STATISTICAL ANALYSIS PLAN
Study BCX7353-304

DATE OF PLAN:

Final Version: 08 July2024

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STUDY DRUG:

Berotralstat, BCX7353

PROTOCOL NUMBER:

BCX7353-304

STUDY TITLE:

A Phase 3 Study to Evaluate the Safety and Pharmacokinetics of Berotralstat Prophylaxis in Children with Hereditary Angioedema Who Are 2 to < 12 Years of Age

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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Technical Summary Report (TSR)

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
BCX7353

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

Title of Study:
A Phase 3 study to evaluate the safety and pharmacokinetics of berotralstat prophylaxis in children with hereditary angioedema (HAE) who are 2 to < 12 years of age

Countries: Multiple study centers in North America, Israel, and Europe

Principal Investigator: Jolanta Bernatoniene, MD
Consultant in Paediatrics, Paediatric Infectious Disease and Immunology, Bristol Royal Hospital for Children, Bristol, United Kingdom

Enrollment period (months): Approximately 24 months	**Phase of development:** 3

Objectives:
Primary:

- To describe the pharmacokinetic (PK) parameters of berotralstat administered orally to pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

Secondary:

- To assess the safety and tolerability of berotralstat administered orally to pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.
- To summarize the effectiveness of berotralstat in pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

Exploratory:

- To assess the palatability/acceptability of berotralstat oral granules in pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

Endpoints:
Primary:

- PK: The primary endpoint is the characterization of the PK profile of berotralstat in subjects aged 2 to < 12 years.

Secondary:

- Safety: The frequency and severity of adverse events (AEs) and serious adverse events (SAEs), laboratory analyses (clinical chemistry, hematology, coagulation), height, weight, vital signs, electrocardiograms (ECGs), and physical examination findings.

- Effectiveness: the frequency of attacks, duration of symptoms, anatomical location of attack, on-demand treatment, number of days with angioedema symptoms, assessment of attack severity, discontinuations due to lack of efficacy, and number of hospitalizations and clinic visits from Week 1 through Weeks 12 and 48.

Exploratory:

- Age-appropriate questionnaire for palatability/acceptability of berotralstat oral granules as assessed by the site following the first dose.

Methodology:

This is a single-arm, open-label study designed to evaluate the PK of berotralstat; plasma concentrations of berotralstat will be measured and used in population PK analyses, allowing for determination of the appropriate weight-based dose for pediatric patients 2 to < 12 years old. In addition, the safety and tolerability of berotralstat will be assessed when given to pediatric subjects who are 2 to < 12 years old as a prophylactic treatment to prevent attacks of HAE. The effectiveness of berotralstat in this population will be summarized using descriptive statistical methods. Subjects will be enrolled into 4 or more dose cohorts; subject weight will be used to determine assignment to each cohort with the higher weight cohorts (Cohorts 1 and 2) enrolling first and in parallel. Cohort 3 will open for enrollment and initiate the 12-week standard-of-care (SOC) phase after ≥ 4 subjects from Cohorts 1 and 2, with ≥ 2 of the subjects from Cohort 2, have reached Week 2. Cohort 4 will open for enrollment and initiate the 12-week SOC phase after ≥ 4 subjects in Cohort 3 have reached Week 2. BioCryst will notify sites when Cohorts 3 and 4 are open for enrollment. Safety assessments by the Data Monitoring Committee (DMC) and PK modelling from all available PK data to confirm the weight band for the cohorts will occur prior to dosing subjects in Cohorts 3 and 4 with berotralstat. Additional dose cohort(s) may be added if indicated based on safety and/or population PK analyses with DMC endorsement.

This study will consist of 2 treatment periods: a 12-week SOC treatment period followed by an open-label berotralstat treatment period lasting up to 144 weeks. The berotralstat treatment period is divided into 3 parts as defined below. Throughout the study, site personnel will monitor subject safety through a combination of in-person clinic visits and tele-communication with the parent/caregiver(s) (P/C). The tele-contact may be either a telephone call or telemedicine visit conducted over the internet.

SOC Treatment Period: Subjects will continue taking their SOC therapy for HAE (either short-term or long-term prophylaxis, or acute treatment for HAE attacks) for 12 weeks from the screening visit. No additional in-person visits are required during the SOC treatment period; however, at approximately 4 and 8 weeks following screening, site personnel will contact the P/C to assess AEs and the overall status of the subject.

