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STATISTICAL ANALYSIS PLAN

Study Title:	A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema
Sponsor	BioCryst Pharmaceuticals, Inc. 4505 Emperor Blvd., Suite 200 Durham, NC 27703 Phone: (919) 859-1302 Fax: (919) 851-1416
Name of Test Drug:	BCX7353
Protocol Number:	BCX7353-203
Phase:	Phase 2
Analysis Plan Version	Version 2.0
Analysis Plan Date	07FEB2017

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LIST OF ABBREVIATIONS

Abbreviation	Term
AAS	Angioedema Activity Score
AE(s)	Adverse Event
AeQoL	Angioedema Quality of Life questionnaire
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval (tau)
BQL	Below the quantification limit
BMI	Body mass index
BP	Blood pressure
$C_{av,ss}$	Average steady-state plasma drug concentration during multiple-dose administration
C1 INH	C1 esterase inhibitor
CI	Confidence Interval
CL/F	Apparent oral clearance
C_{max}	Maximum plasma concentration
C_{tau}	Observed drug concentration at the end of the dosing interval (tau)
CV	Coefficient of Variation
CVb	Between-subject coefficient of variation
DASS	Depression, Anxiety, Stress Scales
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
HAE	Hereditary Angioedema
HR	Heart rate
FAS	Full Analysis Set
λz	Terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities Terminology
n	Number of observations
PD	Pharmacodynamic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
RS	Randomized subjects
SD	Standard Deviation

Abbreviation	Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
$t_{½}$	Half-life
T_{max}	Time of maximum concentration
Vz/F	Apparent volume of distribution of the drug
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the interim and final analyses to be performed for Study BCX7353-203: A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the efficacy of once-daily prophylactic BCX7353 at 4 dose levels, as measured by the number of attacks of HAE observed in patients with HAE enrolled in each treatment group

2.1.2. Secondary Objectives

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

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Number of confirmed HAE attacks: analyzed by treatment group using appropriate descriptive statistics as follows: weekly attack rate, counts of attacks, proportion of subjects with no attacks, and number of attack-free days.

2.2.2. Secondary Endpoints

- Safety and tolerability of BCX7353 as assessed by adverse events (AEs), clinical laboratory tests, electrocardiograms (ECG), vital signs, and physical exam findings
- Number of attacks requiring attack medication (Medications recorded on Diary page to treat HAE attack include Cinryze, Berinert , Firazyr, Ruconest, Tranexamic acid and Kalbitor)
- Duration of attacks
- Severity of attacks
- Attack onset relative to the time of last dose of study drug
- Discontinuations due to lack of efficacy
- Symptoms and anatomical locations of attacks
- Number of emergency room visits and/or hospitalizations

- Quality of life scales, as measured by the Angioedema Quality of life (AE-QoL) and Depression, Anxiety, Stress Scales (DASS)
- BCX7353 steady-state pharmacokinetic (PK) parameters including C_{max}, C_{tau}, T_{max}, AUC_{tau}, AUC_{0-t}, half-life, λ, Vd/F, and CL/F
- *Ex-vivo* kallikrein inhibition
- Cleaved high-molecular-weight kininogen (HK) and C1INH functional level values and change from baseline

3. STUDY DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled, 3-part, parallel-group, dose-response study to evaluate the safety, tolerability, PK, PD, and efficacy of BCX7353 in subjects with HAE. HAE patients with a documented recent history of frequent angioedema attacks who have provided written informed consent will be evaluated for participation in this study at a screening visit. Up to 36 subjects with HAE are planned to be enrolled in Part 1 of the study and will be randomized 1:1 (placebo: active) to receive one of the following treatments:

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

After 24 subjects have completed through the Day 28 dose, there will be an administrative interim analysis of the accrued efficacy data by the Sponsor. Additional administrative analyses may be conducted following completion of Part 1 and Part 2.

If it is desired to more fully characterize the treatment effect of BCX7353 350 mg relative to placebo or to verify assumptions made for sizing this proof-of-concept study, additional subjects will be enrolled to complete Part 1 (up to 36). Enrollment into Part 1 will continue until either a decision is made to halt enrollment in favor of opening Part 2 or enrollment reaches 36 subjects in Part 1. Additionally, upon completion of Part 1 (36 subjects dosed), enrollment into Part 2 of the study may immediately commence.

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

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

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

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

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

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

The overall study design is presented in Figure 1; Figure 2 depicts the schema for conduct of each study part.

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

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

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

Individual subjects may only participate in one Part of the study.

