BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-204

AN OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY OF DAILY ORAL BCX7353 IN SUBJECTS WITH TYPE I AND II HEREDITARY ANGIOEDEMA

Version 9.0 (United States): 23 March 2020

IND No. 135,058

EudraCT No. 2017-003281-27

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

CONFIDENTIAL

Protocol Number:	BCX7353-204
Study Title:	An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema
IND Number:	135058
EudraCT No.	2017-003281-27
Investigational Product:	BCX7353
Indication Studied:	Hereditary Angioedema
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA
Sponsor Medical Monitor:	Sylvia Dobo, MD Phone (24 hours): +1 919-859-7905 Email Address: mm@biocryst.com
Clinical Study Manager:	Daniel Dix Senior Clinical Study Manager BioCryst Pharmaceuticals Office: +1 919-859-7933 Email Address: ddix@biocryst.com
Principal Investigators:	**Global:** Prof. Henriette Farkas MD, PhD, DSc Director of the Hungarian Angioedema Center 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary H-1125 Kutvolgyi ut 4 Phone: +36-1-3251481 Email Address: farkas.henriette@med.semmelweis-univ.hu **United States:** Dr. Aleena Banerji, MD Associate Professor Division of Rheumatology, Allergy and Immunology Massachusetts General Hospital 100 Blossom Street, Cox 201 Boston, Massachusetts, United States 02114 Phone: +1 617-726-3850 Email Address: abanerji@partners.org

Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), International Council for Harmonisation Guidelines and all locally applicable regulations. Essential study documents are currently archived in accordance with applicable regulations
Final Protocol Date:	Version 9.0: 23 March 2020
Previous Versions	Version 8.0: 06 February 2020 Version 7.0: 21 August 2019 Version 6.0: 31 July 2019 (United States) Version 5.0: 07 February 2019 (United States) Version 4.0: 05 October 2018 Version 3.0: 06 December 2017 Version 2.0: 05 December 2017 Version 1.0: 20 September 2017

1.1. Protocol Approval Signature Page

Protocol No: BCX7353-204

Protocol Title: An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema

Date: Version 9.0: 23 March 2020

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

Melanie Cornpropst 23 March 20

Melanie Cornpropst, PharmD, PhD — Date
Vice President, Clinical Development
BioCryst Pharmaceuticals, Inc.

Sylvia Dobo, MD — Date
Vice President, Medical and Safety Science
BioCryst Pharmaceuticals, Inc.

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

1.1. Protocol Approval Signature Page

Protocol No: BCX7353-204

Protocol Title: An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema

Date: Version 9.0: 23 March 2020

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

Melanie Cornpropst, PharmD, PhD — Date
Vice President, Clinical Development
BioCryst Pharmaceuticals, Inc.

24 MAR 2020

Sylvia Dobo, MD — Date
Vice President, Medical and Safety Science
BioCryst Pharmaceuticals, Inc.

24 MAR 2020

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

1.2. Clinical Study Protocol Agreement

Protocol No: BCX7353-204

Protocol Title: An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema

Date: Version 9.0: 23 March 2020

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

_____

Investigator's Signature Date (DD MMM YYYY)

_____

Name (Print)

2. SYNOPSIS

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
BCX7353

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

Title of Study:
An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema

Study center(s):
Protocol Versions 1.0-4.0, 7.0: Multiple study centers in Asia-Pacific, Europe, Israel, and South Africa

Protocol Versions 5.0, 6.0, 8.0, 9.0: Multiple centers in the United States (US) only

Principal Investigators:
Global Principal Investigator: Henriette Farkas MD, PhD, DSc
United States Principal Investigator: Aleena Banerji, MD

Phase of development: 2

Primary Objective:

- To evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 in subjects with hereditary angioedema (HAE)

Secondary Objective:

- To assess the effectiveness (ie, HAE attack frequency, severity and disease activity over time) of BCX7353 during long-term administration
- To evaluate quality of life (QoL) during long-term administration of BCX7353
- To evaluate subject's satisfaction with medication during long-term administration of BCX7353

Methodology:
This is a single-arm, open-label study to evaluate the long-term safety and effectiveness of orally administered BCX7353 in subjects with HAE who are expected to derive benefit from an oral treatment to prevent angioedema attacks.

Subjects who meet the inclusion and exclusion criteria will be enrolled into the study for up to 96 weeks. Subjects enrolled under protocol versions 6.0 and 9.0 will receive BCX7353 150 mg administered orally once daily (QD).

Study visits will occur at Screening, Baseline/Day 1, at Weeks 4, 12, 24, 48, 72, and 96 weeks, until the product is commercially available, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Any subject who discontinues androgen prophylaxis at the time of signing informed consent or at the screening visit will have an additional visit to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyltranspeptidase (GGT), and total and direct bilirubin 2 weeks (+7 days) after androgen discontinuation and before initiating treatment with BCX7353.

Data from ongoing studies BCX7353-302 (Phase 3 study), BCX7353-301 (Phase 3 study) and the current study, BCX7353-204, are reviewed by the BCX7353 data monitoring committee (DMC) at protocol-specified intervals. The DMC may also be convened if a new clinically significant safety signal emerges or at other times as requested. The latest data review was conducted on 31 July 2019. The recommendation of the DMC was that all 3 studies proceed per protocol.

Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related adverse event (AE). The study will be discontinued if ongoing regulatory or institutional review board/ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the ongoing conduct of the study. Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, coagulation and urinalysis), vital signs, electrocardiograms (ECGs), and physical examinations.

The main study will be comprised of adult subjects (≥ 18 years of age); a substudy will be included that allows adolescent subjects ≥ 12 to 17 years of age to screen and enroll. Subjects will document all angioedema attacks that occur while on study. Angioedema attacks will be treated in accordance with the subject's normal standard of care. Treatments for angioedema attacks will not be provided by the Sponsor.

Patient-reported outcomes will be completed by subjects for the disease-specific Angioedema Quality of Life (AE-QoL) questionnaire and Treatment Satisfaction Questionnaire for Medication (TSQM), where validated translations are available. Subjects will be asked about time away from work or school. Additional data collection may be conducted by a specialty pharmacy to better understand the subject experience with the study drug during the subject's participation in the study.

Number of subjects (planned): Approximately 475 subjects globally (approximately 250 subjects are planned to be enrolled in the US)

Inclusion Criteria

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

1) Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy)
2) Subjects with a clinical diagnosis of HAE Type I or II who, in the opinion of the Investigator, are expected to benefit from an oral treatment for the prevention of angioedema attacks. A clinical diagnosis of HAE Type I or II is defined as:
   - A C1 esterase inhibitor (C1-INH) functional level below the assay lower limit of normal as assessed during the screening period by chromogenic assay OR
   - Laboratory documentation of historical C1-INH functional level below the assay lower limit of normal OR
   - Subjects who currently use plasma derived or recombinant C1-INH based therapies for acute attacks or prophylaxis may use one of the following to confirm their diagnosis:
     - SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or II as assessed during the screening period OR
     - A confirmed family history of C1-INH deficiency
3) Subject weight ≥ 40 kg
4) Access to one or more targeted medications for the treatment of acute HAE attacks. The following are acceptable: icatibant, plasma-derived C1-INH (all forms), ecallantide, recombinant C1-INH.
5) Female subjects must agree to use acceptable effective contraception, as defined in Section 8.2.1
6) Able to provide written, informed consent. Subjects aged ≥ 12 to 17 years who are screened for the substudy must be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent
7) In the opinion of the Investigator, the subject is able 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 including diary recording of HAE attacks

Exclusion Criteria

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

1) Pregnancy or breastfeeding or planned pregnancy during the study period.
2) Any clinically significant medical condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's safety or ability to participate in the study. Examples include active malignancy under treatment, uncontrolled cardiovascular disease (recent acute myocardial infarction, unstable angina), organ dysfunction such that supportive care is required (dialysis, oxygen therapy, cirrhotic care).
3) Dementia, altered mental status or any psychiatric condition, that would prohibit the understanding or rendering of informed consent or participation in the study.
4) Clinically significant abnormal ECG including but not limited to, a corrected QT interval using Fridericia's method (QTcF) > 470 msec for women, a QTcF > 450 msec for men, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
5) Use of concomitant medications that are metabolized predominantly by CYP2D6 or CYP3A4 and that have a narrow therapeutic range as defined in Section 9.7.1.
6) Use of oral androgens for treatment of HAE (prophylaxis or acute) within 28 days of the baseline visit or planned initiation during the study.
7) Any laboratory parameter abnormality that, in the opinion of the Investigator, is clinically significant and relevant for this study.
8) Investigational drug exposure within 30 days prior to the screening visit.
9) Severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.
10) History of alcohol or drug abuse within the previous year, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 units of alcohol/day).
11) Current infection with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus.
12) Subjects with an immediate family relationship to either Sponsor employees, the Investigator or employees of the study site who are named on the delegation log.
13) Subjects who are held in an institution by a government or judicial order.

Investigational product, dosage and mode of administration:

BCX7353 capsules, to be administered orally. Subjects will receive a dose of 150 mg QD.

Reference therapy, dosage and mode of administration:

Not applicable.

Duration of treatment:

Subjects will be eligible to receive study drug (BCX7353) for up to 96 weeks, until the product becomes commercially available, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related AE.

Criteria for evaluation:

Safety:

Safety will be evaluated by AEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis), vital signs, ECGs, and physical examinations. An independent DMC will review safety data in accordance with a separate DMC Charter.

Effectiveness:

Effectiveness will be evaluated by the number of angioedema attacks and related details (timing, duration of symptoms, anatomical location, treatment), number of days with angioedema symptoms, assessment of attack severity, discontinuations due to lack of efficacy (through Week 48), and number of hospitalizations and clinic visits.

Patient Reported Outcomes/Quality of Life:

QoL will be assessed using the AE-QoL questionnaire and subject's satisfaction with their medication using the TSQM. The number of days lost from school and/or work will also be assessed.

Statistical methods:

Analysis of Safety: Safety endpoints will be summarized by treatment group and will include the proportion of subjects: with treatment-emergent AEs (TEAEs); who discontinue due to a TEAE; who experience a treatment-emergent serious adverse event (SAE); who experience a Grade 3 or 4 TEAE; who experience a treatment-emergent, treatment-related AE consistent with a drug rash (eg, maculopapular rash, papular rash); and who experience Grade 3 or 4 laboratory abnormalities.

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ classification (SOC). The occurrence of TEAEs will be summarized using MedDRA PT, SOC, and severity. In addition to severity, AEs and SAEs will be summarized based on Investigator assessment of relationship to study drug.

Time to discontinuation due to a TEAE and time to development of drug-related Investigator-identified rash event of special interest (EOSI) will be estimated using the Kaplan-Meier method. For subjects with a drug-related Investigator-identified rash EOSI, clinical and laboratory findings will be summarized as well as the proportion of subjects who successfully continued therapy following onset of rash.

Descriptive statistics for vital signs, weight, and clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded and flagged automatically with a reference range scale. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized. Laboratory toxicity shifts from baseline to the worst post-baseline value as well as the last visit will be summarized. The number and percentage of subjects who have elevations in ALT, AST, or bilirubin abnormalities in relation to fold above ULN will be summarized according to the US Food and Drug Administration's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry.

Clinically significant abnormal ECG findings will be summarized by study visit. Changes from baseline in ECG parameters will also be summarized by study visit. The number and proportion of subjects with clinically important absolute and change from baseline thresholds in QTcF will be summarized.

Analysis of Effectiveness: Effectiveness endpoints will be analyzed by treatment group and will include angioedema attack rate, durability of response, number and proportion of days with angioedema symptoms, angioedema attack medication administrations, discontinuations due to lack of efficacy, and disease severity. The durability of response assessment will be based on attack rate trend over time.

Additional related details of HAE attacks (e.g., symptoms, anatomical location, hospitalizations, emergency room visits, attack severity, attack duration) and number of days lost from work and/or school due to attacks will be listed and summarized using descriptive statistics.

No formal tests of hypotheses will be conducted.

Quality of Life Analyses: The baseline, follow-up, and change from baseline in the domain scores of the AE-QoL as well as the composite score of each instrument will be calculated and summarized by treatment group. Individual items will be analyzed to understand their contribution to the domain sub-scores. A TSQM global satisfaction score will be calculated as validated. Data on the global score as well as relevant subscales will be listed and summarized.