Part 1: After 12 weeks on SOC, subjects will return to the site for the Day 1 (baseline) visit. Prior to the Day 1 visit, subjects must discontinue all prophylaxis for prevention of HAE attacks; use of on-demand medication to manage acute HAE attacks may continue throughout the study. At the Day 1 visit, the site will confirm concomitant medications, review subject diary entries, and discuss any AEs that occurred during the SOC treatment period. If study activities were not completed satisfactorily during this time (eg, diary entries were incomplete or the P/C was not reachable to assess AEs at the prescribed intervals), the subject may be discontinued from the study prior to the berotralstat treatment period at the sole discretion of the investigator. Beginning on Day 1, subjects will take berotralstat orally once each day, with food, for 12 weeks. Additional study visits in Part 1 will occur at Weeks 2, 6, and 12. All safety assessments will be assessed at each visit. In addition to the clinic visits, the site will contact the P/C at Week 9 to assess safety and subject status.

Part 2: Beginning at the Week 12 visit, all subjects will be provided continued access to open-label berotralstat through Week 48 (a total of 36 weeks). Study visits in Part 2 will occur every 12 weeks

(Weeks 24, 36, and 48). Also, during Part 2, sites will contact the P/C at 4-week intervals between study visits (ie, at Weeks 16, 20, 28, 32, 40, and 44) to assess the subjects' overall wellbeing. The contact should be an arranged tele-contact; however, it may become an on-site visit if the investigator or P/C considers an in-person visit necessary for medical management of the subject. HAE attack details will only be collected through Parts 1 and 2.

Part 3: After Week 48, subjects may continue to receive open label berotralstat in Part 3 (Weeks 48 through 144; a total of 96 weeks). Visits in Part 3 will occur every 24 weeks: Weeks 72, 96, 120, and 144. Also, during Part 3, sites will contact the P/C at 12-week intervals between study visits (ie, at Weeks 60, 84, 108, and 132) to assess the subjects' overall wellbeing. The contact should be an arranged tele-contact; however, it may become an on-site visit if the investigator or P/C considers an in-person visit necessary for medical management of the subject. Berotralstat will be provided in Part 3 through Study Week 144 or until another mechanism is available to provide drug to the subject (eg, market access, separate study) or the sponsor discontinues development of the product for the prevention of angioedema attacks in children < 12 years of age.

Subjects who discontinue berotralstat at Week 144 or earlier will be required to attend an end of study (EOS) follow-up visit 3 weeks after study drug discontinuation. Subjects who discontinue the study but will continue to receive berotralstat via another mechanism will have EOS assessments performed at their last regularly scheduled visit.

PK Assessments: At Week 2 (in Part 1), plasma samples for PK analysis will be collected immediately prior to dosing and at designated timepoints post dose. Based on the PK results, the dose regimen of berotralstat may be adjusted for an individual subject or for all subjects in the cohort to ensure the exposure falls within the acceptable safety range; the dose of berotralstat will not be adjusted based on changes to the subject's weight during Part 1. In Part 2, one random sample for PK analysis will be drawn at Weeks 12, 24, 36, and 48. Reduced PK sampling may be performed in smaller subjects, especially subjects in Cohort 4, to maintain blood sample volumes within acceptable ranges. Additional PK samples may be drawn if the berotralstat dose is adjusted.

Number of subjects (planned):

Approximately 30 subjects are planned to be enrolled.

Main criteria for inclusion:

1. Age 2 to < 12 years of age and weighing ≥ 12 kg.

2. Parent/caregiver willing and able to provide written, informed consent (with assent from the child where appropriate).

3. Subjects with a clinical diagnosis of HAE. A clinical diagnosis of HAE is defined as:

   a. Screening results that documented immunogenic C1 esterase inhibitor (C1-INH) antigenic level below the lower limit of normal (LLN) reference range or C1-INH function < 50% and a complement 4 (C4) level below the LLN reference range.

   OR

   b. Laboratory documentation of historical C1-INH functional level below the assay LLN.

   OR

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

OR

d. Historical or new laboratory documentation of a SERPING-1 mutation known or likely to be associated with HAE.

OR

e. For subjects who currently use plasma-derived or recombinant C1-INH-based prophylactic therapies, a confirmed family history of C1-INH deficiency.