Figure 1: Study BCX7353-203 Study Design

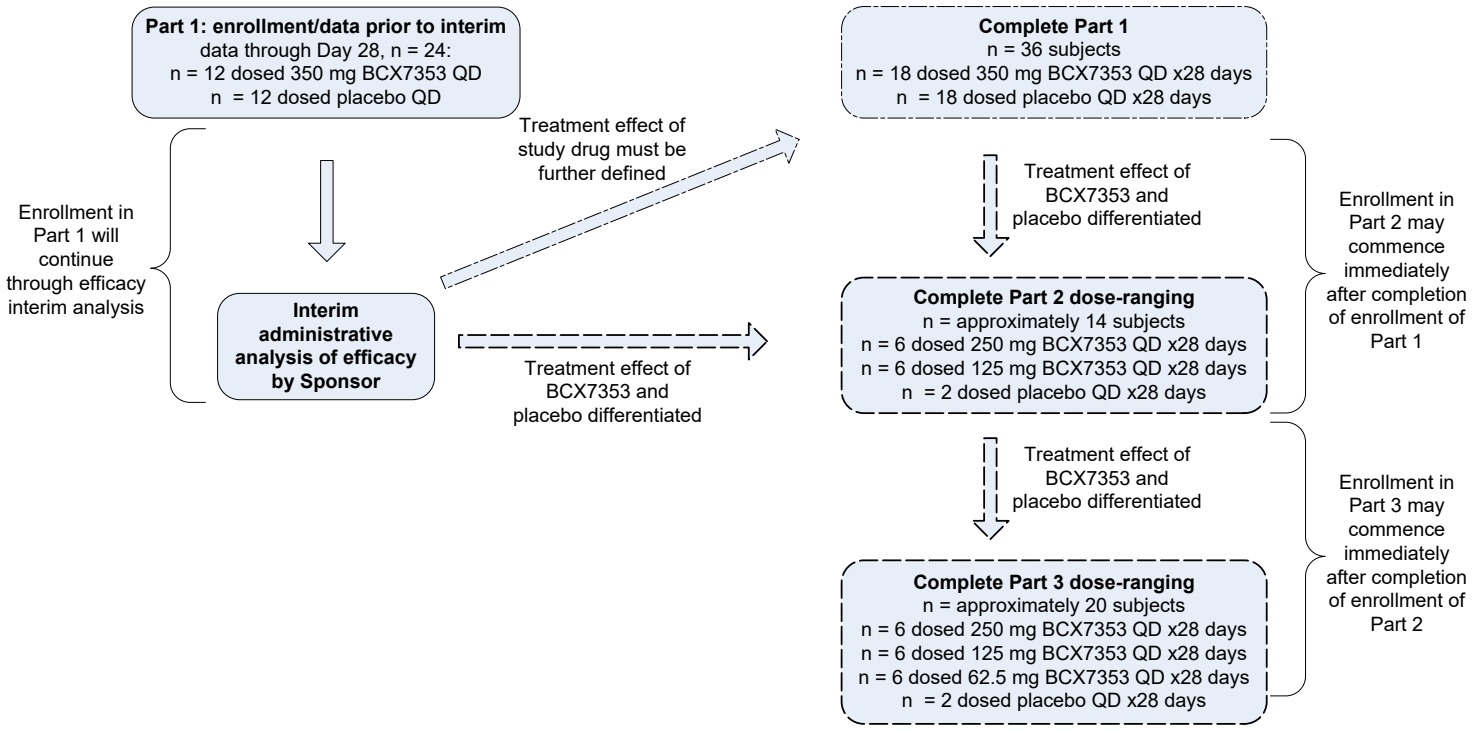

Figure 2: Study Schema – Parts 1, 2 and 3

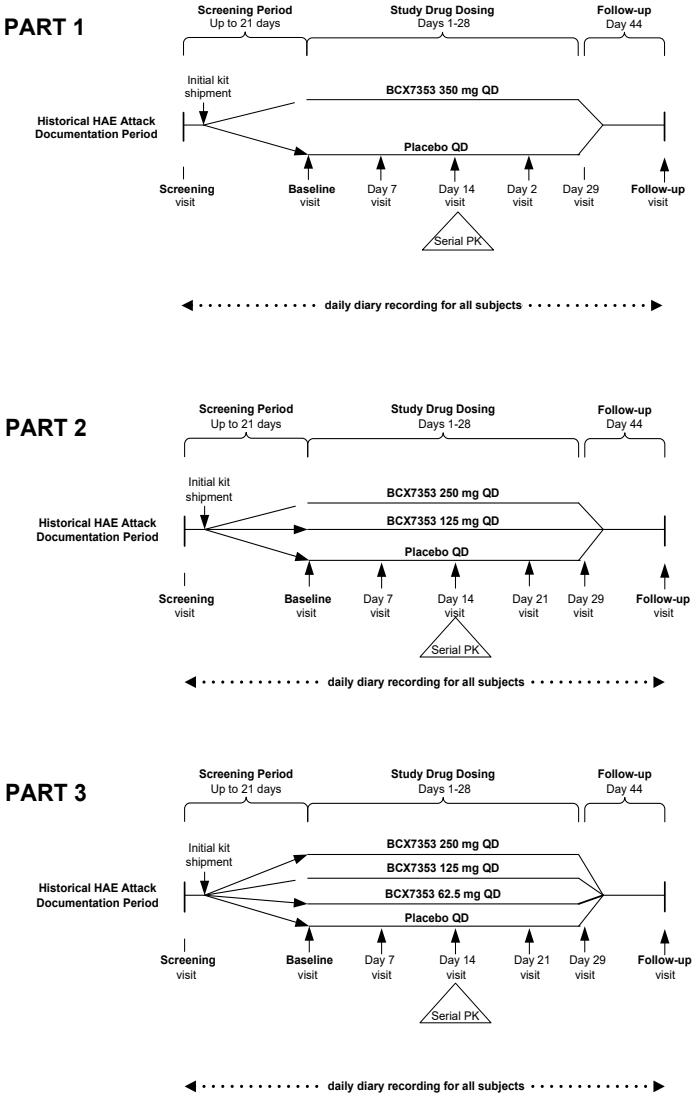

Table 1: Schedule of Assessments

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

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

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

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

d Weight only.
e Analytes to be measured can be found in the protocol. Subjects are required to fast overnight for at least 8 hours prior to blood draw on Days 1, 14, and 29.
f If no prior laboratory results confirming HAE diagnosis are available at screening, C1 INH level and function will be drawn. At baseline (Day 1) and Day 29, all subjects will have a sample for C1 INH function drawn.
g Physical examinations conducted after the screening visit will be targeted to reported signs and symptoms. A complete physical examination will be performed at screening only.
h Bedside 12-lead ECGs will be conducted in triplicate predose on Day 1; all other ECGs will be captured as single assessments. Any scheduled blood draws should occur after obtaining the ECG. Subjects should rest quietly for 10 minutes in a supine position prior to ECGs being performed.
i Vital signs include measurement of heart rate, blood pressure and temperature. Temperature will be measured only at screening and on Day 1.
j A serum pregnancy test will be administered to women of childbearing potential or who are postmenopausal≤ 2 years at screening; all other pregnancy tests performed during the study may be urine pregnancy tests (for women of childbearing potential only).
k FSH will be measured in women declaring themselves postmenopausal≤ 2 years.
L If the site cannot perform D_LCO onsite, the Day 29 sample may also be assessed any time from Day 24 to Day 32.
m A blood sample for HLA-typing will be drawn at the Baseline/Day 1 visit; if a blood sample is not obtained at Baseline, the sample may be drawn at any time during the study.
n Subjects will be randomized by the Sponsor on or after the screening visit and is contingent upon review of screening visit data entered into the eCRF subsequent questions the Sponsor may have. Randomization will trigger shipment of a kit of study drug for the first 14 days and an automatic resupply to arrive on-site at approximately study Day 10 after entry into the eCRF system that the subject has had a Day 1 visit. More details on randomization and kit shipment will be provided to the site.
o The Investigator (or designee) will provide a diary for collection of HAE attacks (screening through follow-up) and study drug dosing (Days 1-28) at screening, Day 1, Day 14 and Day 29. Diaries will be collected on Day 1 (screening diary), Day 14, Day 29 and follow-up. At each visit and phone call, the Investigator (or designee) will review proper recording of attacks and dosing (as applicable) in the diary.
p At any time the diary is in a subject's possession, they will enter HAE attacks and relevant details and dosing information (as applicable) at least once per day.
q On Day 14, a blood sample for plasma PK and plasma kallikrein analysis will be drawn prior to dosing (< 5 min) and at 1, 2, 3, 4, 5, 6, 8, and 24 hours postdose (i.e., on Day 15); Day 29 will be trough samples. If the subject is unable to provide serial PK samples on Day 14, steady state PK samples may be obtained on Day 28, with a 24-hour PK sample drawn at the scheduled visit on Day 29. In this case, trough PK samples will be drawn on Day 14. If the subject has a Day 29 visit for the 24-hour PK sampling, concomitant medications and AEs should also be assessed at the visit. Within 6 hours postdose, an acceptable window around each PK draw is ± 10 minutes. After 6 hours, an acceptable window is ± 20 minutes. Plasma PK and plasma kallikrein samples will be collected prior to in clinic dosing on Day 1 and Day 14. The Day 29 samples will be collected approximately 24 hours post-last dose.
r Cleaved HK and an additional sample for possible exploratory analysis used to elucidate PD properties of BCX7353 will be drawn.
s Subjects will take their study drug in the clinic on Day 1, Day 14 and Day 15 (Day 28 if subjects must complete serial PK on the last dose). Subjects will take all other doses at home as instructed. The last day of study drug dosing is Day 28.
t Subjects unable to undergo the serial PK blood draw on study Day 14 will only have a predose or trough blood sample drawn; a steady-state serial PK blood collection will then be obtained on Day 28 with a 24-hour blood draw conducted at the scheduled visit on Day 29. In the event the serial PK is not conducted on Day 14, the Day 15 visit is not required.

u If the site is unable to conduct all procedures for an individual subject at Baseline on Day 1 because of logistical reasons, refer to the protocol for procedures that may be conducted on Day −1.
v A blood sample for possible exploratory pharmacogenomic testing will be drawn at the Baseline/Day 1 sample only if consent is obtained for this optional testing; if a blood sample is not obtained at Baseline, the sample may be drawn at any time during the study following consent obtained from the subject.
w Study drug may be dispensed to the subject on Day 15 after in-clinic dosing in lieu of dispensing on Day 14 if preferred.
x The AE-QoL questionnaire will not be administered at the Day 14 visit.

4. PLANNED ANALYSES

4.1. Interim Analyses

There will be one planned administrative interim in Part 1 of the study, after 24 eligible subjects complete through the Day 28 dose. Ad hoc analyses to enable discernment of treatment differences between the study drugs may be requested. At the conclusion of the interim analysis, a decision will be made to either continue enrollment into Part 1 or to close Part 1 and initiate Part 2 (dose ranging). A continuation of Part 1 may include up to 12 additional subjects for a total of up to 36 subjects completing Part 1 of the study. Additional administrative interim analyses may be conducted after completion of Part 1 (if more than 24 subjects are enrolled) and after completion of Part 2 to support decision making for future development of the drug.

4.2. Final Analysis

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.

5. SAMPLE SIZE CONSIDERATIONS

Given that the BCX7353 response rate is unknown, the sample size was kept flexible to cover a range of response options that would achieve 90% power with an alpha of 0.05. The study population is expected to have a mean baseline attack rate of 1 attack/week. The expected mean reduction in attack rate of 350 mg BCX7353 QD is at least 70%. The mean reduction in attack rate in the placebo group may be as high as 30%. Sample size sensitivity assessments provided in Tables 2 and 3 are based on various BCX7353 and placebo responses and variability.

Table 2: Power assessment based on sample size and on-study attack rate

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

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

Table 3: Power assessment based on sample size and attack free proportion

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

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

6. ANALYSIS POPULATIONS

6.1. Randomized Set

The randomized set will include all subjects who are randomized.

6.2. Safety Population

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

6.3. Full Analysis Set

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

6.4. Per Protocol Population

The per protocol (PP) population will include all subjects who are randomized, receive at least 90% of the planned 28-days of study drug, based on drug accountability, have post baseline HAE diary data recorded and have no significant protocol violations. Subjects will be analyzed according to the actual treatment received. The PP population will be an additional population for efficacy analyses.

6.5. Pharmacokinetic Population

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

6.6. Pharmacodynamic Populations

6.6.1. Plasma Kallikrein Inhibition

The PD population for plasma kallikrein inhibition (KKI) will include all subjects for whom at least 1 pre- and post-dose plasma kallikrein inhibition result can be estimated. This population will be used for all analyses of plasma kallikrein inhibition.

6.6.2. C1 INH, BMP and Cleaved HK

There will be 3 additional PD populations, one for each of the following PD assessments: C1 INH functional or C4 levels, BMP and cleaved HK. Each PD population will include all subjects with a baseline and at least 1 post-dose value and will be the primary population for the relevant PD analyses.

6.7. Pharmacokinetic and Pharmacodynamic Population

The PK-PD analyses will be based on the subjects with both PK and PD measurements.

7. HYPOTHESES AND TREATMENT COMPARISONS

7.1. Hypotheses

This study is designed to evaluate the efficacy of once-daily prophylactic BCX7353 at 4 dose levels, as measured by the number of attacks of HAE observed in patients with HAE.

An estimation approach will be used to evaluate the dose-response relationship for BCX7353 and the treatment difference vs. placebo.

7.2. Comparisons of Interest

Comparisons of the following efficacy endpoints will be undertaken between each BCX7353 dose group and placebo, if data permit:

- Number of confirmed HAE attacks as weekly attack rate
- Proportion of subjects attack-free during the treatment period
- Number and percent of attack-free days
- Duration of attacks
- Severity of attacks
- AAS
- Attack onset relative to the time of last dose of study drug
- Symptoms and anatomical locations of attacks
- Number of Emergency room visits and/or hospitalizations
- Quality of life scores, as measured by the Angioedema Quality of life (AE-QoL) and Depression, Anxiety, Stress Scales (DASS)
- BCX7353 PK Parameters, Plasma kallikrein inhibition (KKI), PD assessments including C1-INH functional levels and cleaved HK level

8. TREATMENT DESCRIPTIONS FOR DATA DISPLAYS

Data display treatment descriptors with actual treatment dose will be used as shown in Table 4 below.

Table 4: Data Display Treatment Descriptors

Study Part	Treatment Group	Treatment Description	Final Data Display Treatment Description
Parts 1, 2 and 3 Combined	Group 1	placebo QD orally for 28 days	Placebo
Part 1	Group 2	350 mg BCX7353 QD orally for 28 days	BCX 7353 350 mg
Part 2 and 3 Combined	Group 3	250 mg BCX7353 QD orally for 28 days	BCX7353 250 mg
	Group 4	125 mg BCX7353 QD orally for 28 days	BCX7353 125 mg
Part 3	Group 5	62.5 mg BCX7353 QD orally for 28 days	BCX7353 62.5 mg

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

9.1. General Considerations

Tables and listings will be prepared in accordance with the current International Conference on Harmonization (ICH) Guidelines (ICH E3 Structure and Content of Clinical Study Reports 1996). The information and explanatory notes in the "footer" or bottom of each table and listing will include the following information:

- Date of output generation
- SAS® program name, including the path where the program is stored
- Any other output specific details that require further elaboration

In general, tables will be formatted with a column displaying findings for all subjects by treatment group and all subjects active dose combined.

Version 9.2 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings. All SAS programs prepared to analyze the data will be properly annotated so as to permit uninvolved outside statistical experts to replicate all the analyses specified in this SAP.

9.2. Reporting Conventions

Data analyses will be performed by, or under the direct supervision of, BioCryst Pharmaceuticals, Inc., Durham, NC.

Listings will be sorted by treatment, subject, and planned assessment time point. Summaries will be presented by treatment, study day and planned assessment time point. Unless stated otherwise, descriptive summaries will include n, mean, standard deviation, coefficient of variation (CV) or Q1, Q3 and 95% CI, median, minimum, and maximum for continuous variables, and n and percent for categorical variables. In addition, for log normally distributed parameters, the geometric mean with associated 95% CI, between-subject CVs (CVb), and SD of the logs based on the geometric mean, will be included.

The between-subject %CV of the log transformed variable will be calculated as

$\%CVb = 100 * \sqrt{(e^{SD\hat{}2} - 1)}$, with SD of the log-transformed data.