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
ABW	absolute body weight
ACR	spot urine microalbumin to creatinine ratio
AE	adverse event
AE-QoL	angioedema quality of life questionnaire
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the concentration vs. time curve
AUC_{inf}	area under the concentration vs. time curve extrapolated to infinite time
AUC_{last}	area under the concentration vs. time curve from time 0 to the last measurable concentration
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BCRP	breast cancer resistance protein
BK	bradykinin
BMI	body mass index
BMP	di-docosahexaenoyl (22:6)- Bis(mono)acylglycerol phosphate
C1-INH	C1 esterase inhibitor
CK	creatine kinase
C_{max}	maximum plasma concentration of the drug
CRF	case report form
CRA	clinical research associate
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CYP	cytochrome P450
DDI	drug-drug interaction
D_LCO	diffusion capacity for carbon monoxide
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
EC_{xx}	concentration that elicits xx% response
ECG	electrocardiogram
EOSI	event of special interest
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltranspeptidase
GI	gastrointestinal
HAE	hereditary angioedema
HBV	hepatitis B virus

Abbreviation	Explanation
HCV	hepatitis C virus
hERG	human ether-à-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HK	high-molecular weight kininogen
HLA	human leukocyte antigen
IB	Investigator's brochure
IC_{xx}	xx% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IXRS	interactive (web or voice) response system
LFT	liver function test
LLN	lower limit of normal
MATE	multidrug toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
PD	pharmacodynamic
P-gp	p-glycoprotein efflux pump
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	preferred term
QD	once daily
QoL	quality of life
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
R	correlation coefficient
RR	interval between successive heart beats using the R-wave peaks
SAE	serious adverse event

Abbreviation	Explanation
SAP	statistical analysis plan
SJS	Stevens Johnson syndrome
SOC	system organ classification
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TpTe	T peak to T end
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
US	United States

5. INTRODUCTION

5.1. Background

Hereditary angioedema (HAE) with C1-esterase inhibitor (C1-INH) deficiency is an autosomal dominant disorder characterized by recurrent episodes of swelling of the skin, pharynx, larynx, gastrointestinal (GI) 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 (QoL) (Lumry, Castaldo et al. 2010). Although mortality risk from asphyxiation is much higher in undiagnosed patients with HAE, deaths still occur in diagnosed patients with access to care at centers of excellence (Bork, Hardt et al. 2012).

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

BCX7353 is a potent, synthetic, second-generation small molecule inhibitor of plasma kallikrein. In contrast to parenterally administered options commercially available for prophylaxis against HAE attacks, inhibition of kallikrein with an orally bioavailable small molecule such as BCX7353 offers the advantage of oral administration.

5.2. Findings for BCX7353

The principal results of non-clinical, clinical pharmacology, PK, clinical safety and efficacy studies of BCX7353 are described in the BCX7353 Investigator's brochure (IB).

Two Phase 3 studies, BCX7353-301 and BCX7353-302, are ongoing but have results reported for the primary analysis. Study BCX7353-302 Part 1 results are summarized below. Study BCX7353-301 had a safety profile and similar efficacy as Study BCX7353-302 and will not be individually discussed below.

5.2.1. Summary of Study BCX7353-302

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

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

Overall, a total of 160 subjects were screened, 121 subjects were randomized (stratified by baseline attack rate, < 2 vs. ≥ 2 per 28 days), and 120 randomized subjects (99%) were treated. Of these, 108 subjects completed 24 weeks of study drug dosing in Part 1: 37 of 40 BCX7353 150 mg subjects (93%), 37 of 41 BCX7353 110 mg subjects (90%), and 34 of 39 placebo subjects (87%).

The mean baseline rate was 2.98 attacks per month. The majority of subjects (70%) had ≥ 2 attacks per month at baseline, and the attack frequency was generally well distributed across the 3 treatment groups.

The primary efficacy endpoint was the rate of Investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period. This study achieved its primary endpoint for both dose levels, with the 150 and 110 mg doses reducing HAE attacks by 44% ($p < 0.001$) and 30% ($p = 0.024$), respectively, vs. placebo. The attack rate per 28 days over the 24-week Part 1 dosing period was 1.31 for BCX7353 subjects on 150 mg QD, 1.65 for BCX7353 subjects on 110 mg QD, and 2.35 for placebo subjects. These results were supported by sensitivity analyses and were consistent in subgroup analyses. Effects of BCX7353 in reducing attack rate were evident in the first 4 weeks and stable over the entire 24-week duration of Part 1.

Secondary endpoints (change from baseline in the angioedema quality of life questionnaire [AE-QoL], number and proportion of days with angioedema symptoms, and rate of Investigator-confirmed HAE attacks during the effective dosing period [beginning on Day 8 through Week 24]) were analyzed using hierarchical testing. Results for the first secondary endpoint, AE-QoL, were not statistically significant vs. placebo for either treatment group; therefore, inferential statistical testing was not performed on the descending secondary efficacy endpoints.

BCX7353 significantly reduced the use of standard of care acute attack medication per 28 days vs. placebo by 53.6% ($p < 0.001$) for 150 mg and 46.3% ($p < 0.001$) for 110 mg. In responder analyses, 58%, 50%, and 23% of subjects receiving 150 mg BCX7353 had a ≥ 50%, ≥ 70% or ≥ 90% reduction in their HAE attack rates compared to baseline vs. 25%, 15%, and 8% of placebo subjects, $p = 0.005$, $p = 0.002$, and $p = 0.073$ respectively.

Administration of BCX7353 at doses of 150 and 110 mg QD for 24 weeks was safe and generally well tolerated.

Overall 81.7% of subjects experienced a treatment-emergent adverse event (TEAE) on study: 85.0% of 150 mg subjects, 82.9% of 110 mg subjects, and 76.9% of placebo subjects; 39.5% of BCX7353-treated subjects and 33.3% of placebo subjects experienced a drug-related TEAE. Five subjects discontinued study drug due to TEAEs: 1 (2.5%) on 150 mg, 3 (7.3%) on 110 mg, and 1 (2.6%) on placebo. No subjects on 150 mg, 1 subject on 110 mg (2.4%), and 3 subjects on placebo (7.7%) experienced serious adverse events (SAEs) on study; none of these events were drug related. All drug-related TEAEs were mild to moderate on placebo and in the 150 mg group, and the majority of TEAEs in the 110 mg group were mild to moderate; 3/41 (7.3%) 110-mg subjects experienced Grade 3 drug-related TEAEs. Few subjects had treatment-emergent Grade 3 or 4 laboratory abnormalities. One subject on 150 mg BCX7353 who had previously

been exposed to androgens had Grade 4 alanine aminotransferase (ALT) elevation and Grade 3 aspartate aminotransferase (AST) elevation without symptoms, which resolved after discontinuing study drug.

The most common TEAEs across all arms were nasopharyngitis, nausea, and vomiting. Overall, 50.0% and 41.5% of BCX7353 150 and 110 mg subjects, respectively, had gastrointestinal (GI) abdominal-associated TEAEs vs. 35.9% of placebo subjects. There were no drug-related rashes (events of special interest [EOSI]).

Orally administered BCX7353 was a generally safe, well-tolerated, and effective treatment for the prevention of HAE attacks in Part 1 of this study, with better efficacy at the 150 mg dose compared to the 110 mg dose, and no increase in safety risk.

5.2.2. Summary of Interim Data of BCX7353-204 (Current Study)

An interim analysis of this current study has been completed. As of the cut-off date of 20 August 2019, a total of 100 and 127 subjects were treated with BCX7353 110 and 150 mg, respectively and were enrolled across 49 sites in 22 different countries in North America, Europe, Asia, Australia, and Africa. Of the 227 subjects treated with study drug, 103 subjects have completed dosing through Week 48 (30 subjects on BCX7353 110 mg and 73 subjects on BCX7353 150 mg).

Of the 100 subjects initially allocated to BCX7353 110 mg, 22 subjects completed Week 48 and have transitioned to BCX7353 150 mg; however, none of these subjects have data available from a regularly-scheduled study visit after transitioning to the BCX7353 150 mg dose since visits occur only on a quarterly basis. A total of 30 subjects reported 5 TEAEs after switching from BCX7353 110 to 150 mg; all 5 events were assessed by the Investigator as not related to study drug.

Except for race and ethnicity, the safety population was generally quite diverse. The mean age was 40.3 years (range 12 to 72 years), and most subjects were white (84.6%) and non-Hispanic (93.0%). Overall 10 adolescent subjects (4.4%) ≥12 to 17 years of age and 5 elderly subjects (2.2%) ≥ 65 years of age were enrolled in the study.

Overall, oral treatment with BCX7353 150 and 110 mg QD was safe and generally well tolerated. No new safety signals were identified, safety risks were consistent with the risks previously noted in the Phase 2 proof-of-concept Study 203 and consistent with safety seen in the Phase 3 pivotal Study 302 and the Phase 3 Study 301 conducted in Japan. Across both dose groups the mean (range) exposure to study drug was 282.7 (11 to 540) days. Safety monitoring revealed no cardiac, renal, hematologic or neurologic safety concerns. Vital signs and ECG findings during the course of the study were unremarkable and consistent with normal variability.

Fifty-nine subjects (26.0%) prematurely discontinued study drug; 57 subjects (25.1%) discontinued study drug before 48 weeks of dosing. The most common reasons for discontinuation of study drug were perceived lack of efficacy (12.3%) and laboratory abnormalities or TEAEs (8.4%). Overall, more subjects treated with BCX7353 110 mg compared to BCX7353 150 mg discontinued study drug due to perceived lack of efficacy; 17 of 100 subjects (17.0%) vs. 11 of 127 subjects (8.7%). Overall, 19 subjects (8.4%) discontinued study drug due to TEAEs; 6 (6.0%) and 13 subjects (10.2%) in the BCX7353 110 and 150 mg

dose groups, respectively. TEAEs leading to discontinuation in > 1 subject were ALT increased (4 subjects [1.8%]), upper abdominal pain (3 subjects [1.3%]), vomiting (2 subjects [0.9%]), AST increased (2 subjects [0.9%]), hepatic enzyme increased (2 subjects [0.9%]), and liver function test (LFT) abnormal (2 subjects [0.9%]).

The majority of subjects (91.0% and 90.6% of subjects in the BCX7353 110 and 150 mg dose groups, respectively) had at least 1 TEAE during the study. There was no effect of dose on the incidence of AEs. Overall, the most frequently reported TEAEs were nasopharyngitis (30.8%), headache (17.6%), abdominal pain (13.2%), and diarrhea (13.2%).

Long term prior androgen use of ≥ 5 years and discontinuation of androgens within 2 weeks of BCX7353 initiation were correlated with a higher subject incidence of liver-related TEAEs, but not other types of TEAEs. Subjects who discontinued androgens in the 2 weeks prior to initiating BCX7353 (n = 40) experienced liver-related TEAEs in the investigations SOC more frequently than subjects who discontinued androgens ≥ 2 weeks before initiating BCX7353 (n = 113) or those subjects who had never used androgens (n = 74). In these groups, ALT increased, 25.0% vs. 2.7% and 1.4%, respectively; AST increased 17.5% vs. 2.7% and 1.4%, respectively; hepatic enzyme increased, 2.5% vs. 0.9% and 0, respectively; LFT abnormal, 5.0% vs. 0 and 0; and transaminase increased, 2.5% vs. 0 and 0.

Overall, 49.8% of subjects had at least 1 TEAE assessed as drug-related by the Investigator (ie, TEAEs possibly, probably, or definitely related to study drug). Most TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Overall, 15.0% of subjects experienced a Grade 3 or Grade 4 TEAE. The most common Grade 3 or Grade 4 TEAEs were HAE (attacks) (3.5%), ALT increased (2.6%), hepatic enzyme increased (0.9%), LFT abnormal (0.9%), and pneumonia (0.9%). All other Grade 3 or Grade 4 TEAEs occurred in 1 subject each. Overall, long term prior androgen use of ≥ 5 years and discontinuation of androgens within 2 weeks of BCX7353 initiation was correlated with a higher frequency of Grade 3 or Grade 4 liver-related TEAEs.

Overall, 13.2% of subjects experienced a treatment-emergent SAE. Treatment-emergent SAEs that occurred in > 1 subject were HAE attacks (12 subjects [5.3%]) and medical observation (3 subjects [1.3%]). Three subjects (1.3%) experienced 4 treatment emergent SAEs assessed by the Investigator as related to study drug; G3 gastroenteritis and Grade 2 hepatic enzyme increased (n = 1), G3 abnormal LFT (n = 1), and G3 abdominal pain (n = 1). The 2 subjects with the treatment-emergent SAEs of gastroenteritis, hepatic enzyme increased, and abnormal LFT discontinued study drug. No subjects experienced a TEAE that led to death.

Overall, 27 subjects (11.9%) interrupted study drug due to TEAEs. The most common TEAE that led to study drug interruption was HAE (attack) in 5 subjects (2.2%). Overall, TEAEs in the GI SOC led to study drug interruption in the greatest number of subjects; 8 subjects (6.3%) treated with BCX7353 150 mg and 2 subjects (2.0%) treated with BCX7353 110 mg. Overall, 6 subjects (2.6%) discontinued study drug due to a GI TEAE; 2 subjects (2.0%) and 4 subjects (3.1%) in the BCX7353 110 and 150 mg dose groups, respectively.