4. For subjects who are not currently receiving prophylaxis for HAE, documented history of ≥ 2 HAE attacks in the 6 months prior to the enrollment visit.

5. Access to and ability to use 1 or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE.

6. In the opinion of the investigator, the subject would benefit from long-term oral prophylaxis.

7. If sexually active, or become sexually active during the study, must agree to the use of effective contraception.

Main criteria for exclusion:

1. Concurrent diagnosis of any other type of recurrent angioedema.

2. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, myocarditis, pericarditis, congenital heart defects, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.

3. Known family history of sudden cardiac death at a young age (ie, < 40 years of age). Family history of sudden death from HAE is not exclusionary.

4. History of or current implanted defibrillator or pacemaker.

5. Moderate to severe hepatic impairment (Child-Pugh B or C).

6. A calculated creatinine clearance using the Modified Schwartz formula of ≤ 30 mL/min/1.73 m^2 or aspartate aminotransferase or alanine aminotransferase value ≥ 3 × the upper limit of the age-appropriate normal reference range value.

7. History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.

8. Current participation in any other investigational drug study or received another investigational drug within 30 days of enrollment; not willing to refrain from participation in another clinical study after

enrollment and for the duration of the study. [Note: drugs/vaccines approved under Food and Drug Administration (FDA) emergency use authorization (or country-specific analogous regulations) are not considered excluded or prohibited under this criterion.]

9. An immediate family relationship to either sponsor employees, the investigator, or employees of the study site named on the delegation log.

10. Any result at screening that, in the opinion of the investigator, is clinically significant and relevant for this study.

11. Any clinically significant medical condition or medical history (including altered mental status) that, in the opinion of the investigator or sponsor, would interfere with the subject's safety or ability to participate in the study. Examples include but are not limited to active malignancy under treatment, uncontrolled cardiovascular disease, organ dysfunction requiring supportive care.

12. Clinically significant abnormal ECG including but not limited to, a corrected QT interval calculated using Fridericia's correction ($QTcF = QT/RR^{0.33}$) > 450 msec, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.

13. Known hypersensitivity to berotralstat or any of its formulation excipients.

Investigational product, dosage, and mode of administration:

Berotralstat 150 mg capsules in multidose bottles and granules for oral administration packaged in unit-dose packets will be taken orally, once daily (QD), with food. The doses for Cohorts 1, 2, 3, and 4 are shown in the table below. Based on safety assessments and/or the PK data analyses, the weight bands for Cohorts 3 and 4 may be adjusted if needed.

The berotralstat dose for Part 1 will be determined based on subject weight on Day 1; this dose will be changed for an individual subject or for all subjects in the cohort if indicated by safety and/or PK parameters. In Parts 2 and 3, subjects will continue open label berotralstat for a total of up to an additional 132 weeks. The dose in Parts 2 and 3 will be based on subject weight and may be adjusted throughout the 132-week treatment period as indicated based on changes in the subject's weight, safety and/or PK parameters.

Cohort	Dose	Minimum Target Enrollment[a]	Weight Band (From PK modelling)
1	150 mg capsule	n=4	≥ 40 kg
2	108 mg granules	n=4	32 to < 40 kg
3	96 mg granules	n=4	24 to < 32 kg
4	78 mg granules	n=3	12 to < 24 kg

Note: Additional dose strengths ranging from 60 to <150 mg and/or cohorts may be utilized as indicated based on safety and/or PK results.

[a] The n represents the minimum number that will be enrolled into each cohort. Since the total target enrollment is approximately 30 subjects, additional subjects will be enrolled into 1 or more of the cohorts or additional dose cohort(s) may be added. Subject enrollment in any 1 or more cohorts may be suspended to ensure sufficient enrollment of subjects in each cohort.

Reference therapy, dosage, and mode of administration:

This is an open-label trial, and there is no reference therapy. Subjects will remain on their SOC regimen for the 12-weeks comprising the SOC treatment period. SOC may include short-term prophylaxis, long-term prophylaxis, and/or on-demand treatment for acute attacks. Data on AEs and HAE attacks will be collected during this period.

Duration of treatment:

Subjects will continue to take their SOC for 12 weeks following screening. Subjects who continue in the study will take berotralstat capsules (150 mg) or granules for oral administration (in unit-dose packets) for 12 weeks (Part 1) beginning on Day 1. For Parts 2 and 3, subjects will take berotralstat through Weeks 48 (Part 2) and 144 (Part 3), respectively.