For summary tables, the following reporting convention will be used unless otherwise stated:

Frequencies (safety)	Counts (n)	None
	Percentages (%)	1 decimal place
Summary statistic (safety, number of attacks, reported QOL and PK)	n	None
	Mean	i + 1 decimal place
	Median	i decimal places
	SD	i + 1 decimal place
	Min	i decimal places
	Max	i decimal places
	CV%	none
	Geometric n	None
	Geometric Mean	i + 1 decimal place
	Geometric CV%	none
Statistical Analyses, reporting of derived efficacy and QOL endpoints	Derived efficacy end points (%)	1 decimal place
	Other derived efficacy endpoints	2 decimal places
	p-values	if <0.001: presented as <0.001 ; >0.999, presented as >0.999
		if ≥0.001 and <=0.999: presented to 3 decimal places

i refers to the number of decimal places reported in the source workbook or other appropriate source data for the original data

Deviations from the analyses in the SAP will be identified in the final Clinical Study Report.

9.3. Covariates and Subgroups

If data permit, the gender, age and qualifying attack rate(s) will be included as covariates for the primary efficacy assessments. Additional demographic and baseline characteristics (i.e., C1 INH function and country) may also be included as covariates for the efficacy analysis.

If data permit, the primary efficacy analysis maybe performed by subgroups based on gender, median age, country and covariates that are significantly associated with efficacy response.

10. DATA HANDLING CONVENTIONS

10.1. Missing Data and Data Handling Rules

For subjects who prematurely discontinue the study, all available data will be included in the analyses. The planned safety and efficacy analyses will be based on the reported data. Sensitivity analyses on the primary efficacy endpoint will consider imputation methods; details are discussed in section 12.1.3.

Incomplete dates for adverse events and medications

For analysis of AEs and medications, a complete date should be established in order to identify AEs or medication as occurring during treatment or not. For the purpose of handling partially reported start and stop dates for AEs or medication the following algorithm will be applied:

- Missing start day, but month and year present:
  If trial medication had been taken in the same month and year as the occurrence of the AE/medication, then the start day of the event/medication will be assigned to the day of first dose of trial medication.
  Otherwise the start day will be set to the first day of the month.
- Missing start day and month, but year present:
  If trial medication had been taken in the same year as the occurrence of the AE/medication, then the start date of the event/medication will be assigned to the date of first application of trial medication.
  Otherwise the start day and month will be set to 01 January.
- Missing end day, but month and year present:
  The day will be set to the last day of the month.
- Missing end day and month, but year present:
  The end day and month will be set to the date of trial termination.
  However, if trial termination year is greater than the year of the event/medication, then the day and month will be set to 31 December.

In subject data listings, start and stop date of AEs or medication will be displayed as reported.

Missing time of last dose

In case the time of the last dose is not reported, time of dose will be assigned as the median dosing time for the subject.

Incomplete date and time for a subject-reported attack

For HAE attacks reported with a missing stop date and or time, the following algorithm will be applied:

- Missing start time but start date present:
  The start time will be set to 12:00PM.
- Missing start date and time:

The start date will be set to the date for which the question was answered "Yes". The start time will be set to 12:00PM

- Missing stop time, but stop date present:
  The stop time will be set to 11:59PM
- Missing stop date and time:
  The stop date will be set to the attack start date, the stop time will be set to 11:59PM

10.2. Pharmacokinetic Concentration Data

For the creation of individual PK profiles reporting means and medians using the linear scale, all PK concentrations below the quantification limit (BQL) will be set to zero except when the sampling time of an individual BQL value falls immediately between the sampling times of two quantifiable values, in which case it will be set to missing.

When creating geometric summary statistics or log-linear plots, values that are BQL will be set to missing. No other procedures for replacing or imputing missing data are planned for any summarizations. If a subject has data points missing, that subject will be excluded from the analysis for that day and/or time point. If 24 hour samples that were taken post the next day's dose, those samples will be excluded in the summary statistics for the 24 hour time point.

10.3. Baseline Definition

Baseline is the last available assessment prior to the time of first dose unless otherwise specified.

The study qualifying attack rate will be used as baseline for the attack rate endpoint and is defined as follows:

Subject Reported Qualifying attack rate:

$$\frac{\text{Total Number of Qualifying attacks reported} * 7}{\text{Duration of Qualifying reporting period in days}}$$

Duration of qualifying attack reporting period is calculated as number of days as the last date of the period – the first date of the reporting period +1.

Adjusted Qualifying attack rate:

$$\frac{\text{Total Number of Adjusted Qualifying attacks reported} * 7}{\text{Duration of Qualifying reporting period in days}}$$

Duration of qualifying attack reporting period is calculated as number of days as the last date of the period – the first date of the reporting period +1

For subject reported historical attacks on consecutive days, these attacks will be counted as a single attack in the calculation of the adjusted qualifying attack.

10.4. Change from Baseline

Change from baseline is calculated as:

change from baseline value = 'visit' value – baseline value

Percent change from baseline is calculated as

% change from baseline value = ('visit' value – baseline value)*100/Baseline Value

The change and % change from baseline will be indicated as missing, if either the baseline or post-dose value is missing. Baseline is the last assessment prior to the date of first dose.

10.5. Multiple Measurements at One Time Point

Where multiple measurements are recorded for a particular time point, the mean of the measurements will be calculated and used in any derivation of summary statistics. All available data will be listed.

10.6. Treatment Period For Efficacy Analyses

There are 2 treatment periods for efficacy analyses.

1. The entire dosing interval (Days 1 to 28 inclusive) is the date of first dose to the last dose on day 28+24hours, or 24 hour post last dose of the study drug, whichever is earlier.
2. The steady-state or effective dosing interval (Days 8 to 28 inclusive) is the date of first dose +7 days to the last dose on day 28+24hours, or 24 hour post last dose of the study drug, whichever is earlier.

HAE attacks that occur during the treatment period will be included in all relevant efficacy data summaries.

HAE attacks that occur prior to or after the treatment period will also be summarized for the following periods: Qualification Period, screening to baseline Period and the follow-up period.

10.7. Assessment Windows

Nominal times will be used for the descriptive summaries and plots of summary measures. Actual times will be used in the listings, individual concentration-time profiles, and in the calculation of PK parameters.

10.8. Derived Attack Endpoints

Subject-reported attacks will be adjudicated by the independent Clinical Endpoint Adjudication Panel (CEAP). The attacks that have been confirmed by the adjudication committee will be included in efficacy analyses. The details of adjudication are provided in the CEAP charter.

The attack endpoints described in this section are based on confirmed attacks by the CEAP, however the rate of attacks will also be calculated for all subject reported attacks. Efficacy analyses will be conducted for HAE attacks reported over the entire dosing period (Days 1 to 28

inclusive), during the dosing period in which BCX7353 should be at steady-state conditions (Days 8 to 28, inclusive), and during the entire study period (Day 1 to the last HAE diary in the follow-up period).

The efficacy analyses will be calculated for 3 treatment periods:

- Entire Dosing Period

  Duration (days) = 28 or (Date of last dose –date of first dose+1), whichever is earlier
- Effective Dosing Period

  Duration (days) = 21 or (Date of last dose –date of first dose-6), whichever is earlier
- Entire Study Period

  Duration (days) = Date of last HAE Attack Diary collection during the follow-up –date of first dose

All efficacy analyses will also be run by treatment period and population (FAS or PP).

10.8.1. Rate of Attacks

The primary endpoint, confirmed attack rate, is the total number of (count) confirmed attacks during the treatment period and standardized to an appropriate denominator, e.g. 7 days for a weekly attack rate. The weekly attack rate will be calculated for each subject:

$$Weekly\ Attack\ Rate = \frac{\text{Number of Attacks} * 7}{\text{Duration (days)}}$$

Number of attacks is total count of attacks reported during the respective dosing period ("Duration (days)" in the above equation]. The primary endpoint will be calculated for the entire dosing period and for the effective dosing period. The weekly attack rate will also be derived for all subject reported attacks and for confirmed attacks requiring treatment.

The attack rates will also be calculated for pre and post treatment periods:

Attack Rate from Screening to Baseline:

$$= \frac{\text{Total Number of attacks reported} * 7}{\text{Duration of the reporting period in days}}$$

Attacks with a start date after screening and before the date of first dose will be included and the duration of the reporting period is date of first dose – date of screening visit+1.

Attack Rate from date of day 29 to the last follow-up on study:

$$\frac{\text{Total Number of attacks reported} * 7}{\text{Duration of the reporting period period in days}}$$

Attacks that start greater than 24 hours after the last dose will be included. The duration of the reporting period is from the date of last dose+24 hours to the date of last follow-up.

10.8.2. Number and Percentage of Subjects Who Are Attack Free

The following attack free endpoints will be derived for each treatment period (the entire dosing period, and the effective dosing period):

- The number and percentage of subjects who report no attacks during the treatment period for the FAS set and PP population. Subjects who report no attacks and discontinued before the end of the planned treatment period (day 28) are considered attack free.
- The number and percentage of subjects who report no attacks during the treatment period for the FAS set and PP population excluding subjects who discontinue before the planned treatment period (day 28).
- The number and percentage of subjects who report no attacks during the treatment period for the FAS set and PP population. Subjects who discontinue before the planned treatment period (day 28) are considered not attack free.

The above attack free endpoints will also be derived for the entire study period.

10.8.3. Number and Percentage of Attack-Free Days

The number of attack-free days is the sum of the days during the dosing period for which a subject reported no attacks.

The percentage of attack-free days is derived as the total number of days during the dosing period for which subjects reported no attacks divided by the duration of the treatment.

10.8.4. Attack Duration

The duration of each confirmed attack will be calculated in hours, based on the start and stop date and time of the attack. For a confirmed attack that includes more than one subject-reported attack, the duration is calculated from the start of the first subject-reported attack to the end of the last subject-reported attack.

10.8.5. Attack Onset Relative to Prior Dose of Study Drug

For each confirmed attack, the time to attack onset from the time of the prior dose of study drug reported in the subject CRF page will be calculated. If there is no dosing time reported for the dose taken prior to the attack, the attack will not be included in the attack onset analyses.

10.8.6. Angioedema Activity Score (AAS)

The basis of Angioedema Activity Score (AAS) (Weller, Groffik et al. 2013) consists of 5 questions to be answered for each day during which a subject experiences an HAE attack. However, in this study, the answers to the following 4 questions will be collected for each attack:

1. How severe was the physical discomfort caused by this attack, swelling episode or HAE symptom?

2. Were you able to perform your daily activities during this attack, swelling episode, or HAE symptoms
3. Did you feel your appearance was adversely affected by this attack, swelling episode, or HAE symptoms
4. How would you rate the overall severity of this attack, swelling episode, or HAE symptoms

A score between 0 and 3 (inclusive) will be assigned to the responses for each question, and the total score for each confirmed attack will be derived as the sum of the 4 question scores. If more than 2 patient reported attacks are combined as 1 confirmed attack, the most severe response to each individual AAS question will be used for the confirmed attack.