For this study, nonserious treatment-emergent rashes were considered EOSIs for Investigator reporting purposes. Overall, 8 subjects (3.5%) had rash EOSIs assessed by the Investigator as related to study drug but these rashes included non-specific urticaria and brief episodes of erythema. A total of 2 rash events were assessed by the Sponsor medical officer as likely related

to BCX7353 and consistent with delayed-type drug hypersensitivity, i.e. a diffuse maculo-papular rash with pruritus but no systemic or mucosal symptoms. These rashes were consistent with those reported in prior studies, resolving quickly with no reoccurrence with study drug continuation or re-initiation (if drug was held).

GI events were considered AEs of interest; however, they were not considered EOSIs for Investigator reporting purposes. Overall, 105 subjects (46.3%) experienced a GI abdominal TEAE and 6 subjects (2.6%) discontinued due to a GI abdominal event. The most common GI abdominal TEAEs were diarrhea (13.2%), abdominal pain (13.2%), and nausea (7.9%). No dose response was observed. Most events were Grade 1 or Grade 2 in severity. Two subjects (0.9%) experienced 3 serious GI abdominal events, abdominal pain in 1 subject and diarrhea and vomiting in the other subject. The event of abdominal pain was assessed as related to study drug but the diarrhea and vomiting were not because there was another more plausible etiology.

The most common clinically significant chemistry abnormalities were liver-related abnormalities, and the most common abnormality was ALT increased. The majority of treatment-emergent liver abnormalities were Grade 1 or 2; however, 13 subjects (5.7%) experienced a treatment-emergent Grade 3 or 4 ALT laboratory abnormality, and all of these subjects had previously used androgens. All but 1 subject with a Grade 3 or 4 ALT stopped androgens 7 to 9 days from first dose of BCX7353; 1 subject stopped androgens < 2 months from the first dose of BCX7353. No subject had synthetic dysfunction or evidence of hepatitis. Subjects were mostly asymptomatic, although a few subjects had abdominal symptoms that overlapped with the GI symptoms reported with BCX7353 treatment; no subject had signs or symptoms of acute hepatitis. The Grade 3 or 4 ALT elevations in the 13 subjects were primarily laboratory abnormalities without clinical symptoms. All 13 subjects improved or recovered, 5 subjects while continuing on BCX7353; 2 subjects subsequently discontinued study drug for unrelated reasons (perceived lack of efficacy in both subjects). A total of 15 subjects had postbaseline ALT > 3 × upper limit of normal (ULN; 2 subjects with nontreatment emergent ALT values). Of the subjects who had stopped androgens within the previous 2 weeks before initiating BCX7353, the incidence of subjects with ALT > 3 × ULN was 32.5%. Of the subjects with ≥ 5 years of androgen use, the incidence of subjects with ALT > 3 × ULN was 13.0%. One subject had a bilirubin > 1.5 × ULN although no subject had a Grade 3 or Grade 4 bilirubin, and no subject had a concurrent elevation in bilirubin > 1.5 × ULN and ALT or AST > 3 × ULN. No subject met the criteria for Hy's law during the study.

In summary, BCX7353 was safe and generally well tolerated with no new safety signals observed.

Subjects treated with BCX7353 110 or 150 mg QD had durably low attack rates, with no evidence for the development of tolerance to BCX7353. After 1 month of treatment, the 73 subjects in the BCX7353 150 mg dose group who received BCX7353 through Week 48 had a mean (SD) attack rate of 1.18 (1.40) attacks per month. The mean rate of attacks held relatively steady during Months 2 to 12: 1.01 (1.26) attacks per month in Month 6 and 0.81 (1.03) attack per month in Month 12.

The proportion of days with angioedema symptoms was generally similar for both dose groups and declined over time: during Month 1 the median proportion of days with symptoms was 7.1%; during Month 6 the median proportion of days with symptoms was 3.6%; and during Month 12 the median proportion of days with symptoms was 0.0%.

During the first 24 weeks of study, 22 subjects (9.8%) treated with BCX7353 remained attack free, with slightly more subjects in the BCX7353 150 mg group (11.2%) remaining attack free compared with the BCX7353 110 mg dose group (8.0%). During the first 48 weeks of study, 8 subjects (5.0%) treated with BCX7353 remained attack free, with slightly more subjects in the BCX7353 150 mg group (5.8%) remaining attack free compared with the BCX7353 110 mg dose group (3.6%).

A total of 28 of 227 subjects (12.3%) discontinued treatment in the first 48 weeks of the study due to perceived lack of efficacy, with fewer subjects discontinuing treatment in the BCX7353 150 mg dose group compared to the 110 mg dose group (11 [8.7%] vs. 17 [17.0%], respectively). Twenty of the 28 subjects who discontinued study drug due to a perceived lack of efficacy discontinued prior to Week 12. The proportions of subjects who discontinued BCX7353 due to a perceived lack of efficacy was higher for those subjects who had reported either that they had discontinued androgen use < 2 weeks prior to their first dose of BCX7353 (20.0%) or had used androgens for ≥ 10 years (18.2%), compared to subjects who had never used androgens (12.2%). Twelve of the 28 (42.9%) subjects who discontinued BCX7353 due to a perceived lack of efficacy had used androgen therapy for ≥ 10 years before their first dose of BCX7353. Eight of the 28 (28.6%) subjects who discontinued BCX7353 due to a perceived lack of efficacy and had discontinued androgen therapy < 2 weeks before their first dose of BCX7353.

The median duration of an attack was shorter for subjects treated with BCX7353 150 mg vs. 110 mg (median of 17.7 vs. 28.0 hours). This difference was independent of attack location (ie, abdominal-only, peripheral-only, and mixed).

Overall, subjects assessed about 34% of their attacks as negligible or mild in severity with approximately 60% of attacks resulting in no restriction or a slight restriction of daily activities. Overall, approximately 61% of attacks had no or a slight effect on the subject's appearance. There were no notable differences between the dose groups.

Of the on-study adjusted attacks, 85.4% were treated with any medication and 81.6% with SOC-Rx. The most commonly used SOC-Rx were Berinert and Firazyr. There were no notable differences between the dose groups.

Subject reported outcomes were assessed serially using the AE-QoL and TSQM questionnaires administered at study visits. MCID improvements (≥ 6 point improvement) in mean change from baseline AE-QoL total and all domain scores were observed at Week 4: an improvement of 8.9 (19.0) and 11.2 (17.2) points from baseline in mean (SD) AE-QoL total score for the 110 and 150 mg dose groups, respectively. The observed improvement in AE-QoL was durable, holding steady or further improving at all subsequent assessments; for example, at Week 48, the mean (SD) change from baseline improvements in AE-QoL total score were 12.8 (16.0) and 14.7 (17.8) points for the 110 and 150 mg dose groups, respectively. Greater than MCID mean (SD) improvements in change from baseline were observed at Week 48 for the domains: functioning, 16.1 (26.5) point improvement; fatigue/mood, 9.3 (19.0) point improvement; fear/shame, 19.9 (22.2) point improvement; and nutrition, 9.4 (20.6) point improvement.

The TSQM scores improved from baseline (assessment of the subject's usual medication prior to starting BCX7353) to Week 48 on BCX7353 with mean (SD) change from baseline

improvements of 20.5 (24.7) points in convenience, 7.7 (24.2) points in side effects, 7.2 (29.6) points in effectiveness, and 3.6 (28.8) points in global satisfaction.

In summary, subjects had low rates of attacks during the first month of treatment with BCX7353 that were maintained or improved over the 48 weeks. Subjects treated with 150 mg of BCX7353 had a median of 6.5% of study days with angioedema symptoms, assessed about 36% of their attacks as negligible or mild in severity, assessed approximately 64% of attacks as resulting in no restriction or a slight restriction of daily activities, and assessed approximately 63% of attacks as having no or a slight effect on appearance. Attacks were generally shorter in duration for subjects treated with BCX7353 150 mg compared to BCX7353 110 mg, and BCX7353 150 mg QD also improved measures of QoL compared with baseline: at Week 48 a mean improvement > MCID in AE-QoL total score and functioning, fatigue/mood, fears/shame, and nutrition domain scores was observed along with improvements in all TSQM scores.

5.3. Data Monitoring Committee Review of Ongoing Studies BCX7353-302, BCX7353-301 and BCX7353-204

Data from ongoing studies BCX7353-302 (Phase 3 study), BCX7353-301 (Phase 3 study) and the current study, BCX7353-204, are reviewed by the BCX7353 data monitoring committee (DMC) at protocol-specified intervals. The DMC may also be convened if a new clinically significant safety signal emerges or at other times as requested.

The latest data review was conducted on 23 October 2019.

The recommendation of the DMC was that all 3 studies proceed per protocol.

5.4. Rationale for Study

Currently, prophylactic treatments approved in most of the world for prevention of angioedema attacks in HAE are oral androgens and parenteral C1-INH therapies. In addition, the monoclonal antibody lanadelumab was recently approved as prophylactic therapy in some countries. While patient experience has improved with the expansion of approved therapies for HAE, an orphan disease, a 2013 survey of 245 United States (US) physicians that treat HAE indicated that their perception is that only 40% of their patients are fully satisfied with current HAE treatments (Aygoren-Pursun, Bygum et al. 2018). Regular IV infusions of C1-INH for prophylactic use in HAE may lead to an increase in complications over time, such as thrombosis, infection, pain, and limited venous access (Shire 2018). Even patients with HAE with no contraindications to androgens and who tolerate prophylactic androgens face long-term risks with continued treatment. Therefore, there remains a significant medical need to provide additional HAE treatment options that are efficacious, convenient, and well-tolerated.

BCX7353 is an oral kallikrein inhibitor in development for prophylaxis of HAE Type I and II. BCX7353 has activity against plasma kallikrein at low nM concentrations that are attainable and sustained in humans following oral administration. In both the randomized, double blind, 24-week, placebo-controlled Phase 3 study (BCX7353-302) and the proof-of-concept, 28-day, placebo-controlled, Phase 2 study (BCX7353-203), the rate of angioedema attacks in subjects randomized to BCX7353 was statistically significantly lower than in placebo subjects and BCX7353 was safe and generally well-tolerated. Subjects with HAE who have not previously

received BCX7353 will be offered the opportunity to participate in this study when, in the opinion of the Investigator, they are expected to derive benefit from an oral treatment to prevent angioedema attacks.

5.4.1. Rationale for Study Design

This open-label safety study is designed to assess the long-term safety and effectiveness of 1 dose level (150 mg QD) of BCX7353 in subjects who do not currently use prophylactic therapies and in subjects who are switching from other prophylactic therapies to BCX7353. This study offers subjects access to BCX7353 treatment for up to 96 weeks, until the product becomes commercially available, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. This study will provide additional information on the long-term safety and effectiveness of the planned dose (150 mg QD) in US subjects.

While there are approved therapies in many countries for prophylaxis against HAE attacks, including C1-INH infused intravenously or administered subcutaneously, the majority of patients globally are not being treated with prophylactic medications and the degree of individual benefit varies. Eligible subjects may enroll in the current study if the Investigator assesses that they may benefit from daily administration of BCX7353.

Acute attacks of angioedema will be treated in accordance with the subject's normal standard of care. As appropriate, subjects will continue to use their prescribed acute attack medication to treat any acute attacks, as well as continue as needed with their approved prophylactic treatment for HAE attacks as prescribed under the medical management plan advised by their physician.

Efficacy and safety data from the randomized, double-blind, placebo-controlled Phase 3 studies (BCX7353-302 and BCX7353-301) and accumulating safety data on subjects enrolled on earlier versions of the current study protocol (BCX7353-204) support long-term treatment with BCX7353 (Section 5.2). At the writing of this version of the protocol, regulatory filings to both the US and Japan authorities have been completed towards the approval of BCX7353 for marketing.

5.4.2. Rationale for Study Drug Doses and Regimens

The BCX7353 dosage regimen selected for evaluation in this study is 150 mg BCX7353 administered QD (equivalent to 175 mg QD [SN]).

In Study BCX7353-203, the HAE attack rate was significantly lower vs. placebo in subjects who received daily doses of 125, 250, and 350 mg BCX7353 (SN) and the drug was well-tolerated. The plasma drug levels achieved at each dose were generally predictable and had an acceptable level of inter-subject variability.

Two doses (150 and 110 mg QD) were studied in a pivotal Phase 3 clinical trial (BCX7353-302) and versions of the current study globally (BCX7353-204 Versions 1-5). Study BCX7353-302, achieved its primary endpoint for both dose levels evaluated, with the 150 and 110 mg doses reducing HAE attacks by 44% ($p < 0.001$) and 30% ($p = 0.024$), respectively, vs. placebo. Orally administered BCX7353 was a safe, generally well-tolerated, and effective treatment for the prevention of HAE attacks in Part 1 of this study, with better efficacy at the 150 mg dose compared to the 110 mg dose, and no increase in safety risk.

Based on the results of BCX7353-302 of better efficacy and no increase in safety risk at the 150 mg dose, the 150 mg dose will be assessed in the current study of BCX7353 for the prevention of attacks in HAE.