Criteria for evaluation:

Pharmacokinetics:

Plasma PK concentrations will be analyzed using population PK methodology and reported in a separate stand-alone pharmacometric report.

Safety:

Frequency and severity of AEs/SAEs, laboratory analyses (clinical chemistry, hematology, coagulation), height, weight, vital signs, ECGs, and physical examinations.

Effectiveness:

Number of angioedema attacks (timing, duration of symptoms, anatomical location, treatment), number of days with angioedema symptoms, assessment of attack severity, discontinuations due to lack of efficacy, and number of hospitalizations and clinic visits through Week 48.

Statistical methods: Descriptive statistics will be generated for PK, safety, and effectiveness endpoints. Summaries will include sample size (n), mean, standard deviation (SD) and/or standard error of the mean (SEM), median, minimum, and maximum for continuous variables, and counts/frequencies and percent for categorical variables. Results will be presented by weight cohort and study visit where applicable. Interim analyses may be conducted after at least 15 subjects complete 48 weeks of treatment (Part 2) and/or after all subjects complete 48 weeks of treatment. Additional interim analyses may be done during the course of the study as needed to support regulatory filings, safety updates, and publications. No inferential analyses are planned. The final analysis will be conducted following the last study visit and after database lock has occurred.

Pharmacokinetics:

Standard noncompartmental methods will be used to calculate the following individual subject PK parameters from observed plasma concentrations: maximum plasma concentration (C_{max}), area under the concentration-time curve from time 0 to the last measurable concentration ($AUC_{0\text{-}last}$), area under the concentration-time curve from time 0 to 6 hours post-dose ($AUC_{0\text{-}6}$), time to C_{max} (T_{max}), last measurable concentration (C_{last}), and time to C_{last} (T_{last}) as data permit. Descriptive statistics will be calculated for each parameter and may be stratified by cohort and dosing regimen as appropriate.

Population PK modeling approach will be used to estimate the following PK parameters: AUC over the dosing interval (AUC_{tau}) at steady state, C_{max} at steady state, T_{max}, average plasma concentration (C_{avg}) at steady state, concentration at the end of a dosing interval (C_{trough}) at steady state, apparent clearance (CL/F), and apparent total volume of distribution (Vss/F). The results of these analyses will be reported in the stand-alone pharmacometric report.

Safety:

Analysis of safety and tolerability will be descriptive. For treatment emergent adverse event (TEAE) data, both the number of subjects and the total number of events will be reported. An independent DMC will periodically review safety data in accordance with a DMC Charter.

Effectiveness:

Descriptive analysis of secondary effectiveness endpoints will be provided for Part 1 (Weeks 1 to 12) and Parts 1 and 2 combined (Weeks 1 to 48). No effectiveness data will be collected after Week 48.

Initial versions of this statistical analysis plan (SAP) were drafted by PharPoint on behalf of BioCryst Pharmaceuticals, Inc.

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
API	Active Pharmaceutical Ingredient
AST	Aspartate transaminase
AUC	Area under the concentration vs. time curve
AUC_{0-6}	AUC from time 0 to 6 hours
AUC_{0-last}	AUC frum time 0 to C_{last}
AUC_{tau}	AUC over the dosing interval (tau)
BK	Bradykinin
BLQ	Below the limit of quantification
BMI	Body mass index
C1-INH	C1-esterase inhibitor
C1-INHAg	Antigenic C1 esterase inhibitor
C1-INHf	Functional C1 esterase inhibitor
C4	Complement 4
CL/F	Apparent clearance
C_{last}	Last observed measurable concentration
C_{max}	Maximum plasma concentration
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
CSR	Clinical study report
C_{trough}	Concentration at the end of a dosing interval
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
HAE	Hereditary angioedema
HK	High-molecular-weight kininogen
IB	Investigator brochure
ICH-E3	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline E3
ITT	Intent to treat
kg	Kilogram
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NDA	New Drug Application
P/C	Parent/Caregiver

PK	Pharmacokinetic(s)
PKK	Prekallikrein
PT	Preferred term
QD	Once daily
QoL	Quality of life
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SEM	Standard error of the mean
SMQ	Standardized MedDRA query
SOC	Standard of Care
SOP	Standard Operating Procedure
TdP	Torsades de Pointes
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T_{max}	Time to C_{max}
T_{last}	Time to C_{last}
TSR	Technical Summary Report
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WHODD	World Health Organization Drug Dictionary
Wk	Week