10.8.7. Attack HAE Medications

All HAE medications reported taken for a confirmed attack will be included in the analyses.

10.8.8. Attack Symptoms

All symptoms reported for a confirmed attack will be included in the analyses.

10.8.9. Attack Triggers

All attack triggers for a confirmed attack will be included in the analyses.

10.8.10. Attack Location

All anatomical locations of swelling reported for a confirmed attack will be included in the analyses.

11. STUDY POPULATION

11.1. Subject Disposition

A summary table will be generated to provide the following:

- Number of subjects screened
- Number and percentage of screening failures
- Reason for screening failure
- Number and percentage (based on subjects randomized) of subjects in the RS population
- Number of subject randomized and not treated
- Number and percentage (based on subjects randomized) of subjects in the Safety population
- Number and percentage (based on subjects randomized) of subjects in the FAS population
- Number and percentage (based on subjects randomized) of subjects in the PP population
- Number and percentage (based on subjects randomized) of subjects in the PK population
- Number and percentage (based on subjects randomized) of subjects in each PD population

Subject status at study completion will be listed and summarized. The listing will include whether subjects discontinued from the study drug and study and the reasons for the discontinuation of study drug, along with the date of first and last dose and the date of completion or discontinuation from the study drug and study. A summary table will be generated to show:

- Number and percentage of subjects in the Safety population who completed the study
- Number and percentage of subjects in the Safety population who discontinued the study
- Number and percentage of subjects in the Safety population who completed the study drug
- Number and percentage of subjects in the Safety population who discontinued the study drug
- Reason for discontinuation of study drug
- Reason for discontinuation of study

A CONSORT diagram will be created based on the summary tables for the study report.

11.2. Protocol Deviations

Subjects who were randomized but did not satisfy all inclusion and exclusion criteria will be listed. A listing of subjects for whom the treatment blind was broken during the study will also be provided, if appropriate. Subjects with dosing compliance <80% will be considered to have a major protocol deviation. Additional protocol deviations will be reviewed in a data review meeting to classify protocol deviations based on BioCryst Classification of protocol deviation Memo, and to discuss any statistical analysis issues.

11.3. Potential Revisions to the SAP

Potential revisions to the SAP include the refinement of the following: computational algorithms, rules for handling missing or otherwise unclear data, population definitions, and protocol deviations. Statistical methods may be modified if the underlying assumptions of intended methods are violated upon inspection at or before the Data Review Meeting. All revisions will be reported in the study report.

11.4. Demographic and Baseline Characteristics

11.4.1. Demography

The Safety, FAS and PP populations will be the primary populations for analyses of demographics. Demographics, including age, gender, race, ethnicity, weight, height, and body mass index (BMI) will be listed and summarized.

Body mass index (kg/m^2) will be calculated using the standard formula:

$$\text{BMI } (kg/m^2) = \text{Weight } (kg)/[\text{Height } (m)]^2$$

11.4.2. HAE and HAE Medication History

HAE and HAE medication history will be summarized for the following where possible:

- HAE History
- Past on-Demand Treatments of HAE
- Current on-Demand Treatments of HAE
- Past Prophylactic Treatments of HAE

All HAE medical and medication history collected on the CRF will be listed.

11.4.3. Medical History

Medical history will be listed.

11.4.4. Physical Examination

Physical examination will be listed.

11.5. Concomitant Medications

Medications received prior to the date of first dose are considered as prior medications. Medications will be considered as concomitant if the start date of the medication is on or after the date of first intake of study drug or if the start date is prior to the first date of study drug but the medication is ongoing during the treatment period in the study.

Medication verbatim text will be coded using the World Health Organization (WHO) Drug Dictionary. Use of non-study medications will be summarized (number and percentage of subjects) by treatment and WHO preferred name. Multiple drug use (by preferred name) will be counted once only per subject. No inferential statistics will be provided.

Medications that were used for HAE related indications will be summarized separately (plasma-derived C1-INH Berinert, Cinryze will be combined together). Medication data will be listed.

12. EFFICACY ANALYSES

The efficacy data will be summarized descriptively using the FAS and PP populations. Placebo subjects will be pooled across study parts for the final analyses. An overall summary by treatment group will be provided for each dosing period (i.e., entire and effective) defined in section 10.8 to show:

- Number and percentage of subjects who reported at least 1 attack (non-adjudicated), and total number of subject reported attacks
- Number of and percentage of subjects who reported at least 1 confirmed attack , and total number of confirmed attacks
- Number of and percentage of subjects who reported at least 1 confirmed attack that required treatment, and total number and percentage of confirmed attacks that required treatment
- Number of and percentage of subjects who reported at least 1 confirmed attack that did not require treatment, and total number and percentage of confirmed attacks that did not require treatment

Inferential comparisons of the efficacy endpoints will be performed for each BCX7353 dose vs. Placebo and for pairwise dose groups. The FAS and PP populations will be used for the comparisons of efficacy endpoints. All efficacy data collected on CRF will be listed. A separate listing will be provided for the derived efficacy endpoints.

12.1. Statistical Analysis Methods

12.1.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the number of confirmed HAE attacks in the FAS and PP populations. The number of HAE attacks will be analyzed by treatment group using appropriate descriptive statistics for the weekly attack rate, change and percentage change from baseline in attack rate, proportion of subjects with no attacks, and number of attack-free days. Efficacy analyses will be conducted for HAE attacks reported over the entire dosing interval (Days 1 to 28 inclusive) and during the effective dosing period in which BCX7353 should be at steady-state conditions (Days 8 to 28, inclusive). Efficacy endpoints will be summarized and listed for each treatment group.

Between-treatment comparisons (active vs. placebo and between active dose groups) for the weekly attack rate will be performed using an analysis of variance model and an analysis of covariance (ANCOVA) model. The adjusted qualifying attack rate will be included as a covariate in the ANCOVA model. The LSM for each treatment arm and the relative difference and associated 95% confidence intervals in attack rate between placebo and each active arm will also be calculated. If the difference between the 350mg and placebo is statistically significant,

additional dose response assessments will be analyzed based on the Tukey, Ciminera, and Heyse trend test.

The between treatment comparisons for the proportion of subjects who are attack free will be compared using a Fisher's exact test. If data warrant, a general linear model (Logistic regression) will also be used to test the dose response.

There will be no adjustments for multiplicity or previous interim analyses, if conducted, and all statistical tests will be 2-sided with an alpha of 0.05.

12.1.2. Supportive Analyses

The distribution of the HAE attacks will be examined. Cumulative distribution function of the confirmed attack rate will be produced by treatment group. A supportive analysis will be performed using a Poisson-regression model based on the number of confirmed attacks. The model will include Treatment and weekly interval as fixed effects.

The difference between the on treatment attack rate and the adjusted qualifying attack rate will be derived and summarized in tabular and graphical formats. Scatter plots of the adjusted qualifying attack vs. the confirmed attack rate and change from the adjusted qualifying attack rate will be presented. The individual attack rate over time will plotted.

12.1.3. Sensitivity analyses

Missing data may have impact on the interpretation of the study results. To examine the nature of missing data, subjects who do not have HAE attack diary data completed for 28 days since the date of first dose will be listed. The number and percentage of subjects with missing data, the missing data pattern and total number of days with missing HAE attack diary data will be presented in tabular or graphical format.

Sensitivity analyses will be performed using the same ANCOVA model including the fixed term for treatment group and the adjusted qualifying attack rate(s), and for the following attack-rate scenarios:

1. Attack Rate based on available Diary data

The attack rate will be derived as the total number (count) of confirmed attacks during the treatment period divided by the number of days HAE attack diary was completed. The attack rate will be calculated for each subject:

$$Weekly\ Attack\ Rate = \frac{\text{Number of Attacks} * 7}{\text{Number of days HAE Diary was completed}}$$

2. Attack Rate based on Baseline observation carried forward (BOCF)

For randomized and treated subjects who have missing HAE diary data during the 28 days of planed treatment period data due to any reason, their qualifying attack rate will be carried forward (BOCF) to derive the on treatment attack rate. The attack rate will be calculated for each subject:

$$Weekly\ Attack\ Rate = \frac{(\text{Number of Attacks Reported} + \text{Number of attacks imputed}) * 7}{28}$$

Number of attacks imputed is derived based on the adjusted qualifying attack rate for the days HAE attack diary were not completed.

$$\text{Number of attacks imputed} = \frac{\text{Number of days missed} * \text{Qualifying attack rate}}{7}$$

3. Sensitivity analyses based on subject reported attacks will be performed using the similar ANCOVA model including the fixed term for treatment group and the subject reported qualifying attack rate(s) as a covariate.

12.1.4. Analysis of Secondary Efficacy Endpoints

The number and percentage of attack-free days will be analyzed similarly to the attack rate endpoint. The secondary efficacy endpoints including attack location, duration, symptoms of attacks, and number and percent of attacks requiring attack medication will be summarized for each treatment group.

The between-treatment comparisons for the weekly attack rate will be also be performed separately by attack location (peripheral or abdominal) using the ANCOVA model as described for the primary endpoint.

The attack onset relative to the time of last dose of study drug, discontinuations due to lack of efficacy and number of emergency room visits and/or hospitalizations will also be reported by treatment group.

AAS will be summarized descriptively by treatment group for each AAS question at attack level and at subject level. The most severe response from all confirmed attacks will be used at subject level summary. The between treatment group comparisons for the total AAS score and individual AAS question scores will be performed using an ANCOVA model. The adjusted qualifying attack rate will be included as a covariate.

The following additional efficacy analyses will also be performed:

- The attack rate in the pre and post treatment periods
- Time intervals between attacks

Time intervals between attacks will be derived as follows:

Subjects with no attack: Interval = duration of treatment or 28
Subjects with 1 attack: Interval = the Max of the duration of (the first dose to start of the attack) or (stop of attack to the end of the dose)

Subjects with >1 attack: Interval = the duration between the stop of the first attack and start of the next attack (subjects with N attacks will have n-1 intervals)

- Time to first attack after the study medication

The time to first attack after the first study medication will be summarized descriptively and graphically using Kaplan-Meier method. The Kaplan-Meier (KM) estimate for the median, and the first and third quartiles will be determined along with approximate 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. Subjects who do not have an attack will be censored at the date of last dose for the KM analysis.