5.4.3. Study Population Rationale

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

In the ongoing BCX7353-204 trial, asymptomatic and transient transaminase elevations have occurred almost exclusively in subjects who have recently (ie, < 2 weeks prior to starting BCX7353) discontinued androgens (BCX7353 IB). Currently the physiological and HAE attack changes that may occur with androgen cessation are not well described. Since androgen use (both current and past) is prevalant in the global HAE community, this protocol will provide data to better characterize androgen discontinuation in HAE patients and allow the development of guidance for treaters and patients who wish to switch from androgens to BCX7353. In order to reduce the incidence of transaminase elevations on study, subjects will be required to have last used androgens at least 28 days prior to initiation of BCX7353.

To date, the BCX7353-204 trial has been conducted primarily outside of the US, including many areas where use of long-term prophylaxis for HAE attacks is uncommon. Since use of prophylactic therapy for HAE attacks is prevalent in the US HAE community, this protocol will provide data to allow the development of guidance for treaters and patients who wish to switch from another prophylactic therapy to BCX7353.

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

Although there is no evidence of embryofetal developmental toxicity with BCX7353 in reproductive toxicology studies, appropriate precautions are still warranted with respect to administering BCX7353 to women of reproductive age, in accordance with International Council for Harmonisation (ICH) guidelines. Women of childbearing potential may be enrolled in this

study provided they meet the contraceptive requirements and have a negative pregnancy test (Section 8.2.1).

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

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

All subjects must have access to appropriate treatments for the treatment of acute attacks (ie, icatibant, plasma-derived C1-INH [any form]), ecallantide, recombinant C1-INH). Each subject will continue to use their prescribed acute medication to treat any attacks, under the medical management plan advised by their physician, throughout the study. This is consistent with guidance documents that strongly support the position that all subjects with C1-INH deficiency should have access to medications for treating attacks (Cicardi, Bork et al. 2012, Zuraw, Banerji et al. 2013).

While there are approved therapies in many countries 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 guideline published on the management of HAE by the US HAE Association Medical Advisory Board suggests that decisions on when to use prophylaxis should be individualized (Zuraw, Banerji et al. 2013):

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

Subjects may receive prophylactic therapies (eg, C1-INH, tranexamic acid, lanadelumab). Investigators may make modifications to the dose and schedule of the prophylactic therapy, including tapering or discontinuation of dosing, according to the degree of benefit of daily oral BCX7353 treatment. Recommended strategies for switching to BCX7353 prophylaxis from another therapy are provided in Section 9.7.

Androgen use, however, is prohibited within 28 days of the baseline visit and at any time during the study to reduce the incidence of transaminase elevations (see Section 9.7.1).

5.5. BCX7353 Risk/Benefit Analysis

Given that BCX7353 is a small molecule kallikrein inhibitor with data available from completed Phase 1 single and multiple dose studies, a Phase 2 study in subjects with HAE, and two ongoing randomized, double-blind, placebo-controlled Phase 3 studies, there is an acceptably low risk of severe or serious adverse reactions. Potential risks and findings from nonclinical and clinical studies of BCX7353 are discussed in the Section 6 of the IB (Summary of Data and Guidance for the Investigator).

5.6. Benefits of Trial Participation

Study subjects will receive regular medical care for the duration of the study. Subjects may experience a reduction in the number of attacks while receiving BCX7353. BCX7353 produced a statistically significant and clinically meaningful reduction in the rate of HAE attacks compared to placebo for the primary endpoint in the ITT population of Study BCX7353-302.
The development of BCX7353 may be of benefit to the wider community/patients with HAE.

5.7. Overall Benefit-Risk Assessment

The risks from daily oral administration of BCX7353 seen to date in both preclinical and clinical studies were primarily mild, monitorable, and reversible. Overall, the clinical efficacy and safety data support a favorable benefit risk profile for BCX7353. In the 24-week, adequate, well-controlled pivotal efficacy and safety trial in adolescents and adults with Type I or II HAE, BCX7353 150 mg QD treatment for 24 weeks versus placebo resulted in statistically significant and clinically meaningful reductions in monthly HAE attack rate, monthly rate of HAE attacks requiring acute rescue therapy, the monthly rate of moderate or severe HAE attacks, and the monthly rate of laryngeal HAE attacks. Results of sensitivity and subgroup analyses of the HAE attack rate were consistent with those of the primary efficacy analysis. The safety data from controlled trials and long-term open-label studies is sufficient to assess the safety of BCX7353 in the proposed rare disease HAE population. Important potential risks are delayed-type hypersensitivity reactions (rash) and transaminase elevations. Hypersensitivity rash was identified as a signal early in development; few events were reported, and these were mild to moderate, self-limited, not dose dependent, and resolved with continued dosing without recurrence. Increases in ALT/AST were generally transient, asymptomatic, not dose dependent, and heavily confounded by prior administration of androgens. The overall benefit-risk balance is therefore considered to be acceptable.

6. TRIAL OBJECTIVES

6.1. Objectives

6.1.1. Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 in subjects with HAE

6.1.2. Secondary Objectives

- To assess the effectiveness (ie, HAE attack frequency, severity, and disease activity over time) of BCX7353 during long-term administration
- To evaluate QoL during long-term administration of BCX7353
- To evaluate subject's satisfaction with medication during long-term administration of BCX7353

7. OVERALL STUDY DESIGN AND PLAN

This is a single-arm open-label study designed to evaluate the long-term safety of prophylactic treatment with daily oral BCX7353 in subjects with HAE. The study will also evaluate the long-term effectiveness and impact on QoL or general well-being of subjects who receive BCX7353 prophylactic treatment, and the subject's satisfaction with the medication. Based on the final results from Part 1 of the randomized, double-blind, placebo-controlled efficacy study (BCX7353-302), the dose of BCX7353 used in this study is 150 mg QD.

Subjects may be enrolled once all eligibility criteria and study requirements are met. On-treatment study visits will occur at Weeks 4, 12, 24, 48, 72, and 96. An independent DMC has been reviewing the safety data from this study in concert with the accumulating safety information generated across the BCX7353 clinical development program. The DMC met at a frequency of approximately every 12 weeks until a total of approximately 200 subjects across the Phase 3 Study, BCX7353-302, and the current study (BCX7353-204) completed 48 weeks of dosing with active drug. Since a total of over 200 subjects have completed 48 weeks across the studies, the DMC is now provided with data every 6 months until the last subject completes the study or approval is obtained in the first country globally. A formal meeting of the DMC members will not be required; however, if the data review identifies any concern, the DMC members may elect to hold a formal DMC meeting. In addition, the emergence of a new, clinically significant safety signal may prompt an ad hoc DMC review.

Approximately 475 subjects will be enrolled into the study, with approximately 250 subjects planned to be enrolled in the US. Subjects will be eligible to receive BCX7353 for up to 96 weeks, until the product becomes commercially available, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first.

A study schema is shown in Figure 1.

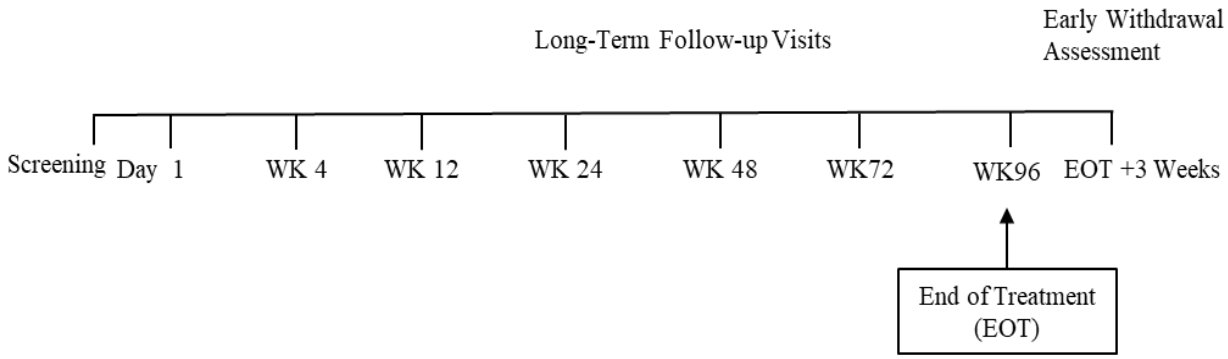
All subjects will be instructed to complete their diaries to document all angioedema attacks that occur.

Acute attacks of angioedema will be treated in accordance with the subject's normal standard of care. Treatment for acute attacks of HAE will not be provided by the Sponsor.

Subjects will complete the angioedema quality of life questionnaire (AE-QoL) to assess health-related QoL and the Treatment Satisfaction Questionnaire for Medication (TSQM) to assess their satisfaction with the study medication. Additionally, subjects will be assessed if days were lost from school and/or work.

Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, coagulation and urinalysis), vital signs, ECGs, and physical examinations at the study visits indicated in the schedule of assessments (see Table 3).

Figure 1. Study Schema



Abbreviations: EOT = end of treatment; WK = week.

7.1. Endpoints

7.1.1. Safety Endpoints

The primary objective of the study is to obtain long-term safety of BCX7353. The safety endpoints will include the following:

- The proportion of subjects who discontinue BCX7353 due to a TEAE
- The proportion of subjects with treatment-emergent SAEs
- The proportion of subjects with TEAEs
- The proportion of subjects with treatment-emergent Grade 3 or 4 AEs
- The proportion of subjects with treatment-emergent, treatment-related AE consistent with a drug rash
- The proportion of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities

7.1.2. Effectiveness Endpoints

Effectiveness endpoints will include the following:

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Patient-reported outcomes (HAE disease-specific AE-QoL questionnaire scores and TSQM Global Satisfaction scores)
- Number of attacks requiring attack medication
- Discontinuations due to lack of efficacy (through Week 48 only)
- Severity of attacks

Additional related details of HAE attacks (eg, symptoms, anatomical location, hospitalizations, emergency room visits, attack severity, attack duration) and number of days lost from work and/or school due to attacks will be summarized.

All attacks recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in effectiveness analyses. These rules, which have been constructed in concert with HAE-treating physicians, are outlined in the Statistical Analysis Plan (SAP).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

Approximately 475 subjects are planned to be enrolled globally in the study, with approximately 250 subjects planned to be enrolled in the US, which includes any adolescent subjects enrolled in the substudy.

8.2. Subject Selection

8.2.1. Inclusion Criteria

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

1. Males and nonpregnant, nonlactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy).
2. Subjects with a clinical diagnosis of HAE Type I or II who, in the opinion of the Investigator, are expected to benefit from an oral treatment for the prevention of angioedema attacks. A clinical diagnosis of HAE Type I or II is defined as:
    - A C1 esterase inhibitor (C1-INH) functional level below the assay lower limit of normal as assessed during the screening period by chromogenic assay OR
    - Laboratory documentation of historical C1-INH functional level below the assay lower limit of normal OR
    - Subjects who currently use plasma derived or recombinant C1-INH based therapies for acute attacks or prophylaxis may use one of the following to confirm their diagnosis:
        - SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or II as assessed during the screening period OR
        - A confirmed family history of C1-INH deficiency
3. Subject weight ≥ 40 kg.
4. Access to one or more targeted medications for the treatment of acute HAE attacks. The following are acceptable: icatibant, plasma-derived C1-INH (any form), ecallantide, recombinant C1-INH.
5. Female subjects must meet at least 1 of the following requirements:

a. Be a woman of childbearing potential (defined as a nonmenopausal adult or adolescent-female who has not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure) who agrees to use at least an acceptable effective contraceptive method during the study and for a duration of 30 days after last dose of study drug. One or more of the following methods are acceptable:

   - Surgical sterilization (ie, bilateral tubal occlusion or vasectomy of male partner)
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS) (implanted any time prior to or during screening)
   - Implantable or injectable progesterone hormonal contraception initiated at least 7 days prior to the screening visit
   - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal or oral progesterone norethindrone-based hormonal contraception initiated at least 28 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 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.

   Female subjects of childbearing potential who declare themselves as either sexually abstinent or exclusively having female sexual partners do not need to use an acceptable method of contraception. This declaration should be reviewed with the subject throughout the study to ensure continued accuracy. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject."

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

6. Able to provide written, informed consent. Subjects aged ≥ 12 to 17 years who are screened for the substudy must be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent.
7. In the opinion of the Investigator, the subject is able 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 including diary recording of HAE attacks.

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. Pregnancy or breast feeding or planned pregnancy during the study period.

2. Any clinically significant medical condition or medical history that, in the opinion of the Investigator or Sponsor, would interfere with the subject's safety or ability to participate in the study. Examples include active malignancy under treatment, uncontrolled cardiovascular disease (recent acute myocardial infarction, unstable angina), organ dysfunction such that supportive care is required (dialysis, oxygen therapy, cirrhotic care).

3. Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or participation in the study.

4. Clinically significant abnormal ECG including but not limited to, a QTcF > 470 msec for women, a QTcF > 450 msec for men, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.

5. Use of daily concomitant medications that are predominantly metabolized by CYP2D6 or CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study, as defined in Section 9.7.1.

