhibition and for correlation with PK or BCX7353 concentrations.

13.2.2.4.2. C1 INH

There will be 1 additional PD population, for C1 INH functional levels. This PD population will include all subjects with a baseline and at least 1 postdose value and will be the primary population for the relevant PD analyses.

13.2.3. 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 group 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 and duration of exposure will be presented for each treatment group. Treatment adherence, dose modifications and reason for dose modifications will be provided as summaries.

13.2.4. Analysis of Efficacy Variables

As discussed in Section 7.2.1, each subject-reported HAE attack must be confirmed by an independent adjudication panel prior to inclusion in any statistical analysis or summary of efficacy.

There are no formal hypotheses planned for the study. The primary efficacy endpoint is the number of confirmed HAE attacks in the FAS population. The number of HAE attacks will be analyzed by treatment group using appropriate descriptive statistics as follows: weekly attack rate, counts of attacks, proportion of subjects with no attacks, and number of attack-free days. The relative change in attack rate from placebo will also be calculated for each active arm. Efficacy analyses will be conducted for HAE attacks reported over the entire dosing interval (Days 1 to 28 inclusive) and during the dosing period in which BCX7353 should be at steady-state conditions (Days 8 to 28, inclusive).

Efficacy endpoints will be summarized and listed for each treatment group. Between-treatment comparisons (active vs placebo and between active dose groups) for continuous efficacy variables will be performed using an analysis of variance (ANOVA) and an analysis of covariance (ANCOVA) model. The between treatment comparisons for the proportion of subjects who are attack free will be compared using a Fisher's exact test. A general linear model will be used to test the dose response. Additional statistical models may be considered and details will be provided in the statistical analysis plan.

There will be no adjustments for multiplicity and all statistical tests will be 2-sided with an alpha of 0.05.

Secondary efficacy endpoints including attack severity, location, duration and symptoms of attacks, and number of attacks requiring attack medication will be summarized for each treatment group.

13.2.5. 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 Day 1 without an associated onset time may have occurred after the initiation of study drug. Hence, AEs occurring on Day 1 with no associated onset time will be assumed to be treatment emergent. 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 study visit and treatment group. Laboratory abnormalities will be graded according to the DMID Adult Toxicity Table (Publish Date: Draft, November 2007, see Appendix 16.1).

Any graded abnormality that occurs following the initiation of study drug and represents at least 1-grade increase from the baseline assessment is defined as treatment emergent. The number and percentage of subjects 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. D_LCO results will be presented as change from baseline in mL/min.

Clinically significant abnormal morphological ECG findings will be summarized by study visit.

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.

13.2.6. Pharmacokinetic Analysis

Concentrations of BCX7353 will be determined by validated plasma assays and will be summarized by treatment and displayed in figures. Plasma PK parameters for each subject will be estimated over the sampling interval using non-compartmental analysis (WinNonlin v 6.3 or higher, Pharsight Corp) and summarized by treatment and dose using descriptive statistics.

The PK parameters that may be estimated are listed in Table 7. Additional analyses may be conducted as appropriate.

Table 7: Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval (tau) (i.e., 24 hours for once daily dosing)
C_0	Observed concentration predose
$C_{av,ss}$	Average steady-state plasma drug concentration during multiple-dose administration
C_{max}	Maximum observed concentration of drug
C_{tau} (steady state only)	Observed drug concentration at the end of the dosing interval (tau)
CL/F	Apparent oral clearance after administration of the drug calculated as Dose/AUC_{tau}
λ_z	Terminal elimination rate constant, estimate by log linear regression of the terminal elimination phase of the concentration of drug versus time curve
V_z/F	Apparent volume of distribution of the drug
$t_{1/2}$	Estimate of the terminal elimination half-life of the drug
T_{max}	Time of C_{max}

In all derivations of PK parameters, zero will be substituted for concentrations below the quantification limit (BQL) of the assay. Samples which are BQL, but are between 2 samples with detectable concentrations will be excluded from PK analysis.

Dose proportionality will be analyzed using a power model and an ANOVA model based on dose normalized PK parameters. Additional analyses may be conducted as appropriate.

13.2.7. Pharmacodynamic Analysis

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

C1 INH functional levels and absolute change from baseline will be summarized.

13.2.8. Pharmacokinetic/Pharmacodynamic Analyses

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

13.2.9. Quality of Life Analyses

The change from baseline in the domain scores of the AE-QoL (function, fatigue, nutrition & fear/shame) and the DASS (depression, anxiety, stress) as well as the composite score of each instrument will be compared between the treatment and placebo groups. Individual items will be plotted to understand their contribution to the domain sub-scores.

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 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 (or designee) 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 subjects, parts of the trial or the entire trial, are defined in Section 8.3. 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 End of Trial is defined as the completion of the Last Subject's last scheduled study visit.

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. 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.

BioCryst will ensure that the use and disclosure of protected health information obtained during a research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, where this rule is applicable. The Rule provides federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in BioCryst-sponsored clinical trials. "Authorization" is required from each research subject, i.e., specified permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the ICF

(approved by the IRB/IEC) or it may be a separate document, (approved by the IRB/IEC) or provided by the Investigator or Sponsor (without IRB/IEC approval). 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.

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16. APPENDICES

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

http://www.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/Documents/dmidadulttox.pdf

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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