- Time to first attack after the last dose

The time to first attack after the last dose will be summarized descriptively and graphically using Kaplan-Meier method. The Kaplan-Meier (KM) estimate for the median, and the first and third quartiles will be determined along with approximate 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. Subjects who do not have an attack will be censored at the date of last follow-up assessment for the KM analysis.

- Time to treatment

The time to treatment defined as the time from the start of an attack to the use of the first HAE medication reported in the diary will be derived for each attack and summarized by treatment, by country and site at attack level.

The time to first HAE medication will also summarized graphically using KM method. The KM estimate for the median and the first and third quartiles will be determined along with approximate 95% confidence intervals. Brookmeyer-Crowley method will be used for the confidence interval calculation. Subjects who do not take medication will be censored at end of the attack.

12.1.4.1. Angioedema Quality of Life (AE-QoL)

The AE-QoL (Weller, Groffik et al. 2012) consists of four domains and a total score.

Dimensions	Item
Functioning	1. Impairment of work
	2. Impairment of physical activity
	3. Impairment of spare time activities
Fatigue/Mood	4. Impairment of social relations
	6. Difficulties of falling asleep
	7. Waking up during the night
	8. Feeling tired during the day
	9. Difficulties in concentrating
	10. Feeling downhearted
Fears/Shame	12. Feeling burdened at having swellings
	13. Fear of new suddenly appearing swellings

	14. Fear of increased frequency of swellings
	15. Ashamed to visit public places
	16. Embarrassed by the appearance of swellings
	17. Fear of long term negative drug effects
Nutrition	5. General limitations in foods and eating
	11. Limitations in the selection of food and beverages
Total Score	Items 1 to 17

The AE-QoL domain scores and the AE-QoL total score are calculated using the following formula:

(Σ items – min Σ items)/(max Σ items – min Σ items) x 100

where

Σ items= Sum of reported item scores per CRF

min Σ items= Sum of the Minimum possible score for each domain

max Σ items= Sum of the Maximum possible score for each domain

The calculated AE-QoL ranges from 0 (best) to 100 (worst).

The actual and change from baseline scores by domain and total will be summarized by visit and treatment. The AE-QoL change from baseline will be analyzed using an ANCOVA model. The estimated treatment difference for each BCX7353 dose– Placebo at each visit (ie, Baseline, and Day 29) will be displayed together with the 95% confidence interval and the associated p-value. Least Squares Means (LS Means) for each visit will also be presented with the standard error and the number of subjects contributing to the LS Means. The responses to the individual AE-QoL questions will also be listed.

12.1.4.2. Depression, Anxiety, Stress Scales (DASS)

The DASS (Crawford and Henry 2013) is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. Each of the three DASS scales contains 14 items, divided into subscales of 2-5 items with similar content. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Subjects are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items.

The rating scale is as follows:

0 Did not apply to me at all

1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

Scores of Depression, Anxiety and Stress are calculated by summing the scores for the relevant items.

The depression scale items are 3, 5, 10, 13, 16, 17, 21, 24, 26, 31, 34, 37, 38, 42.
The anxiety scale items are 2, 4, 7, 9, 15, 19, 20, 23, 25, 28, 30, 36, 40, 41.
The stress scale items are 1, 6, 8, 11, 12, 14, 18, 22, 27, 29, 32, 33, 35, 39.

The score for each of the subjects over each of the sub-scales, are then evaluated as per the severity-rating index below.

	Depression	Anxiety	Stress
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely Severe	28+	20+	34+

A total DASS score will be derived as the sum of three scales. DASS (total and individual scale score) will be analyzed similarly as AE-QOL. The actual and change from baseline scores by domain and total will be summarized by visit and treatment. The DASS change from baseline will be analyzed using an ANCOVA mixed model. The estimated treatment difference for each BCX7353 dose– Placebo at each visit (ie, Baseline, and Day 29) will be displayed together with the 95% confidence interval and the associated p-value. Least Squares Means (LS Means) for each visit will also be presented with the standard error and the number of subjects contributing to the LS Means.

The number and percentage of subjects in the severity-rating index categories will also be summarized by treatment and visit. The responses to the individual DASS questions will also be listed.

The relationship among the AE-QOL, DASS domains and confirmed weekly HAE attack rate will be provided descriptively and graphically using Pearson or Spearman correlation coefficient statistics and scatter plots.

12.2. Extent of Exposure

The number of subjects exposed to study drug and the duration of treatment will be summarized by treatment group.

12.3. Treatment Compliance

Treatment compliance will be computed by determining the number of capsules taken relative to the number of capsules that should have been administered. Treatment compliance based on the

drug accountability page and dosing diary will be calculated separately using the same formula below.

For compliance (%) based on the dosing diary:

compliance (%)= (number of capsules taken)/(number of capsules expected)*100

For compliance (%) based on the drug accountability page:

number of capsules taken= the number of capsules dispensed – the number of capsules returned

number of capsules expected= (date of the last dose-date of the first dose+1)*3

Summary of treatment compliance will be presented by treatment group and method. The number and percentage for compliance expressed as a categorical variable (<80%, ≥80%) will be also presented by treatment group and method.

12.4. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 18.1). System organ class (SOC), high level group term, high level term, preferred term, and lower level term will be attached to the clinical database. A table showing the mappings of AE verbatim text to the coded terms will be provided.

Adverse events with an onset date and time prior to the first dose of study drug for the study will be assigned as a pre-dose AE for the listing and will not be included in the summaries.

Treatment-emergent AEs are defined as AEs that occurred on or after date of first dose of study drug and up to +30 days after the last dose. Investigators are not required to contact subjects after the last follow-up if it occurs prior to 30 days from last dose.

12.4.1. Adverse Event Severity and Toxicity Grading

Adverse events are graded by the Investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening) according to DMID Adult Toxicity Table (Draft, publish date : November 2007).

12.4.2. Summaries of Adverse Events

Summaries of treatment emergent AEs will be provided for the Safety Population. No inferential statistics will be provided. A brief summary of AEs will show, by treatment group, the number and percentage of subjects who 1) had any AE, 2) had any drug-related event, 3) permanently discontinued from study drug due to an AE, 4) had any serious adverse event (SAE), 5) had any Grade 3 or higher AE, 6) had any Grade 3 or higher drug-related AE, 7), had any AE leading to interruption of study drug, 8), drug related SAE, or 9) died. Drug-related events are defined as those AEs in which the Investigator believes were possibly, probably, or definitely related to the study drug.

AEs will be summarized by treatment group. For each SOC and preferred term, the number and percentage of subjects reporting an event will be calculated. In summary tables, SOCs and events within a SOC will be presented by decreasing frequency count based on the total number

of events. Multiple events (by subject or SOC as appropriate) will be counted only once per subject per dose in each summary. For summaries that use severity grade, the most severe event will be selected.

The following summary tables (number and percentage of subjects) of treatment-emergent AEs (by SOC and preferred term) will be provided by treatment group:

- Overall summary of Treatment-Emergent adverse events
- Summary of treatment-emergent adverse events
- Summary of drug-related, treatment-emergent adverse events
- Summary of treatment-emergent adverse events by severity
- Summary of treatment-emergent Grade 3 or Grade 4 adverse events
- Summary of drug-related, treatment-emergent Grade 3 or Grade 4 adverse events
- Summary of serious treatment-emergent adverse events
- Summary of treatment-emergent adverse events leading to permanent discontinuation of study drug
- Summary of treatment-emergent adverse events leading to interruption of study drug
- Summary of drug-related, treatment-emergent serious adverse events
- Summary of Treatment-Emergent Rashes Considered Related to Study Drug

Data listings will be provided for all AE data. In addition to listing all AEs, distinct data listings will also be provided for 1) Grade 3 or Grade 4 AEs, 2) AEs leading to permanent study discontinuation, 3) SAEs and deaths, 4) Rashes.

12.5. Clinical Laboratory Evaluations

Summaries of clinical laboratory data will be provided for subjects in the Safety Population based on central lab data. No inferential statistics will be provided. All laboratory assessments collected after date of first dose of study drug and up to +30 days after the last dose will be included in the summary tables. All laboratory data will be listed.

12.5.1. Summaries of Numeric Laboratory Results

Quantitative values and change from baseline in quantitative values will be summarized by planned nominal time and treatment for each quantitative lab. Listings of all laboratory results and reference ranges will be provided. Laboratory values that fall outside the reference range will be flagged.

12.5.2. Graded Abnormalities

Clinical laboratory results will be graded according to criteria specified in the protocol using DMID Adult Toxicity Table (2007), if applicable.

Any graded abnormality that occurs following the initiation of study drug and up to +30 days after the last dose, and represents at least 1-grade increase from the baseline assessment is defined as treatment emergent. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group. A laboratory shift table will be provided to show the baseline grade to the maximum post baseline grade. Laboratory values that do not meet the graded laboratory abnormalities are assigned grade 0 in the shift table.

12.6. Vital Signs

Vital sign data (blood pressure [BP], heart rate [HR], and body weight) will be summarized by treatment, visit, and planned time and will be listed by subject, visit, treatment, planned time and actual date and time. Change from baseline for BP, HR, and body weight will also be summarized.

12.7. Electrocardiograms

The ECG data and change from baseline values will be listed and summarized by treatment, visit and planned time. The number and proportion of subjects with QTcF >450, >480 or >500 msec; or changes of >30 -≤60 msec, or >60 msec will be summarized by treatment over time.

Clinically significant abnormal ECG findings will also be summarized.

12.8. Pulmonary Diffusion

Pulmonary diffusion data, including actual and percent change from baseline values will be listed and summarized by treatment and visit.

12.9. Pregnancy

If any female subjects or female partners of male subjects become pregnant during the study, a listing will be provided.

12.10. Other Safety data

Number and percentage of attacks that required additional medical care and type of medical care will be summarized by treatment group, if data warrant.

13. PHARMACOKINETIC ANALYSES

13.1. Drug Concentration Measures

Plasma concentrations of BCX7353 will be measured by a validated assay. These plasma concentrations will be listed for all subjects with a result (including those from placebo-treated subjects) and summarized by active treatment and time using the Safety Population. Linear and semi-log figures for individual subjects as well as mean and median concentration-time data will be generated.

13.2. Deriving and Summarizing Pharmacokinetic Parameters

Steady-state BCX7353 (metabolites if measured) plasma PK parameters will be estimated over the sampling interval for each subject using noncompartmental analysis (Phoenix WinNonlin version 6.4 or later, Certara, LP). Steady-state BCX7353 PK parameters collected on Day 14 or Day 28 will be combined by treatment group for summary statistics. The PK population will be used for the evaluation of PK parameter data.