6. Use of oral androgens for treatment of HAE (prophylaxis or acute) within 28 days of the baseline visit or planned initiation during the study.

7. Any laboratory parameter abnormality that, in the opinion of the Investigator, is clinically significant and relevant for this study.

8. Investigational drug exposure within 30 days prior to the screening visit.

9. Severe hypersensitivity to multiple medicinal products or severe hypersensitivity/ anaphylaxis with unclear etiology.

10. History of alcohol or drug abuse within the previous year, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 units of alcohol/day).

11. Current infection with hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

12. Subjects with an immediate family relationship to either Sponsor employees, the Investigator or employees of the study site who are named on the delegation log.

13. Subjects who are held in an institution by a government or judicial order.

8.3. Subject Discontinuation from the Study and from Study Drug

8.3.1. Subject Discontinuation from the Study

Participation in the study is strictly voluntary; a subject may withdraw consent to contribute additional study information at any point. A subject who withdraws consent or is discontinued from study drug (see Section 8.3.2) will be requested to attend an end-of-study visit to complete all end-of-study evaluations. Subjects who discontinue the study but will continue to receive BCX7353 via another mechanism will have end-of-study assessments performed prior to

receiving BCX7353 outside of the study protocol.Although a subject may withdraw from the study at any time without specifying a reason for withdrawal, if known, the reason for withdrawal will be recorded in the subject's medical records (source documents) and the CRF. If the reason for subject withdrawal is not known, the subject must be contacted to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 12. If at any point in the study, the clinic is unable to contact the subject after appropriate attempts have been made, according to local clinic standards, the subject will be considered lost to follow-up.

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

8.3.2. Subject Discontinuation from Study Drug

A subject will be permanently withdrawn from study drug for any of the following bulleted reasons, which will be recorded in the source documents and CRF. When medically feasible, the Medical Monitor must be consulted prior to subject discontinuation. In all cases, subjects who prematurely and permanently discontinue study drug should complete all scheduled procedures for the end-of-study visit outlined in Table 3.

- Emergence of any laboratory abnormality or AE that in the judgment of the Investigator compromises the ability of the subject to continue study-specific procedures or it is considered not to be in the subject's best interest due to an altered benefit-risk profile
- Reoccurrence of treatment-emergent AST or ALT elevation > 5 × ULN (confirmed) if BCX7353 is restarted after meeting hold criteria as outlined in Section 12.2.2.
- Treatment-emergent ALT or AST > 3 × ULN combined with either laboratory abnormalities indicative of significant hepatic toxicity (ie, meeting Hy's law, total bilirubin> 2 × ULN OR with an INR > 1.5) or with symptomatology of acute hepatitis (ie, severe fatigue, nausea, vomiting, right upper quadrant pain and tenderness, fever, rash, and/or eosinophilia [> 5%])
- Subsequent determination that inclusion/exclusion criteria were not met
- Intercurrent illness or emergence of a new illness/medical condition that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Subject noncompliance with study drug or to the protocol
- Subjects with BCX7353-related Grade 3 or 4 rash as described by the Division of Microbiology and Infectious Diseases (DMID) criteria "skin-mucocutaneous" will be discontinued from study, if suspected to be due to BCX7353, and treated according to best medical practice. All subjects with a suspected drug rash should undergo specific rash evaluation as described in Section 11.1.12. A Grade 3 rash is defined as vesiculation or moist desquamation or ulceration, and a Grade 4 rash is defined as exfoliative dermatitis, mucous membrane involvement or erythema multiforme or

suspected SJS or necrosis requiring surgery. Subjects with a Grade 1 or 2 study drug-related rash may continue BCX7353 if the Investigator and subject deem it appropriate.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug and Study Drug Product

BCX7353 is an oral small molecule inhibitor of plasma kallikrein. All subjects will receive up to 96 weeks of BCX7353 capsules for oral administration at a dose 150 mg QD.

The study drug consists of BCX7353 capsules. The capsules are comprised of the API (BCX7353) blended with the excipients pregelatinized starch, polyplasdone XL, colloidal silicon dioxide, and magnesium stearate in a gelatin capsule.

Subjects will receive a daily dose of 150 mg supplied as 1 capsule per day.

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

9.2. Description of Study Drug Packaging, Labeling, and Storage

The study drug will be packaged in bottles. As the pharmaceutical development program for BCX7353 progresses, alternate packaging configurations may be introduced. Subjects will be dispensed a sufficient number of capsules to cover at least a 1-month dosing period. Additional visits for dispensing of study drug supply may occur after Week 24 as needed.

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

Study drug must be stored between 15°C and 25°C (room temperature).

Details on the study drug packaging, labeling, shipment, storage and dispensing will be provided in the Investigational Medicinal Product (IMP) manual.

9.3. Treatment Allocation and Study Drug Blinding

This is an open-label study. Subjects will receive BCX7353 150 mg administered orally QD.

Sites will request a kit allocation for eligible subjects in the interactive (web) response system (IXRS), preferably after all baseline assessments to confirm eligibility have been completed. If required by site procedures (i.e., dispensing of allocated study drug must occur through a pharmacy), the request may be made on the business day prior to the planned baseline visit.

During the conduct of the study, responsibility for kit supply and resupply may be transferred to a specialty pharmacy selected by the Sponsor and subjects may receive study drug directly from the specialty pharmacy. Detailed instructions will be provided at the time of implementation.

9.4. Study Drug Administration and Treatment Compliance

Subjects will be instructed to take 1 BCX7353 capsule orally QD at approximately the same time each day, with whichever meal is typically the largest of the day. Subjects will be instructed to take study drug with food, or within 30 minutes after consuming food. It is recommended that the study drug be administered with food to help minimize GI effects. If GI-related symptoms are noted as an AE, the site should query the subject and record whether the drug is being taken as instructed (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 their regular dosing schedule on the next day.

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

If a specialty pharmacy is used, specialty pharmacy staff may contact subjects directly to better understand the subject experience with study drug during the subject's participation in the study.

9.5. Study Drug Dose Modification

No dose reductions are permitted.

Study drug interruptions are discussed in Section 12.1.8.

9.6. Study Drug (Investigational Medicinal Product) Accountability

Accountability of study drug dispensed and returned (as applicable) will be performed at Baseline and at each study visit. Returned study drug bottles and/or kits must be retained and reviewed during monitoring visits by the clinical research associate (CRA) (Section 14.2).

The Investigator/pharmacist/pharmacy must maintain accurate records of the disposition of all study drugs received from the Sponsor, issued to the subject (including date), and any drug destroyed. The Sponsor will supply a specific drug accountability form. At the end of the study, information describing study drug supplies (eg, kit numbers) and disposition of supplies for each subject must be provided, signed by the Investigator or designee, and collected by the CRA. If any errors or irregularities in any shipment of study medication to the site are discovered at any time, the Sponsor (and or designee) must be contacted immediately.

At the end of the study or at other times as agreed by all involved parties, all study drug not dispensed or administered will either be collected and returned to the Sponsor or destroyed on site as dictated by the appropriate Standard Operating Procedure.

9.7. Concomitant Medications

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

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

Subjects whose illness is being treated with C1-INH, tranexamic acid, or lanadelumab prophylaxis regimens are allowed to continue on their regimen; however, the Investigator is encouraged to assess response to BCX7353 therapy and reduce and/or discontinue prophylactic C1-INH, tranexamic acid, or lanadelumab use over time if clinically warranted.

Steady state levels of BCX7353 are reached with daily dosing between 6 and 12 days. Therefore, the following strategies are recommended for subjects who are beginning BCX7353 in place of another method of prophylaxis:

Table 2. Recommended Strategies for Switching to BCX7353 Prophylaxis from Another Therapy

Current Prophylactic Therapy	Timing of BCX7353 Initiation
Androgens (eg, danazol)	Discontinue androgens. Day 1 of BCX7353 dosing may occur a minimum of 28 days after the last dose of androgens. *Androgens may be discontinued or tapered in accordance with the usual practice of the Investigator; however, last dose must occur a minimum of 28 days prior to BCX7353 initiation.*
Tranexamic acid	Discontinue tranexamic acid dosing 14 days after first dose of BCX7353.
C1-INH (eg, Cinryze, Haegarda)	Discontinue existing C1-INH dosing schedule 14 days after first dose of BCX7353.
Lanadelumab-flyo	Day 1 of BCX7353 dosing to occur on same day as lanadelumab injection. No further dosing of lanadelumab is required after initiating BCX7353.

9.7.1. Prohibited Medications

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

- Angiotensin-converting enzyme inhibitors within 7 days of the baseline visit or planned initiation during the study (potential for exacerbation of HAE)
- Investigational drug exposure within 30 days prior to the screening visit or initiation during the study

- Use of daily concomitant medication that is predominantly metabolized by CYP2D6 or CYP3A4 and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study. For the purposes of this protocol, these are: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, thioridazine, haloperidol, methadone, procainamide, and amitriptyline. Note: Topical or ophthalmic tacrolimus or sirolimus are allowed.
- Use of oral androgens within 28 days of the baseline visit or planned initiation during the study (i.e., danazol, stanozolol, oxandralone, methyl-testosterone). Note: Testosterone replacement therapy is allowed.

10. STUDY CONDUCT

10.1. Overview

This is an open-label study to evaluate the long-term safety and effectiveness of 150 mg QD of orally administered BCX7353.

Subjects will be eligible to receive study drug (BCX7353) for up to 96 weeks, until the product becomes commercially available, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related AE. The Study will be discontinued if ongoing regulatory or Institutional Review Board/Ethics Committee (IRB/EC) approval is withdrawn, or in the event that technical or logistical factors prevent the ongoing conduct of the study. Subjects who discontinue study drug will return to the clinic for an end-of-study visit 3 weeks after the last dose of study drug. Subjects who discontinue the study but will continue to receive BCX7353 via another mechanism will have end-of-study assessments performed prior to receiving BCX7353 outside of the study protocol.

10.2. Schedule of Assessments

The schedule of assessments for this study is presented in Table 3 and procedures are described in Section 11.

Table 3. Schedule of Assessments: Study BCX7353-204

Assessment	*Screening Period*	*Baseline Visit*[a]	*Treatment Period (Visit schedule)*						*End of Study Assessment*
	Screening Visit (Up to Day -28)	**(Day 1)**	**Week 4 (Day 29 ± 2 days)**	**Week 12 (Day 85 ± 2 days)**	**Week 24 (Day 169 ± 6 days)**	**Week 48 (Day 337 ± 6 days)**	**Week 72 (Day 505 ± 6 days)**	**Week 96 (Day 673 ± 6 days)**	**3 weeks (± 3 days) after last dose of study drug**
Informed consent/assent (as applicable)[b]	X	X							
Inclusion-exclusion criteria	X	X							
Medical and medication history, HAE medical and medication history[c]	X	X							
Weight/height/BMI[d]	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	X	X	X	X	X	X	X
Pregnancy test[f]	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X
FSH[h]	X								
HIV, HCV, HBV serology	X								
Diagnosis of HAE established[i]	X								
Androgen discontinuation (if applicable)[j]	X								
Clinical chemistry/ hematology/ coagulation[k]	X	X	X	X	X	X	X	X	X
Urinalysis[k]	X	X	X	X	X	X	X	X	X
Sample for HLA analysis[l]		X							
Optional sample for exploratory PG[m]		X							
ECG[n]	X	X	X	X	X	X	X	X	X
AE-QoL, assessment of days lost from work and/or school and TSQM[o]		X	X	X	X	X	X	X	X
Concomitant medications[p]	X	X	X	X	X	X	X	X	X
Plasma PK sample[q]		X	X	X					X[q]
AEs	X	X	X	X	X	X	X	X	X
Diary instruction/ review/set-up[r]	X	X	X	X	X	X	X	X	X
Diary completion[s]	←	―	―	―	―	―	―	―	→
Study drug dosing		←	―	―	―	―	―	―	→
Study drug accountability/ dispensing[r]		X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life questionnaire; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BMI = body mass index; C1-INH = C1 esterase inhibitor; ECG = electrocardiogram; EOS = end of

study; FSH = follicle stimulating hormone; GGT = gamma glutamyltransferase; HAE = hereditary angioedema ; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IXRS = interactive (voice/web) response system; LDH =lactate dehydrogenase; LLN = lower limit of normal; PG = pharmacogenomic; QoL = quality of life; QTcF = QT interval corrected using Fridericia's method; TSQM = Treatment Satisfaction Questionnaire for Medication.

[a] The baseline visit should be within 28 days of the screening visit unless the screening visit is extended for previous androgen use, coming off other prophylactic therapies or elevated liver enzymes (with Medical Monitor permission).

[b] Informed consent/assent (as applicable) will be signed at the screening visit.

[c] Medical history and medication history will be completed at screening.

[d] BMI calculation and height at screening; weight is to be recorded at each in-clinic visit. Adolescents should also have height recorded at Week 48.

[e] Full physical examinations will be performed at screening; symptom-directed physical examinations will be performed at all post-screening visits.