2. INTRODUCTION

Hereditary angioedema (HAE) with C1-esterase inhibitor (C1-INH) deficiency is an autosomal dominant disorder characterized by recurrent episodes of swelling of the skin, pharynx, larynx, gastrointestinal (GI) tract, genitals, and extremities (Longhurst and Cicardi 2012). The frequency of attacks varies between subjects, from rarely in some patients to every few days in others. Angioedema attacks may or may not be precipitated by a stimulus (such as stress, trauma, or estrogen) and are typically rapid in onset, with symptoms subsiding gradually over the following 3 to 5 days (Zuraw and Christiansen 2011). Oropharyngeal swelling can be life-threatening (Bork et al. 2012), while attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring, and have a significant impact on functionality and quality of life (QoL) (Lumry et al. 2010). Although mortality risk from asphyxiation is much higher in undiagnosed patients with HAE, deaths still occur in diagnosed patients with access to care at centers of excellence (Bork et al. 2012).

Extensive evidence from animal models and clinical studies supports the role of bradykinin (BK) as the principal mediator of the signs and symptoms that characterize attacks of HAE (Han et al. 2002; Kaplan 2010; Zuraw and Christiansen 2011). Plasma kallikrein is a serine protease integral to the contact activation pathway (Saxena et al. 2011). Kallikrein circulates in plasma as a zymogen, prekallikrein (PKK), bound to 1 of its main substrates, high-molecular-weight kininogen (HK). During contact activation, PKK is cleaved by activated factor XII, forming the active protease kallikrein. Kallikrein in turn cleaves HK, producing BK (Kaplan and Ghebrehiwet 2010). The activation of the bradykinin B2 receptor by BK ultimately results in vasodilatation, increased vascular permeability, and smooth muscle contraction, all of which lead to the tissue swelling that characterizes HAE (Kaplan 2010).

Berotralstat (also known as BCX7353 and Orladeyo®) is a potent, synthetic, small-molecule inhibitor of plasma kallikrein that has been approved in the United States (US), European Union (EU), United Kingdom (UK), Japan, and other markets. Berotralstat is indicated for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older. In contrast to parenterally administered options commercially available for prophylaxis against HAE attacks, inhibition of kallikrein with an orally bioavailable small molecule such as berotralstat offers the advantage of oral administration.

HAE is an autosomal dominant disorder; thus, the disease is inherited in an autosomal dominant pattern with nearly 100% penetrance. Family history is negative in about 25% of cases, suggestive of de novo mutations (Agostoni and Cicardi 1992). HAE attacks can be painful, disabling, and disfiguring, and have a significant impact on functionality and QoL (Lumry et al. 2010). Upper airway attacks are potentially fatal.

The mean age of HAE diagnosis varies greatly and is significantly affected by family history and symptoms. The age of symptom onset ranges from 1 to 20 years with increases around 3 to 6 years of age and puberty (Farkas 2010). However, only 2 therapies are currently approved for prophylaxis in children < 12 years, both of which are administered by injection (intravenous or subcutaneous) and both of which are only approved for children aged 6 years and older. Given the advantage of an orally administered drug in this pediatric population, BioCryst is conducting

this study to define the safety, tolerability, and pharmacokinetics (PK) of berotralstat in pediatric patients aged 2 years and older to expand the label and provide an oral therapeutic option for young children who suffer from this debilitating rare disease.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is:

- To describe the PK parameters of berotralstat administered orally to pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

3.1.2. Secondary Objectives

The secondary objectives in this study are:

- To assess the safety and tolerability of berotralstat administered orally to pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.
- To summarize the effectiveness of berotralstat in pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

3.1.3. Exploratory Objective

The exploratory objective of this study is:

- To assess the palatability/acceptability of berotralstat oral granules in pediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint is the characterization of the PK profile of berotralstat in subjects aged 2 to < 12 years.

3.2.2. Secondary Endpoints

The secondary endpoint of safety will be measured by frequency and severity of adverse events (AE) and serious adverse events (SAE), laboratory analyses (clinical chemistry, hematology, coagulation), height, weight, vital signs, electrocardiograms (ECG), and findings from physical examinations.

Safety endpoints will be assessed at the end of each Part (ie, Weeks 12, 48, and 144/end of study [EOS]).