The PK parameters that may be estimated are listed below. Additional analyses may be conducted as appropriate.

Pharmacokinetic Parameter	**Definition**
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval (tau) (ie, 8 hours for q8h dosing)
$C_{av,ss}$	Average steady-state plasma drug concentration during multiple-dose administration
C_{max}	Maximum observed concentration of drug
C_{tau}	Observed drug concentration at the end of the dosing interval (tau)
$t_{1/2}$	Estimate of the terminal elimination half-life of the drug, calculated as $0.693/\lambda_z$
CL/F	Apparent oral clearance after administration of the drug calculated as $Dose/AUC_{tau}$
λ_z	Terminal elimination rate constant, estimate by linear regression of the terminal elimination phase of the natural logarithm of concentration of drug versus time curve
V_z/F	Apparent volume of distribution of the drug
T_{max}	Time of C_{max}

For the calculation of individual PK parameters, all PK concentrations that are BQL will be set to zero except when an individual BQL value falls immediately between two quantifiable values, in which case it will be set to missing. Actual elapsed time from dosing will be used to estimate

all the individual plasma PK parameters.

The appropriateness of estimation of λ_z and λ_z-derived parameter estimates will depend on an accurate estimation of the terminal elimination phase of the analyte, based upon inspection of individual subject PK profiles. λ_z and λ_z -derived parameter estimates that are considered by the Clinical Pharmacologist at BioCryst to be unreliable may be excluded from the summary statistics. In general, a minimum of three time points in the terminal phase with unadjusted R^2 $\geq$0.7 will be required to report λ_z.

Plasma PK parameters, except T_{max}, will also be summarized based on log transformed data.

Dose proportionality will be analyzed using a power model, and the slope and its 90% confidence interval will be estimated. A secondary assessment of dose proportionality will be made using log transformed dose normalized AUC and C_{max}, which will be analyzed by using an analysis of variance including terms for dose effects. Each dose will be compared with the 125mg dose on a pair-wise basis, with the ratio and its 90% confidence interval estimated .

The trough plasma BCX7353 concentrations obtained pre-dose or 24 hour post-dose on Days 14, 15, 28 and 29 (as applicable) will be plotted and summarized by treatment group. Achievement of steady-state will be assessed by calculating the 90% CI of the slope of the linear regression of Days 14-29 trough concentration versus Day for each treatment group.

The number and proportion of subjects with average plasma BCX7353 trough concentrations (C_{tau}) above 4x and 8x kallikrein inhibition EC_{50} values (35.8 ng/mL and 71.6 ng/mL will be summarized by treatment group.

For each subject, the percent of plasma BCX7353 trough concentrations (C_{tau}) above 4x and 8x kallikrein inhibition EC_{50} will be derived and summarized by treatment group.

14. PHARMACODYNAMIC ANALYSES

14.1. Kallikrein Inhibition, Cleaved HK Fragments, and C1 INH

On–treatment plasma kallikrein inhibition data (assessed with and without stimulation by ellagic acid) will be expressed as percent inhibition compared to subject baseline activity. Ex vivo plasma kallikrein activity will be listed by subject, treatment, day, and time and summarized separately by treatment, day, and time. Descriptive statistics will be reported. Mean and individual plasma kallikrein inhibition versus time profiles will be plotted by treatment group. Plasma kallikrein inhibition data from Day 14 or Day 28 will be combined by treatment group for analysis. The difference between each active treatment group vs placebo and between active doses in plasma kallikrein inhibition will be analyzed using a repeated measures analysis of variance with time, treatment and time by treatment as fixed effects. Subject will be fitted as a random effect in the model. The point estimates and corresponding 95% confidence interval (CI) for treatment differences will be calculated at each time point.

Cleaved HK fragments and C1 INH functional levels and absolute change from baseline will be summarized by treatment group. The HK end of treatment /Baseline ratio will also be listed and summarized by treatment group. The difference between each active treatment group and placebo and the pairwise difference between active doses in C1inh Change from baseline, cleaved HK change from baseline and HK end of treatment /Baseline ratio will be analyzed using ANOVA with treatment as fixed effects. Baseline value will be included as a covariate. The point estimates and corresponding 95% confidence interval (CI) for treatment differences will be calculated for each comparison.

14.2. Correlations of Dose or Drug Exposure with Pharmacodynamic Responses and Efficacy Outcomes

The following dose-response and exposure-response analyses of the relationships between pharmacokinetic, pharmacodynamic and efficacy measures will be explored using descriptive statistics, correlation assessment and model-based techniques as data permit:

- Correlation and exposure-response between plasma kallikrein inhibition and BCX7353 plasma concentrations
- Correlation and exposure-response between BCX7353 PK Parameters (C_{max}, AUC_{tau}, mean C_{tau}) and confirmed weekly HAE attack Rate
- Correlation between BCX7353 PK Parameters (C_{max}, AUC_{tau}, mean C_{tau}) and cleaved HK Change from baseline to the end of study and HK Follow-up/Baseline Ratio
- Correlation between the percent of plasma BCX7353 trough concentrations (C_{tau}) above 4x and 8x kallikrein inhibition EC_{50} and confirmed attack rate

The correlation and exposure-response assessments will be presented graphically using a scatter plot along with the fitted regression line. Person correlation coefficient and p-value will be included on the plot.

- Plasma BCX7353 concentration, PK Parameters (C_{max}, AUC_{tau}, mean C_{tau}), and PD (HK, C1INH) data will be presented by attack free status

The PK and PD parameter will be summarized by subgroup based on attack free status for the subjects received the active BCX7353 dose. The between group difference will be estimate based on an ANCOVA model including fixed effect of subgroup. The qualifying attack rate will be included as a covariate.

- Comparison of confirmed attack rate between subgroup based on average plasma BCX7353 trough concentrations (C_{tau}) above 4x and 8x kallikrein inhibition EC_{50} values

The confirmed attack rate will be summarized by subgroup based on the average plasma BCX7353 trough concentrations (C_{tau}) for subjects received the active BCX7353 doses. The between group difference will be estimate based on an ANCOVA model including fixed effect of subgroup. The qualifying attack rate will be included as a covariate.

Additional PK-PD analysis may be explored as data permit.

15. REFERENCES

SAS Institute Inc., SAS® Version 9.1 Software, Cary, North Carolina, USA.

Weller, K., A. Groffik, et al. (2012). "Development and construct validation of the angioedema quality of life questionnaire." Allergy **67**(10): 1289-1298.

Weller, K., A. Groffik, et al. (2013). "Development, Validation and initial Results for the Angioedema Activity Score (AAS)." Allergy **68(9)**: 1185-92.

Crawford, J. R. and J. D. Henry (2013). "The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample." British J Clin Psychol **42**: 111-131.

16. TABLES, FIGURES AND LISTINGS

Tables	Title	Population
Study Population		
14.1.1	Summary of Study Disposition	All Subjects
14.1.2	Summary of Study Disposition by Country and Site	Safety
14.1.2	Summary of Study Completion	Safety
14.1.3.1	Summary of Demography	FAS
14.1.3.2	Summary of Demography	PP
14.1.3.3	Summary of Demography	Safety
14.1.3.4	Summary of Sub-groups	Safety
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14.1.4.1	Summary of Concomitant Medications	Safety
14.1.4.2	Summary of Concomitant Medications for HAE	Safety
14.1.5.1	HAE Demography – HAE History	Safety
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14.1.5.3	HAE Demography – Current on-Demand Treatments of HAE	Safety
14.1.5.4	HAE Demography – Past Prophylactic Treatments of HAE	Safety
14.1.5.5	Summary of Pretreatment Attack Rate (include Subject reported qualifying rate, adjusted qualifying rate, Screening attack rate)	Safety
14.1.5.6	Summary of Attack Confirmation	Safety
14.1.6.1	Summary of Inclusion/Exclusion Criteria Deviations	Safety
14.1.6.2	Summary of Protocol Deviation	Safety
Efficacy Tables for Entire Dosing Period and Entire Study Period **All tables will be repeated for the PP population** **Table Numbering: FAS tables will end as .1; PP tables will end as .2**		
14.2.1.1.1	Overall Attack Summary during Entire Dosing Period	FAS
14.2.1.1.2	Overall Attack Summary during Entire Dosing Period	PP
14.2.1.1.3	Overall Attack Summary during Entire Study Period	FAS
14.2.1.1.4	Overall Attack Summary during Entire Study Period	PP
14.2.1.2	Summary of Rate of Confirmed Attacks during Entire Dosing Period (include the difference from the adjusted qualifying rate on the same table)	FAS/PP
14.2.1.2.3	Summary of Rate of Confirmed Attacks during Entire Study Period (include the difference from the adjusted qualifying rate on the same table)	FAS
14.2.1.2.4	Summary of Rate of Confirmed Attacks during Entire Study Period (include the difference from the adjusted qualifying rate on the same table)	PP
14.2.1.3	Summary of Number of Confirmed Attacks by Week during Entire Dosing Period	FAS/PP
14.2.1.4	Summary of Rate of Confirmed Attacks Requiring Treatment during Entire Dosing Period	FAS/PP
14.2.1.5	Summary of Rate of Confirmed Abdominal Attacks during Entire Dosing Period	FAS/PP
14.2.1.6	Summary of Rate of Confirmed Peripheral Attacks during Entire Dosing	FAS/PP