[f] For women of childbearing potential, regardless of contraception or lifestyle, a serum pregnancy test will be administered at screening, urine pregnancy tests will be assessed at all subsequent visits as indicated in the table.

[g] To include blood pressure and pulse rate. Temperature and respiratory rate will be captured at screening and baseline only.

[h] For a woman who declares that she has been post-menopausal ≤ 2 years

[i] Subjects with a clinical diagnosis of HAE Type I or II who, in the opinion of the Investigator, are expected to benefit from an oral treatment for the prevention of angioedema attacks. A clinical diagnosis of HAE Type I or II is defined as: A C1-INH functional level below the assay lower limit of normal as assessed during the screening period by chromogenic assay OR laboratory documentation of historical C1-INH functional level below the assay lower limit of normal OR subjects who currently use plasma-derived or recombinant C1-INH based therapies for acute attacks or prophylaxis may use one of the following to confirm their diagnosis: SERPING-1 gene mutation known or likely to be associated with HAE Type I or II as assessed during the screening period OR a confirmed family history of C1-INH deficiency.

[j] Subjects who discontinue androgen prophylaxis at the time of signing informed consent or at the screening visit should have ALT, AST, ALP, LDH, GGT, and total and direct bilirubin measured 2 weeks (+7 days) after androgen discontinuation.

[k] See Table 4 for analytes to be assessed.

[l] The sample for HLA may be drawn at baseline or at any subsequent visit.

[m] A blood sample for possible exploratory pharmacogenomic testing will be drawn for all subjects at the baseline/Day 1 visit; however, the sample will be analyzed only if consent/assent is obtained for this optional analysis. 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.

[n] All ECGs during the study will be single assessments with the exception of baseline which will be obtained in triplicate. An ECG should be repeated for a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec. Prior to obtaining an ECG, subjects should rest quietly. ECGs should be obtained prior to any blood sampling.

[o] AE-QoL and TSQM will be administered once at baseline and at each visit through the End of Study visit. Additional questions regarding loss of time from work/school will be instituted at each visit to more fully characterize QoL. Administration of the AE-QoL and TSQM questionnaires and assessment if time was lost from school and/or work should be completed by the subjects prior to the other assessments during the visits to prevent influencing subject perceptions, if possible.

[p] Concomitant medications will be reviewed at each visit and on treatment, new concomitant medications will be reviewed to determine whether there are any contraindications.

[q] For adolescent subjects only (≥12 to 17 years of age). The actual date and time of PK blood draw, and time of last study drug dose (relative to PK blood draw) will be captured in the CRF. Samples for PK will be collected through the Week 12 visit. PK sample is required at the EOS visit only if the EOS visit is occurring prior to Week 12.

[r] Site staff will review the diary instructions with the subjects at the first clinic visit (Screening visit). Subjects will be instructed to bring the completed diary with them to their visits. Any issues with the entered data in the diary will be discussed with the subject and corrections will be made by the subject as required. Subjects will enter HAE attacks and relevant details (screening through follow-up).

[s] Sites will request kit assignment in the IXRS for eligible subjects at the Day 1 visit. During the conduct of the study, responsibility for kit allocation/distribution may be transferred to a specialty pharmacy selected by the Sponsor.

10.3. Study Visits

Details for all study visits are found in Table 3: Schedule of Assessments.

10.3.1. Screening Visit

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

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.

Subjects who discontinue androgen prophylaxis at the time of signing informed consent or at the screening visit will also have ALT, AST, ALP, LDH, GGT and total and direct bilirubin measured 2 weeks (+7 days) after androgen discontinuation.

With Medical Monitor permission, screening may be extended for an additional 42 days (for a total of 70 days) for subjects transitioning from other prophylactic therapies, including those that have AST or ALT elevations > 3 × the ULN at any pre-dose visit.

Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, will be approved or denied on a case-by-case basis by the Sponsor Medical Monitor. Retesting of specific assessments without entirely rescreening a subject may be permitted.

Subjects who were screen failures on a BCX7353 study may be screened or rescreened for the current study where there is a reasonable expectation that the subject will be eligible.

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

10.3.2. Baseline Visit (Day 1)

Subjects who meet all study eligibility criteria, and who agree to participate will be asked to return for a scheduled baseline visit (Day 1) within 28 days of the screening visit. Screening may be extended with Medical Monitor permission for subjects transitioning from other prophylactic therapies as stated above.

Inclusion/exclusion criteria and HAE medical and medication history will be reviewed to ensure continued subject eligibility prior to dosing.

After completion of all Baseline assessments as listed in Table 3: Schedule of Assessments, study drug should be dispensed (see Section 9.4).

10.3.3. Week 4 Visit

Subjects will return to the clinic during Week 4 (study Day 29 ± 2 days).

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

Subjects will be reminded to continue to fill out any HAE attacks in their diary and to bring their diary with them to all visits.

10.3.4. Week 12, 24, 48, 72, and 96 Visits

Subjects will return to the clinic for additional visits for up to 96 weeks, until the product becomes commercially available, or until the Sponsor discontinues development of the product for the prevention of angioedema attacks, whichever comes first. Study visits are planned to occur at Week 12 (Day 85 ± 2 days), Week 24 (Day 169 ± 6 days), Week 48 (Day 337 ± 6 days), Week 72 (Day 505 ± 6 days), and Week 96 (Day 673 ± 6 days).

Subjects will be reminded to continue to fill out any HAE attacks in their diary and to bring their diary with them to all visits.

10.3.5. End of Study Visit

Subjects who discontinue study drug will return to the clinic 3 weeks (21 ± 3 days) after the date of their last dose for their end of study or withdrawal assessment. Subjects who discontinue study drug must undergo all study-related procedures outlined in Table 3. Subjects who discontinue the study but will continue to receive BCX7353 via another mechanism will have end-of-study assessments performed at their last regularly scheduled visit.

If an AE is ongoing at the end of study visit, additional clinic visit(s) or telephone contact(s) may be warranted (see Section 12.1.2).

11. ASSESSMENTS

The schedule of procedures and assessments to be conducted throughout the study are outlined in Table 3, with details on the conduct of the procedures/ assessments provided below.

Even if not provided by the Investigator, routine and appropriate preventative care such as mammograms, cervical and testicular cancer screenings, etc., should be obtained by the subject and results provided to the Investigator to demonstrate ongoing general health due to the longstanding duration of this trial.

11.1. Investigator-Completed Assessments

Demographic information, including year of birth, sex, race, and ethnicity will be captured for each subject participating in the study at the screening visit. Medical and medication history will be captured at the screening visit and updated at baseline.

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

Additionally, subjects will be queried if time was lost from school and/or work, beginning at baseline and at each visit.

11.1.1. HAE Medical and Medication History

An HAE medical history questionnaire provided by the Sponsor will be completed at screening. All questions on the medical history/medication questionnaire should be completed by the Investigator (or designee) from historical source documentation when available, with subject input as necessary to complete the remaining questions.

11.1.2. Physical Examination

A full physical examination will be conducted at screening. All subsequent physical examinations will be abbreviated (i.e., targeted or symptom-directed) to include, at a minimum, evaluation of any new signs or symptoms.

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

11.1.3. Weight/Body Mass Index

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

BMI should be calculated using the following formula:

BMI = weight (kg)/height $(m)^2$

BMI and height are only to be captured at the screening visit. Adolescents will also have height captured at Week 48.

11.1.4. 12-lead Electrocardiograms

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

Qualified site personnel must review the ECGs and automated findings for gross abnormalities and to review any interval measurements of concern (absolute readings and for post-baseline ECGs, a change from baseline). For all ECGs, the clinical interpretation of the ECG and calculated QTcF (if not automated by the ECG machine and including adjudication of any automated measurements or diagnoses) should be recorded directly on a hard copy of the ECGs. Copies of the ECGs may be requested by the Sponsor. All subject identifiers will be masked prior to provision to the Sponsor.

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

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 pulse rate should be taken after the subject has rested. Blood pressure measurements must be obtained with an appropriate cuff size and with the subject's arm supported at the level of the heart. It is acceptable to obtain a pulse rate from the

blood pressure or ECG machine. Temperature and respiratory rate will be captured at screening and baseline only.

11.1.6. Clinical Laboratory Evaluations

Blood and urine samples will be obtained per the schedule of events. Individual laboratory tests to be performed are provided in Table 4.

All laboratory samples will be collected using kit supplies provided by the central laboratory, which will also analyze all samples. If results are obtained from both central and local laboratories for the same assessments at a single study time point, only the central laboratory results will be used for study purposes. Additionally, urine pregnancy tests will be provided by the central laboratory but will be analyzed at the clinical site. A laboratory reference manual will be provided to the site detailing kit contents, reordering instructions, sample collection, handling, storage and shipment.

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

Table 4. Clinical Laboratory Evaluations

Hematology • Basophils • Eosinophils • Hematocrit • Hemoglobin • Lymphocytes • Mean cell hemoglobin (MCH) • Mean cell hemoglobin concentration (MCHC) • Mean cell volume (MCV) • Monocytes • Neutrophils • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count **Urinalysis** • Bilirubin • Blood • Glucose • Ketones • Leukocytes • Nitrites • pH • Protein • Specific gravity • Urobilinogen • Reflex to microscopy for abnormal findings **Coagulation** • Prothrombin time (PT) • Activated partial thromboplastin time (aPTT) • International normalized ratio (INR)	**Clinical Chemistry** • Alanine aminotransferase (ALT) • Albumin • Alkaline phosphatase • Amylase • Aspartate aminotransferase (AST) • Bilirubin (total) • Bilirubin (direct; only if total is elevated) • Blood urea nitrogen (BUN) • Calcium • Chloride • Creatinine • Gamma glutamyl transferase (GGT) • Glucose or glucose • Lactate dehydrogenase (LDH) • Lipase (reflex if amylase is > 2 × ULN) • Magnesium • Potassium • Phosphate (inorganic) • Protein (total) • Sodium • Uric acid	**Other Tests** **Virology (Screening Only)** • Hepatitis B surface antigen • Hepatitis C antibody; reflex to hepatitis C virus RNA if antibody is positive • HIV antibody **Pregnancy tests** • Serum β-HCG (females of childbearing potential) • Urine β-HCG (females of childbearing potential) • Reflex to serum β-HCG for a positive urine β-HCG **FSH (postmenopausal females ≤ 2 years)**

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 and Follicle-Stimulating Hormone

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

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

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

11.1.9. HAE Diagnostic Criteria

Subjects with a clinical diagnosis of HAE Type I or II who, in the opinion of the Investigator, are expected to benefit from an oral treatment for the prevention of angioedema attacks. A clinical diagnosis of HAE Type I or II is defined as:

- A C1 esterase inhibitor (C1-INH) functional level below the assay lower limit of normal as assessed during the screening period by chromogenic assay OR
- Laboratory documentation of historical C1-INH functional level below the assay lower limit of normal OR
- Subjects who currently use plasma derived or recombinant C1-INH based therapies for acute attacks or prophylaxis may use one of the following to confirm their diagnosis:
    - SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or II as assessed during the screening period OR
    - A confirmed family history of C1-INH deficiency

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

11.1.10. Other Laboratory Assessments

All subjects will have a blood sample for HLA analysis drawn at baseline/Day 1 (or any other time point on study if not obtained at baseline). 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.

11.1.11. Pharmacokinetics

A blood sample for PK analyses will be drawn on adolescent subjects (≥12 to 17 years of age) at Baseline and study visits through Week 12. The time of last study drug dose and time of PK blood draw will be recorded in the CRF.

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

11.1.12. Pharmacogenomic Testing

For subjects who, are willing to participate and sign separate informed consent, possible exploratory pharmacogenomics testing may be performed. 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.

11.1.13. Rash Assessment

Because of the potential for a study drug-related rash, all sites should be prepared to report details of suspected drug rashes and provide photographs.

Subjects should be medically evaluated for any diffuse maculopapular rash that could be drug-related. Rashes that resolve rapidly and therefore cannot be medically evaluated will not result in a protocol deviation. The site must enter the event into EDC as an AE (flagged as an EOSI) and inform the Sponsor Medical Monitor via the EOSI form of all BCX7353-related maculopapular rashes (Section 12.1.5.1) after assessment. If the rash is assessed as not maculopapular (eg, urticarial) or not related to BCX7353 (i.e., has a clear alternative etiology), then the rash is reported as an AE, treated per Investigator judgement, and no further special assessment is required.

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

- Full dermatological exam to include the scope of the rash (location), vital signs, and mucosal examination. The notes documenting the examination should include detailed description of the rash; presence or absence of desquamation; presence or absence of blistering and if present, its extent; presence or absence of mucosal involvement and if present, its extent; and any other associated abnormal physical findings.
- Vital signs including temperature
- High resolution photographs taken to provide both detail regarding the rash (close-up) and details regarding the extent of the rash (whole body or body part). Cameras must be able to provide clear images taken in close proximity to the skin. The picture should include a ruler (centimeter) for scale. Every attempt to protect subject anonymity should be made.
- All detailed clinical information regarding the rash, examination, treatment and interpretation of the event needs to be reported on an SAE/Event of Special Interest (EOSI) report form as per Section 12.1.5.1.