Tables	Title	Population
	Period	
14.2.1.7	Summary of Rate of Subject-Reported Attacks during Entire Dosing Period	FAS/PP
14.2.1.8	Statistical Analysis of Rate of Confirmed Attacks during Entire Dosing Period	FAS/PP
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14.2.1.9	Statistical Analysis of Rate of Confirmed Attacks during Entire Dosing Period - Poisson-regression Model	FAS/PP
14.2.1.10	Statistical Analysis of Rate of Confirmed Attacks Requiring Treatment during Entire Dosing Period	FAS/PP
14.2.1.11	Sensitivity Statistical Analysis of Rate of Confirmed Attacks Excluding Missing Diary Days during Entire Dosing Period	FAS/PP
14.2.1.12	Sensitivity Statistical Analysis of Rate of Confirmed Attacks during Entire Dosing Period (BOCF)	FAS/PP
14.2.1.13	Statistical Analysis of Rate of Confirmed Abdominal Attacks during Entire Dosing Period	FAS/PP
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14.2.1.15	Statistical Analysis of Rate of Subject-Reported Attacks during Entire Dosing Period (subject reported qualifying rate will be used as covariate)	FAS/PP
14.2.1.16	Summary of Proportion of Subjects who are Attack-free during Entire Dosing Period (include sensitivity analyses of missing=failure; missing=excluded)	FAS/PP
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14.2.1.17	Summary of Number of Attack-free days during Entire Dosing Period	FAS/PP
14.2.1.18	Summary of Percent of Attack-free days during Entire Dosing Period	FAS/PP
14.2.1.19	Statistical Analysis of Number of Attack-free days during Entire Dosing Period	FAS/PP
14.2.1.20	Statistical Analysis of Percent of Attack-free days during Entire Dosing Period	FAS/PP
14.2.1.21	Assessment of Dose Response - Entire Dosing Period	FAS/PP
Efficacy Tables for Effective Dosing Period **All tables will be repeated for the PP population** **Table Numbering: FAS tables will end as .1; PP tables will end as .2**		
14.2.2.1	Overall Attack Summary during Effective Dosing Period	FAS/PP
14.2.2.2	Summary of Rate of Confirmed Attacks during Effective Dosing Period (include the difference from qualifying on the same table)	FAS/PP
14.2.2.3	Summary of Number of Confirmed Attacks by Week during Effective Dosing Period	FAS/PP
14.2.2.4	Summary of Rate of Confirmed Attacks Requiring Treatment during Effective Dosing Period	FAS/PP
14.2.2.5	Summary of Rate of Confirmed Abdominal Attacks during Effective Dosing	FAS/PP

Tables	Title	Population
	Period	
14.2.2.6	Summary of Rate of Confirmed Peripheral Attacks during Effective Dosing Period	FAS/PP
14.2.2.7	Summary of Rate of Subject-Reported Attacks during Effective Dosing Period	FAS/PP
14.2.2.8	Statistical Analysis of Rate of Confirmed Attacks during Effective Dosing Period	FAS/PP
14.2.2.9	Statistical Analysis of Rate of Confirmed Attacks during Effective Dosing Period - Poisson-regression Model	FAS/PP
14.2.2.10	Statistical Analysis of Rate of Confirmed Attacks Requiring Treatment during Effective Dosing Period	FAS/PP
14.2.2.11	Sensitivity Statistical Analysis of Rate of Confirmed Attacks Excluding Missing Diary Days during Effective Dosing Period	FAS/PP
14.2.2.12	Sensitivity Statistical Analysis of Rate of Confirmed Attacks during Effective Dosing Period (BOCF)	FAS/PP
14.2.2.13	Statistical Analysis of Rate of Confirmed Abdominal Attacks during Effective Dosing Period	FAS/PP
14.2.2.14	Statistical Analysis of Rate of Confirmed Peripheral Attacks during Effective Dosing Period	FAS/PP
14.2.2.15	Statistical Analysis of Rate of Subject-Reported Attacks during Effective Dosing Period (subject reported qualifying rate will be used as covariate)	FAS/PP
14.2.2.16	Summary of Proportion of Subjects who are Attack-free during Effective Dosing Period (include sensitivity analyses of missing=failure; missing=excluded)	FAS/PP
14.2.2.17	Summary of Number of Attack-free days during Effective Dosing Period	FAS/PP
14.2.2.18	Summary of Percent of Attack-free days during Effective Dosing Period	FAS/PP
14.2.2.19	Statistical Analysis of Number of Attack-free days during Effective Dosing Period	FAS/PP
14.2.2.20	Statistical Analysis of Percent of Attack-free days during Effective Dosing Period	FAS/PP
14.2.2.21	Assessment of Dose Response - Effective Dosing Period	FAS/PP
The following will be provided for the Entire Dosing Period All tables will be repeated for the PP population Table Numbering: FAS tables will end as .1; PP tables will end as .2		
14.2.3.1.1	Summary of Time intervals between Attacks	FAS/PP
14.2.3.2	Summary of AAS Categorical Response -Attack level	FAS/PP
14.2.3.3	Summary of AAS Categorical Response -Subject level (worst response for each AAS question)	FAS/PP
14.2.3.4	Summary of AAS Total Score (include AAS total and Domain Total Score)	FAS/PP
14.2.3.5	Statistical Analysis of AAS Total Score (include AAS total and Domain Total Score)	FAS/PP
14.2.3.6	Summary of Attack Duration at Subject Level – Confirmed Attacks	FAS/PP
14.2.3.7	Summary of Attack Duration of All Confirmed Attacks	FAS/PP
14.2.3.8	Summary of Attack Triggers – Confirmed Attacks	FAS/PP
14.2.3.9	Summary of Attack Symptoms – Confirmed Attacks	FAS/PP
14.2.3.10	Summary of Number of Symptoms – Confirmed Attacks	FAS/PP

Tables	Title	Population
14.2.3.11	Summary of Attack Location – Confirmed Attacks	FAS/PP
14.2.3.12	Summary of Attack Onset time from the last dose– Confirmed Attacks	FAS/PP
14.2.3.13	Summary of Administrations of Acute HAE Medications – Confirmed Attacks	FAS/PP
14.2.3.14	Number and Percentage of Attacks Requiring Additional Medical Care	FAS/PP
14.2.3.15	Summary of time to treatment –Confirmed Attacks (overall, by country and by site)	FAS/PP
14.2.3.16	Time to Treatment (KM estimates)	FAS/PP
14.2.3.17	Summary of Qualifying, Screening Attack and Post Treatment HAE attack Rate	FAS/PP
14.2.3.18	Statistical Analysis of Post Treatment HAE attack Rate	FAS/PP
14.2.3.19	Time of First Attack after the First Dose (KM estimates)	FAS/PP
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14.2.4.1	Summary of AeQoL scores	FAS/PP
14.2.4.2	Statistical Analysis of AeQoL Scores	FAS/PP
14.2.4.3	Correlation among AeQoL and Attack Rate	FAS/PP
14.2.4.4	Summary of DASS Severity-Rating Index Categories	FAS/PP
14.2.4.5	Summary of DASS scores	FAS/PP
14.2.4.6	Correlation among DASS Domains and Attack Rate	FAS/PP
14.2.4.7	Correlation between AeQoL and DASS Domains	FAS/PP
14.2.5.1	Statistical Analysis of DASS Scores	FAS/PP
Pharmacokinetic Analysis		
14.2.5.2	Summary of Plasma BCX7353 Concentration	PK
14.2.5.3	Summary of Derived Plasma BCX7353 Pharmacokinetic Parameters	PK
14.2.5.4	Summary of Trough BCX7353 Concentration	PK
14.2.5.5	Assessment of Dose Proportionality based on Power Model	PK
14.2.5.6	Assessment of Dose Proportionality based on ANOVA	PK
14.2.5.7	Assessment of Steady State	PK
14.2.5.8	Number and Percent of Average Ctrough above 4xEC50 and 4xEC80	PK
14.2.5.9	Summary of Percent of Ctrough above 8xEC50 and 8xEC80	PK
Pharmacodynamic Analysis		
14.2.6.1	Summary of Plasma Kallikrein Inhibition	KKI PD
14.2.6.2	Summary of Plasma Kallikrein Inhibition without Ellagic Acid Stimulation	KKI PD
14.2.6.3	Statistical Analysis of Plasma Kallikrein Inhibition	KKI PD
14.2.6.4	Statistical Analysis of Plasma Kallikrein Inhibition without Ellagic Acid Stimulation	KKI PD
14.2.6.5	Summary of C1INH Functional and C4 Levels	C1INH PD
14.2.6.6	Summary of Cleaved HK Fragments	Cleaved HK PD
14.2.6.7	Statistical Analysis of Cleaved HK Fragments	Cleaved HK PD
14.2.6.8	Summary of BMP Levels	BMP PD

Tables	Title	Population
PKPD/Efficacy Analysis (PK-PD include subjects with measurements for both PK-PD/Efficacy data)		
14.2.7.1	Summary of Plasma Kallikrein Inhibition by Attack Free Response	KKI PD
14.2.7.2	Summary of Plasma BCX7353 Concentration by Attack Free Response	PK
14.2.7.3	Summary of Trough BCX7353 Concentration by Attack Free Response	PK
14.2.7.4	Summary of Derived Plasma BCX7353 Pharmacokinetic Parameters by Attack Free Response	PK
14.2.7.5	Summary of cleaved HK levels by Attack Free Response	HK PD
14.2.7.6	Summary of C1INH and C4 levels by Attack Free Response	C1INH PD
Additional PKPD and Efficacy analyses maybe performed if data permit.		
Safety		
14.3.1.1.1	Summary of Treatment Exposure	Safety
14.3.1.1.2	Summary of Study Drug Compliance – Drug Accountability	Safety
14.3.1.2	Overall Summary of Treatment-Emergent Adverse Events	Safety
14.3.1.3	Summary of Treatment-Emergent Adverse Events	Safety
14.3.1.4	Summary of Drug-related Treatment-Emergent Adverse Event	Safety
14.3.1.5	Summary of Treatment-Emergent Adverse Events by severity	Safety
14.3.1.6	Summary of Treatment-Emergent Grade 3 or Grade 4 Adverse Events	Safety
	Summary of Drug-related Treatment-Emergent Grade 3 or Grade 4 Adverse Events	Safety
14.3.1.7	Summary of Treatment-Emergent Serious Adverse Events	Safety
14.3.1.8	Summary of Treatment-Emergent Adverse Events leading to Permanent Discontinuation of Study Drug	Safety
14.3.1.9	Summary of Treatment-Emergent Adverse Events leading to Interruption of Study Drug	Safety
14.3.1.10	Summary of Drug-related Treatment-Emergent Serious Adverse Event	Safety
14.3.1.11	Summary of Treatment-Emergent Rashes Considered Related to Study Drug	Safety
14.3.5.1	Summary of Laboratory Values by Visit – Hematology	Safety
14.3.5.2	Summary of Laboratory Values by Visit – Chemistry	Safety
14.3.5.3	Summary of Laboratory Values by Visit – Urinalysis	Safety
14.3.5.4	Summary of Graded Shift in Laboratory Abnormalities - Hematology	Safety
14.3.5.5	Summary of Graded Shift in Laboratory Abnormalities – Chemistry	Safety
14.3.5.6	Summary of Treatment-Emergent Laboratory Abnormalities	Safety
14.3.5.7	Summary of Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities	Safety
14.3.5.8	Summary of Lab Toxicity Grade Increase from Baseline	Safety
14.3.6.1	Summary of Vital Signs by Visit	Safety
14.3.6.2	Summary of Body Weight by Visit	Safety
14.3.6.3	Summary of QTcF Categorical Findings by Visit	Safety
14.3.6.4	Summary of 12-lead Electrocardiograms Parameters by Visit	Safety
14.3.6.5	Summary of 12-lead Electrocardiograms Assessment by Visit	Safety
14.3.6.6	Summary of Pulmonary Diffusion data by Visit	Safety
14.3.6.7.1	Summary of Fold x ULN for Liver Function Tests	Safety

Tables	Title	Population
14.3.6.7.2	Summary of Fold x ULN for Liver Function Tests –Subjects with Prior Androgen Use	Safety
14.3.6.7.3	Summary of Fold x ULN for Liver Function Tests –Subjects without Prior Androgen Use	Safety
14.3.6.8.1	Summary of Fold x from Baseline for Liver Function Tests	Safety
14.3.6.8.2	Summary of Fold x from Baseline for Liver Function Tests –Subjects with Prior Androgen Use	Safety
14.3.6.8.3	Summary of Fold x from Baseline for Liver Function Tests –Subjects without Prior Androgen Use	Safety
14.3.6.9.1	Summary of Number of Subjects with Elevations in Post Baseline Liver Function Tests	Safety
14.3.6.9.2	Summary of Number of Subjects with Elevations in Post Baseline Liver Function Tests –Subjects with Prior Androgen Use	Safety
14.3.6.9.3	Summary of Number of Subjects with Elevations in Post Baseline Liver Function Tests –Subjects without Prior Androgen Use	Safety

Figures	Title	Population
Study population		
14.1.1	Consort Diagram	All subjects
14.1.2	Time to study drug discontinuation	RS
Efficacy **All Efficacy Figure will be repeated for the PP population** **Table Numbering: FAS tables will end as .1; PP tables will end as .2**		
14.2.1.1	Plot of Estimated Treatment Effect (If data permit, Forest plot to show estimated between treatment difference and 95%CI, for overall and by each subgroup)	FAS
14.2.1.2	Plot of Individual Attack Rate by Treatment –Confirmed Attack	FAS
14.2.1.3	Cumulative Distribution Function of the Confirmed Attack Rate	FAS
14.2.1.4	Plot of Individual Attack Rate by Treatment – Subject Reported Attack	FAS
14.2.1.5	Plot of Confirmed Attack and Acute HAE Medications	FAS
14.2.1.6	Plot of Qualifying Attack Rate (Histogram Plot)	FAS
14.2.1.7	Plot of Individual Attack Rate Overtime (Line plot for each subject)	FAS
14.2.1.8	Plot of On-study Confirmed Attack Rate vs Qualifying Attack Rate	FAS
14.2.1.9	Plot of Difference between On-study Confirmed Attack Rate and Qualifying Attack Rate vs Qualifying Attack Rate	FAS
14.2.1.10	Plot of Percentage of Difference between On-study Confirmed Attack Rate and Qualifying Attack Rate vs Qualifying Attack Rate	FAS
14.2.1.11	KM Plot of Time to First Attack after Last Dose	FAS
14.2.1.12	KM Plot of Time to First Attack after First Dose	FAS
14.2.1.13	KM Plot of Time to Treatment	FAS
14.2.1.XX	**Correlation Plots of AE-Qol, DASS and Confirmed Attack endpoints (will plot the domains with significant correlation at P<0.10)**	FAS
Pharmacokinetic Analysis		
14.2.2.1	Mean Plasma BCX7353 Concentration-time plot –linear Scale	PK
14.2.2.2	Mean Plasma BCX7353 Concentration-time plot – semi-logarithmic scale	PK
14.2.2.3	Median Plasma BCX7353 Concentration-time plot –linear Scale	PK
14.2.2.4	Median Plasma BCX7353 Concentration-time plot – semi-logarithmic scale	PK
14.2.2.5	Individual Plasma BCX7353 Concentration-time plot –linear Scale	PK
14.2.2.6	Individual Plasma BCX7353 Concentration-time plot - semi-logarithmic scale	PK
14.2.2.7	Mean Trough Plasma BCX7353 Concentration-time plot –linear Scale	PK
14.2.2.8	Median Trough Plasma BCX7353 Concentration-time plot –linear Scale	PK
14.2.2.8	Individual Trough Plasma BCX7353 Concentration-time plot (line plot)	PK

Figures	Title	Population
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14.2.3.2	Plot of Individual Ex-vivo Kallikrein Inhibition - Time Profile by Treatment	PD
14.2.3.3	Plot of Least Squares Mean of Treatment Differences from Placebo in Ex-vivo Kallikrein Inhibition	PD
Pharmacokinetic/Pharmacodynamic Analyses (PK-PD include subjects with measurements for both PK-PD)		
14.2.4.1	Plot of Plasma Kallikrein Inhibition and Plasma BCX7353 Concentration	KKI PD
14.2.4.2	Exposure-response Analysis of Ex-vivo Kallikrein Inhibition	KKI PD
14.2.4.3	Plot of Plasma Kallikrein Inhibition by Attack Free Status	KKI PD
14.2.4.4	Plot of Percent of plasma BCX7353 trough concentrations (C_{tau}) above 4x kallikrein inhibition EC_{50} (35.8 ng/mL) and confirmed attack rate	PK
14.2.4.5	Plot of Percent of plasma BCX7353 trough concentrations (C_{tau}) above 8x kallikrein inhibition EC_{50} (71.6 ng/mL) and confirmed attack rate	PK
14.2.4.6	Plot of Average Plasma BCX7353 trough concentrations (C_{tau}) and confirmed attack rate	PK
14.2.4.7	Plot of Plasma BCX7353 Concentration by Attack Free Status	PK
14.2.4.8	Plot of Selected Plasma BCX7353 PK Parameters by Attack Free Status	PK
14.2.4.9	Plot of Rate of Attack vs. Plasma BCX7353 PK Parameters (one plot for each PK parameter of interest)	PK
14.2.4.10	Plot of Plasma BCX7353 PK Parameters VS HK parameters	PK and Cleaved HK PD
14.2.4.11	Plot of Cleaved HK Concentration by Attack Free Status	Cleaved HK PD
14.2.4.12	Plot of C1INH Concentration by Attack Free Status	C1 INH PD
The PKPD/Efficacy plots will be performed as data permit, additional figures may also be added.		
Safety Figures		
14.3.1.1	Time course of AST in individuals with treatment-emergent AST abnormalities (spaghetti plot, 1 line for each subject and page by treatment,)	Safety
14.3.1.2	Time course of ALT in individuals with treatment-emergent ALT abnormalities	Safety
14.3.1.3	Time course of ALP in individuals with treatment-emergent ALP abnormalities	Safety
14.3.1.4	Time course of GGT in individuals with treatment-emergent GGT abnormalities	Safety
14.3.1.5	Time course of Direct Bilirubin in individuals with treatment-emergent Direct Bilirubin abnormalities	Safety
14.3.1.6	Time course of Total Bilirubin in individuals with treatment-emergent Total Bilirubin abnormalities	Safety

Figures	Title	Population
14.3.1.7	Peak ALT: Placebo versus BCX7353 subjects	Safety

Listings	Title	Population
Study Population		
16.2.1.1	Subject Randomization	Safety
16.2.1.2	End of Study Record	Safety
16.2.2.1	Inclusion/Exclusion Criteria not Met	Safety
16.2.2.2	Protocol Deviations	Safety
16.2.2.3	Subjects for Whom the Treatment Blind Was Broken	Safety
16.2.4.1.1	Demography	Safety
16.2.4.1.2	HAE Demography – HAE History	Safety
16.2.4.2.1	HAE Demography – Past on-Demand Treatments of HAE	Safety
16.2.4.2.2	HAE Demography – Current on-Demand Treatments of HAE	Safety
16.2.4.2.3	HAE Demography – Past Prophylactic Treatments of HAE	Safety
16.2.4.3	Medical History	Safety
16.2.4.4	Prior Medications	Safety
16.2.4.5	Concomitant Medications	Safety
16.2.4.6	Concomitant Medications for indication related to HAE	Safety
Efficacy		
16.2.6.1	Attack Diary (include multiple listings)	Safety
16.2.6.2	Attack Diary Results Adjudicated by the Independent Clinical Endpoint Adjudication Panel (CEAP)	Safety
16.2.6.3	Efficacy Endpoints	FAS
16.2.6.4	Efficacy Endpoints	PP
16.2.6.5	Pretreatment and Post Treatment Attack Rate	Safety
16.2.6.6	Angioedema Quality of Life	Safety
16.2.6.7	DASS	Safety
Pharmacokinetic		
16.2.6.5	Plasma BCX7353 Concentration Data	Safety
16.2.6.6	Plasma BCX7353 PK Parameter Data	PK
Pharmacodynamic		
16.2.6.7	Ex-vivo Kallikrein Inhibition Data	Safety
16.2.6.8	C1INH Data	Safety
16.2.6.9	Cleaved HK Data	Safety
16.2.6.10	BMP data	Safety
Safety		
16.2.5.1	Dosing Record	Safety
16.2.5.2	Study Drug Accountability	Safety
16.2.7.1	Adverse Events	Safety

Listings	Title	Population
16.2.7.2	Adverse Events Grade 3 or Grade 4	Safety
16.2.7.3	Adverse Events Leading to Permanent Discontinuation from Study/Study Drug	Safety
16.2.7.4	Serious Adverse Events	Safety
16.2.7.5	Adverse Events - Rash	Safety
16.2.7.6	Death (please provide a blank table if no death reported)	Safety
16.2.8.1	Clinical Chemistry	Safety
16.2.8.2	Clinical Hematology	Safety
16.2.8.4	Other Lab tests	Safety
16.2.8.5	Serum Pregnancy	Safety
16.2.8.6	Urine Pregnancy	Safety
16.2.8.7	Graded laboratory abnormalities	Safety
16.2.8.8	Grade 3 or Grade 4 laboratory abnormalities	Safety
16.2.8.9	Pregnancy (List female subjects or female partners of male subjects become pregnant)	Safety
16.2.9.1	Vital Signs	Safety
16.2.9.2	Twelve-lead Electrocardiograms	Safety
16.2.9.3	Physical Exam	Safety
16.2.9.4	Pulmonary Diffusion	Safety
16.2.9.5	Liver Function Tests	Safety
16.2.9.6	Listing of all LFT Test Results in x ULN for Subjects with any Abnormal LFT Finding	Safety
16.2.9.7	Listing of LFT Fold Change From Baseline for Subjects with any Abnormal LFT Finding	Safety
16.2.9.8	Elevation of ALT in Temporal Association with Nausea, Vomiting, Anorexia, Abdominal Pain, or Fatigue	Safety