Most subjects will not need further evaluation for appropriate diagnosis or treatment. However, if laboratory evaluations (i.e. blood safety assessment labs) are done, these should be performed through the central lab. If they are performed at a local lab, include a redacted copy of the results or enter the values on the EOSI report. If it is determined by the Investigator or another clinician that a biopsy would be appropriate, a redacted copy of the pathology report as part of the EOSI reporting procedure should be sumbited. If the study site cannot perform a biopsy (if indicated) or any of the above mandatory assessments (i.e., photographs), then it is appropriate to refer the subject 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, submit the redacted written consultation report.

Dosing of BCX7353 may continue in subjects experiencing a Grade 1 or 2 drug rash if the subject and Investigator agree. The EOSI form and any additional information should be received by the Sponsor in a timely manner for Sponsor review. The Investigator's intention regarding BCX7353 dosing (i.e., continuation, temporary interruption or discontinuation) should be clearly stated on the EOSI form. The Sponsor may discuss the drug rash with the Investigator if there are questions or concerns.

11.2. Subject-Completed Assessments

11.2.1. Patient-Reported Outcomes

The disease-specific questionnaire, AE-QoL, and TSQM will each be administered once at baseline, at each visit through Week 96 (or end of treatment), and at the end-of-study visit.

An assessment of days lost from work or school during the previous 12 months will be captured at the baseline visit. Days lost from work or school since the previous visit will also be captured at each study visit through Week 96 (end of treatment) and through the end-of-study visit 3 weeks after the last dose of study drug.

Additionally, other patient-reported outcomes may be implemented at any study visit to fully characterize QoL.

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

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

11.2.2. HAE Attack and Dosing Diary

The Sponsor will supply diaries to all sites. Sites will dispense diaries to subjects at screening. Diaries will be collected at each visit 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 recalling whether symptoms of an HAE attack were experienced. Subjects need only to fill out the diary details section when there is 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.

Further training on completing the diary should be provided at each clinic visit.

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 based on outstanding questions a subject may have or incorrect assumptions/interpretation of diary questions.

Subjects should bring their diary to each study visit. It is also acceptable for completed diaries to be returned to the site on a monthly basis after Week 4.

12. ADVERSE EVENT MANAGEMENT AND REPORTING

12.1. Adverse Events

AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period. 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 or with the clinical study itself is implied. An AE may be an unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (eg, requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be AEs. If the diagnostic procedure prompts no additional treatment, visits, or monitoring, it will not meet the definition of an adverse event.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 12.1), 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 trial. AEs should only be reported if the abnormalities are changes from baseline and are clinically significant as described above.
- Pre-existing medical conditions (other than the condition being studied) judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period. When recording such events on an AE/SAE eCRF page, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, “more frequent headaches”).

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

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

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

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

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

AEs are designated as “non-serious” or “serious.”

12.1.1.2. Serious Adverse Event

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

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

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

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

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

Overdose will be considered an SAE only if any of the seriousness criteria are met. Any clinical complication in association with the overdose should be reported as an AE or SAE (as applicable) along with the overdose (see Section 12.2.2). 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, non-serious treatment-emergent maculopapular rashes that are deemed related to BCX7353 will be considered EOSIs. This does not include other types of rashes such as urticaria or eczema. All treatment-emergent skin conditions should be reported as AEs but only maculopapular rashes deemed related to BCX7353 should be considered EOSIs.

An EOSI event in and of itself will not be considered serious unless it meets the seriousness criteria above. Events of maculopapular rash assessed as possibly, probably, or definitely related to BCX7353 regardless of severity must be reported to the Sponsor Medical Monitor as described in Section 12.1.5.1. Management of BCX7353 drug-related rash is provided in Section 11.1.12.

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

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

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

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

study until they are resolved, or are judged medically stable, or are otherwise medically explained.

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

12.1.3. Definition of Severity

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

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

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

12.1.4. Definition of Relationship to Study Drug

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

Not Related:	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident, and no temporal relationship exists between the study drug and the event.

Unlikely:	The event does not follow a reasonable temporal sequence from drug administration and is readily explained by the subject's clinical state or by other modes of therapy administered to the subject.
Possibly Related:	There is some temporal relationship between the event and the administration of the study drug and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident.
Probably Related:	The event follows a reasonable temporal sequence from drug administration, abates upon discontinuation of the drug, and cannot be reasonably explained by the known characteristics of the subject's clinical state.
Definitely Related:	The event follows a reasonable temporal sequence from study drug administration, follows a known or suspected response pattern to the study drug, is confirmed by improvement upon stopping the study drug (dechallenge), and reappears upon repeated exposure (rechallenge, if rechallenge is medically appropriate).

The Sponsor may upgrade causality if deemed appropriate.

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

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

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

Email: mm@biocryst.com

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

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

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

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

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

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

12.1.5.1. Reporting Events of Special Interest

Although not an SAE, all events of diffuse maculopapular rash assessed as related to BCX7353 regardless of severity, must be reported to the Sponsor Medical Monitor in writing via email using the SAE/EOSI report form after the Investigator's assessment of the event. High resolution photographs must also be submitted as described in Section 11.1.12. In addition, the event must be recorded on the AE CRF in real time. All additional follow-up evaluations of the event must be reported to BioCryst or its designee as soon as they are available. The SAE/EOSI report form should be sent to the following email address:

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

Email: mm@biocryst.com

This method of reporting will allow BioCryst to obtain more information than can be captured in the eCRF for this event. The report form will allow a full clinical description and information regarding the evaluation that cannot be documented in the EDC due to free text limitations to be shared with BioCryst. Therefore, the initial report and photographs should be submitted by the Investigator within a very short period of time.

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

12.1.6. Pregnancy

Any female subject who becomes pregnant during the course of the study should have study drug discontinued immediately and must be followed through the end of the pregnancy. Male subjects whose partners become pregnant do not need to discontinue study drug. 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 pregnant partners of study participants will be obtained prior to reporting any details of the pregnancy. Information related to the pregnancy must be given on a "Pregnancy Confirmation and Outcome" form that will be provided by the Sponsor or its designee so that the pregnancy may be followed and an outcome determined. Any AEs or SAEs experienced by a pregnant subject are to be reported as directed above in Section 12.1.2 and Section 12.1.5. Any complications reported in a subject's pregnant partner should be reported on the Pregnancy Confirmation and Outcome form. All pregnancies must be followed to outcome which occurs

when an infant is delivered (live or still born), there is fetal demise, or there is an abortion (spontaneous or induced). Abortion (spontaneous or induced), fetal demise, and still birth along with congenital abnormalities in the newborn, should be reported as separate SAEs.

12.1.7. Serious Breaches of Good Clinical Practice

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

12.1.8. Treatment Interruptions

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

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

12.2. Toxicity Management

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

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

12.2.1. Rash

Special evaluation of BCX7353 related maculopapular drug rash is required as per Section 11.1.12 and special reporting is described in Section 12.1.5.1.

Management of rash should be based on best medical practice and address the subject's presentation. If a subject experiences a Grade 3 or 4 rash suspected to be due to BCX7353, the subject should have BCX7353 dosing stopped immediately as per Section 8.3.2. Grade 3 rashes would include rashes with vesiculation, moist desquamation, or ulceration and Grade 4 rashes would encompass rashes with mucous membrane involvement or significant exfoliation, erythema multiforme, suspected Stevens-Johnson syndrome, or necrosis requiring surgery.

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

Investigators and subjects may elect to continue dosing if the subject experiences a Grade 1 or 2 rash that is deemed related to BCX7353 but the subject is considered to be deriving benefit. By DMID criteria, this reaction would be described as pruritus and/or erythema (Grade 1) or a diffuse maculopapular rash and/or dry desquamation (Grade 2). In addition, subjects would have to be constitutionally well (no fever, no change in appetite, no malaise, etc.), have no mucosal involvement, no vesicles and have no evidence of any hypersensitivity involving the liver or kidney. If laboratory assessment is performed mild or moderate eosinophilia may be present but should not prevent continuation of study drug if all other criteria are met. Rash treatment should primarily address symptoms (i.e., antihistamines, topical antipruritics and/or topical corticosteroids). Oral corticosteroids should be avoided, as there is no evidence that oral corticosteroids benefit patients with bland drug-related cutaneous reactions.

If the subject's rash does not improve, or worsens to include vesicles, wet desquamation or ulceration (Grade 3), then BCX7353 should be immediately discontinued. Subjects who remain on study drug should be followed closely until the rash resolves.

12.2.2. Aminotransferase (ALT or AST) Elevation

All baseline or treatment-emergent ALT or AST elevations > 3 × ULN (ie, Grade 3 and above) should be confirmed within 72 hours with repeat assessment of ALT and AST as well as total bilirubin, ALP, prothrombin time /INR, and complete blood count for eosinophil levels. If subjects are asymptomatic with no other pertinent laboratory abnormality, study drug may be continued under close observation with every 2 week assessment of transaminase levels, total bilirubin, and ALP. These may be done at a local laboratory as long as results are reported to the Investigator as soon as they are available and the investigative site contacts the subject to ascertain any symptoms. If either ALT or AST continue to increase and the subject remains asymptomatic, study drug dosing must be held if:

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

The subject should continue regular assessments as deemed appropriate by the Investigator of ALT, AST, total bilirubin, ALP, prothrombin time/INR, and complete blood count for eosinophil levels until ALT and/or AST are < 3 × ULN.

Provided specific criteria are met, the Investigator and subject may elect to resume BCX7353 dosing. All of the following criteria must be met for dosing to resume:

- The subject is considered to have been deriving benefit from BCX7353 prior to holding study drug.
- Transaminases return to ≤ 2 × ULN for subjects whose baseline transaminase levels were above the ULN, and ≤ ULN for those whose baseline transaminase levels were ≤ ULN.
- Subjects have not initiated or restarted androgens during the period BCX7353 was held.
- The subject agrees to continue every 2 week monitoring of ALT, AST, total bilirubin, ALP, CBC (eosinophil levels) and prothrombin/INR until levels appear stable and

transaminase levels remain < 3 × ULN for at least 1 month after restarting BCX7353 dosing.

If at any time, the criteria as outlined in Section 8.3.2 is met, the study drug must be permanently discontinued.

12.2.3. Overdose

To date there is no experience with overdose of oral BCX7353. Single doses of up to 1000 mg, 7 days of dosing up to 500 mg/day, and 14 days of dosing with 350 mg/day revealed no clinically significant safety concerns in healthy subjects in Study BCX7353-101. In Study BCX7353-102, multiple dosing with 350 mg BCX7353 for up to 9 days either following or current with single doses of CYP probe substrate drugs in healthy subjects overall did not reveal any new safety concerns. Safety data generated in Study BCX7353-203, 28-day dosing with up to 350 mg/day, revealed no clinically significant safety concerns in subjects with HAE. Subsequently, subjects enrolled in BCX7353-106 were exposed to BCX7353 450 mg QD for 14 days without any unexpected AEs or increased AE severity.

In the event that study personnel become aware of an overdose of study drug/IMP (≥ 150 mg 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

Data from ongoing studies BCX7353-302 (Phase 3 study), BCX7353-301 (Phase 3 study) and the current study, BCX7353-204, are reviewed by the BCX7353 data monitoring committee (DMC). Since a total of over 200 subjects have completed 48 weeks across the studies, the DMC will be provided with data for review every 6 months until the last subject completes the study or the product is approved in the first country globally. A formal meeting of the DMC members will not be required; however, if the data review identifies any concern, the DMC members may elect to hold a formal DMC meeting. Where possible, scheduled DMC meetings for this protocol may be aligned with those of other protocol(s). The DMC may also be convened if a new clinically significant safety signal emerges or at other times as requested.

The latest data review was conducted on 23 October 2019.

The recommendation of the DMC was that all 3 studies proceed per protocol.

A separate DMC Charter will describe membership, roles, timing of DMC review, and responsibilities of the DMC members.

13. STATISTICS

13.1. Sample Size Considerations

No sample size calculations were conducted for this open-label, long-term safety study. Approximately 475 subjects may be enrolled in this study, with approximately 250 subjects planned to be enrolled in the US, to provide access to BCX7353 for additional subjects who, in the opinion of the Investigator, are expected to benefit from treatment with an oral treatment for the prevention of angioedema attacks.

13.2. Stratification

Not applicable.

13.3. Statistical Methods

A detailed SAP will be developed to describe the methods of analyses and summaries, including all endpoints, time points, populations, missing data, etc. Deviations from the analyses outlined in the SAP will be described in the CSR.

13.3.1. Analysis Populations

The analysis populations are defined below.

13.3.1.1. Screen Failures

Subjects who give written informed consent but are not assigned to study treatment and are noted as screen failures in the CRF are considered screen failures.

13.3.1.2. Safety Population

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

13.3.1.3. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who are allocated to study drug. The ITT population will be used as the primary population for effectiveness analyses. Subjects will be analyzed based on the treatment to which they were allocated.

13.3.2. General Considerations for Data Analysis

In general, descriptive summaries will include n, mean, standard deviation, median, minimum, and maximum for continuous variables and n and percent for categorical variables. Summaries will be presented by treatment group and by study visit.

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

13.3.3. Missing Data

For subjects who prematurely discontinue the study, all available data will be included for the key safety and effectiveness analyses.

13.3.4. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race or ethnicity, height, weight, BMI, and HAE history will be summarized by treatment group.

Subject disposition will be presented for all subjects. The number of subjects who completed through each study visit and those that 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 also be presented. Treatment adherence, dose interruptions and reason for dose interruptions will be provided as summaries or listed as appropriate.

13.3.5. Analysis of Safety Variables

Safety endpoints that will be summarized, at a minimum by treatment group, include the proportion of subjects 1) with TEAEs; 2) who discontinue BCX7353 due to TEAEs; 3) with treatment-emergent SAEs; 4) with treatment-emergent Grade 3 or 4 AEs; 5) with treatment-emergent treatment-related AEs consistent with a drug rash as identified by the Investigator (eg, maculopapular rash, papular rash identified as an EOSI), and 6) with treatment-emergent Grade 3 or 4 laboratory abnormalities.

Time to discontinuation due to a TEAE, and time to development of drug-related rash will be estimated using the Kaplan-Meier method. For those with a drug-related rash, clinical and laboratory findings will be summarized and the proportion of subjects who successfully continued therapy following onset of rash.

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) PT and SOC. The occurrence of TEAEs will be summarized using MedDRA PT, SOC, and severity. Separate summaries of TEAEs, treatment-emergent SAEs, AEs considered to be related to study drug, and AEs leading to study drug interruption will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries for vital signs, weight, bedside ECG parameters, and clinical laboratory results will be presented. Laboratory abnormalities will be graded according to the DMID Adult Toxicity Table (Publish Date: Draft, November 2007; 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. Laboratory toxicity shifts from baseline to worst postbaseline assessments will be summarized.

The number and percentage of subjects having elevations in liver enzyme abnormalities (ALT, AST, or bilirubin) in relation to fold above ULN will be summarized according to the FDA's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (FDA 2009).

Clinically significant abnormal morphological ECG findings will be summarized.

The change from baseline in QTcF will be determined by routine ECGs. At each time point ECGs are analyzed, an individual subject's change from baseline will be calculated as:

Δ_{ik}= (QTcF for subject at time point k – Baseline QTcF)

Where QTcF measurements will be the average of triplicate ECGs at baseline and single values at each time point.

For routine ECGs, the number and proportion of subjects with QTcF ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec; or changes of ≤ 30, > 30 to ≤ 60, or > 60 msec will be summarized.

Physical examination findings will be listed.

Concomitant medications and those discontinued during the study will be coded using the World Health Organization drug dictionary and summarized. Subjects with medications changes prior to baseline may also be summarized.

13.3.6. Analysis of Effectiveness Variables

The following effectiveness endpoints will be summarized and listed by treatment group:

- Number and rate of HAE attacks
- Durability of response
- Number and proportion of days with angioedema symptoms days
- Patient-reported outcomes: HAE disease-specific AE-QoL questionnaire scores and TSQM Global Satisfaction scores
- Number of attacks requiring attack medication
- Discontinuations due to lack of efficacy (through 48 weeks only)
- Disease severity

All attacks recorded by the subjects will be reviewed and confirmed or rejected according to a set of pre-defined rules prior to inclusion in effectiveness analyses. These rules, which will be constructed in concert with HAE-treating physicians, will be outlined in the SAP.

The attack rate will be calculated as the number of attacks per month (28 days) by treatment for each subject, adjusted for the total duration of treatment. The attack rate will be listed and summarized using all available data. The durability of response assessment will be based on attack rate trend over time. Alternatively, the attack rate change may also be assessed relative to recent HAE attack documentation. Summaries and/or comparisons of effectiveness endpoints may be performed for those who received concomitant C1-INH and those who did not.

Additional related details of HAE attacks (e.g., hospitalizations and emergency room visits) and number of days lost from work and/or school due to attacks will be summarized and listed. Summaries may be produced separately for pre-96 week attacks and post-96 week attacks as fewer details are collected in the diary post 96 weeks.

Details of these analyses will be provided in the SAP.

13.3.7. Interim and Final Analyses

Interim analyses may be performed during the course of the study as needed to support regulatory filings and safety updates. The final analysis will be performed when the last subject has completed the final study visit, the data are cleaned, and the database has been authorized for analysis.

13.3.8. Quality of Life Analyses

Scores at each visit and change from baseline in the domain scores of the AE-QoL (function, fatigue, nutrition, and fear/shame) as well as the composite score will be summarized by treatment group.

The change from baseline in TSQM Global Satisfaction scores as well as effectiveness, side effects, and convenience subscales will be summarized.

13.3.9. Pharmacokinetic Analyses

Plasma samples for determination of BCX7353 concentrations are planned to be collected at Baseline and Weeks 4 and 12 for adolescent subjects only (≥12 to 17 years of age). The resulting PK data may be pooled in a meta analysis to facilitate population PK analyses.

14. STUDY ADMINISTRATION

14.1. Regulatory and Ethical Considerations

14.1.1. Regulatory Authority Approvals

This study will be conducted in compliance with the protocol; GCPs, including ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH E6); FDA/European Medicines Agency regulatory requirements and other national laws as applicable; and in accordance with the ethical principles of the Declaration of Helsinki. In addition, the study will be conducted in compliance with all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

14.1.2. Institutional Review Board and Ethics Committee Approvals

Before initiation of the study at an investigational site, the protocol, the ICF, the subject information sheet (if applicable), and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study must be obtained before the study center can be initiated or the IMP can be released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained, in particular, for changes to the study such as modification of the protocol, the ICF, the written information provided to subjects, and/or other procedures.

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

Written reports of clinical study status will be submitted to the IRB/IEC annually or more frequently if requested by the IRB/IEC. A final study notification will also be forwarded to the IRB/IEC after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations. The study will be considered 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: Adults

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

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

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

In the event the subject is requested to undergo a skin biopsy due to rash, a separate informed consent will be required. Subjects with a Grade 1 or 2 rash remaining on study drug may undergo a biopsy, for which a separate informed consent will be obtained.

14.1.4. Subjects Informed Consent: Adolescents

Subject informed consent must be obtained from each parent/caregiver prior to performing any study-related procedures. Similarly, assent will be obtained from subjects ≥ 12 years to 17 years of age prior to performing any study-related procedures. If the local requirements limit the age of assent, then assent will be obtained based on those requirements. Each parent/caregiver and subject should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent and assent process should take place under conditions where the parent/caregiver has adequate time to consider the risks and benefits associated with his/her child's participation in the study. Subjects will not be screened or treated until the parent/caregiver and subjects has signed an approved ICF and assent form written in a language in which the subject is fluent. The ICF and assent forms that are used must be approved both by

BioCryst and by the reviewing IRB/IEC. The ICF and assent forms should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policy.

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

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

In the event the subject is requested to undergo a skin biopsy due to rash, a separate informed consent and assent form will be required. Subjects with a Grade 1 or 2 rash remaining on study drug may undergo a biopsy, for which a separate informed consent and assent will be obtained.

14.1.5. Investigator Reporting Requirements

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

14.2. Study Monitoring

During trial conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on CRFs 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 Principal Investigator(s) and their relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.3. Quality Assurance

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

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

14.4. Study Termination and Site Closure

Overall, the Sponsor may suspend enrollment into the study, suspend treatment of ongoing subjects, or terminate the study to ensure that subjects' safety and welfare are protected. The entire study, or individual sites, may be terminated for any of the following reasons:

- changes in scientific knowledge that lead to a negative impact on the risk/benefit profile for subjects
- request of BioCryst or competent public authorities / IRB / EC
- if recruitment cannot be completed in specified time frame
- if the permit to manufacture or import IMP is revoked
- if the study drug becomes commercially available

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 CRFs completed to the greatest extent possible.

An individual trial center that is determined to be unsuitable by Sponsor, competent public authorities or EC may be terminated, without affecting the other trial sites.

Except for those situations outlined in Section 8.3, no other formal stopping rules for individual subjects, parts of the trial or the entire trial, will be defined. Individual subjects will be discontinued from the study following the emergence of any laboratory abnormality or AE that in the judgment of the Investigator compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest.

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, CRFs, and medical/hospital records), all original signed ICFs, all CRFs, 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 and Data

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

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

14.7. Study Publication

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

15. REFERENCES

Aygoren-Pursun, E., A. Bygum, V. Grivcheva-Panovska, M. Magerl, J. Graff, U. C. Steiner, O. Fain, A. Huissoon, T. Kinaciyan, H. Farkas, R. Lleonart, H. J. Longhurst, W. Rae, M. Triggiani, W. Aberer, M. Cancian, A. Zanichelli, W. B. Smith, M. L. Baeza, A. Du-Thanh, M. Gompels, T. Gonzalez-Quevedo, J. Greve, M. Guilarte, C. Katelaris, S. Dobo, M. Cornpropst, D. Clemons, L. Fang, P. Collis, W. Sheridan, M. Maurer and M. Cicardi (2018). "Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema." N Engl J Med **379**(4): 352-362.

Bork, K., J. Hardt and G. Witzke (2012). "Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency." J Allergy Clin Immunol **130**(3): 692-697.

Bork, K., G. Meng, P. Staubach and J. Hardt (2006). "Hereditary angioedema: new findings concerning symptoms, affected organs, and course." Am J Med **119**(3): 267-274.

Bouillet, L., H. Longhurst, I. Boccon-Gibod, K. Bork, C. Bucher, A. Bygum, T. Caballero, C. Drouet, H. Farkas, C. Massot, E. W. Nielsen, D. Ponard and M. Cicardi (2008). "Disease expression in women with hereditary angioedema." Am J Obstet Gynecol **199**(5): 484 e481-484.

Caballero, T., H. Farkas, L. Bouillet, T. Bowen, A. Gompel, C. Fagerberg, J. Bjokander, K. Bork, A. Bygum, M. Cicardi, C. de Carolis, M. Frank, J. H. Gooi, H. Longhurst, I. Martinez-Saguer, E. W. Nielsen, K. Obtulowitz, R. Perricone, N. Prior and C. I. D. W. Group (2012). "International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency." J Allergy Clin Immunol **129**(2): 308-320.

Cicardi, M., K. Bork, T. Caballero, T. Craig, H. H. Li, H. Longhurst, A. Reshef, B. Zuraw and Hawk (2012). "Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group." Allergy **67**(2): 147-157.

Cornpropst, M., S. Dobo, J. Collier, A. Rose, R. Wilson, Y. S. Babu, P. Collis and W. Sheridan (2016). "BCX7353, a Potent Inhibitor of Plasma Kallikrein, Shows Sustained Maximal Enzyme Inhibition When Dosed Orally Once Daily: Results from a Phase I Trial in Healthy Subjects." Elsevier(AAAAI, Los Angeles).

FDA (2009). "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation." US DHHS, FDA, CDER(https://www.fda.gov/downloads/guidances/UCM174090.pdf).

Kaplan, A. P. (2010). "Enzymatic pathways in the pathogenesis of hereditary angioedema: the role of C1 inhibitor therapy." J Allergy Clin Immunol **126**(5): 918-925.

Kaplan, A. P. and B. Ghebrehiwet (2010). "The plasma bradykinin-forming pathways and its interrelationships with complement." Mol Immunol **47**(13): 2161-2169.

Longhurst, H. and M. Cicardi (2012). "Hereditary angio-oedema." Lancet **379**(9814): 474-481.

Lumry, W. R., A. J. Castaldo, M. K. Vernon, M. B. Blaustein, D. A. Wilson and P. T. Horn (2010). "The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression." Allergy Asthma Proc **31**(5): 407-414.

Saxena, P., P. Thompson, Y. d'Udekem and I. E. Konstantinov (2011). "Kallikrein-kinin system: a surgical perspective in post-aprotinin era." J Surg Res **167**(1): 70-77.

Shire (2018). "Takhyzyro (lanadelumab-flyo) injection, for subcutaneous use US Prescribing Information." 9.

Weller, K., M. Magerl, A. Peveling-Oberhag, P. Martus, P. Staubach and M. Maurer (2016). "The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference." Allergy **71**(8): 1203-1209.

Zuraw, B. L., A. Banerji, J. A. Bernstein, P. J. Busse, S. C. Christiansen, M. Davis-Lorton, M. M. Frank, H. H. Li, W. R. Lumry and M. Riedl (2013). "US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency." J Allergy Clin Immunol Pract **1**(5): 458-467.

Zuraw, B. L. and S. C. Christiansen (2011). "Pathophysiology of hereditary angioedema." Am J Rhinol Allergy **25**(6): 373-378.

16. APPENDICES

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

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

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

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