The other secondary endpoint of effectiveness will be measured by assessing the following from Week 1 through Weeks 12 and 48:

- Frequency (number) and rate of HAE attacks
- Attack duration
- Anatomical location of attacks
- Number and proportion of attacks requiring on-demand treatment
- Number and proportion of days with angioedema symptoms
- Assessment of attack severity
- Discontinuations due to lack of efficacy
- Number of hospitalizations and clinic visits

3.2.3. Exploratory Endpoints

Acceptability/palatability of the berotralstat oral granules will be assessed in children receiving the granules using an age-appropriate scale. Acceptability/palatability of the berotralstat granules will be assessed by site personnel at the time of first dose (Day 1) for Cohorts 2, 3 and 4.

3.3. Statistical Hypotheses

No formal hypotheses are being tested in this study.

4. STUDY DESIGN

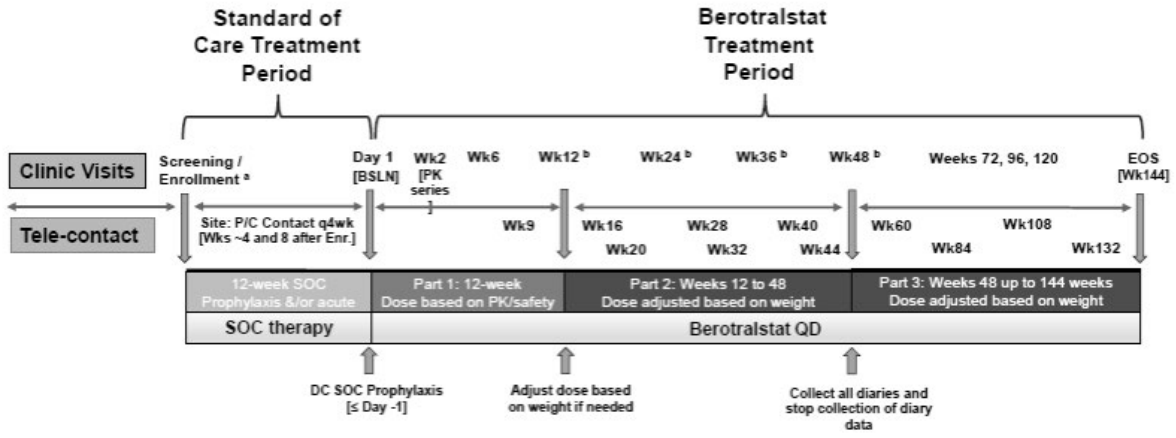
This is a sequential, 3-part, open-label study. A subject's participation in this study is expected to be a minimum of 24 weeks in the Standard of Care (SOC) treatment period through Part 1 of the study (12 weeks) and up to an additional 132 weeks in Parts 2 and 3 for a maximum duration of 144 weeks during Parts 1, 2 and 3.

Subjects will be enrolled into 4 or more dose cohorts; subject weight will be used to determine assignment to each cohort with the 2 higher weight cohorts (Cohorts 1 and 2) enrolling first and in parallel. Safety assessments and population PK modelling will then be used to confirm the weight bands for sequentially enrolling Cohorts 3 and 4.

Throughout the study, site personnel will monitor subject safety through a combination of in-person clinic visits and tele-communication with the parent/caregiver(s) (P/C). The tele-contact may be either a telephone call or telemedicine visit conducted over the internet.

A schematic of study visits is shown in Figure 1:

Figure 1: Study Schema



Abbreviations: BSLN=Baseline; DC=discontinue; Enr=enrollment; EOS = end of study; P/C=parents and/or caregivers; PK=pharmacokinetic; QD=once daily; SOC=Standard of Care; Wk=Week.

[a] Subjects will be enrolled at the screening visit. If, after the screening visit, laboratory results are returned that indicate the subject no longer meets the inclusion and exclusion criteria, the subject will be considered a screen failure.

[b] Indicates visits where single, random, plasma sample is collected for PK.

4.1. Standard of Care Treatment Period

Subjects will continue taking their SOC therapy for HAE (either short-term or long-term prophylaxis, or acute treatment for HAE attacks) for 12 weeks from the screening visit. No additional in-person visits are required during the SOC treatment period; however, at approximately 4- and 8-weeks following screening, site personnel will contact the parent/caregiver (P/C) to assess AEs and the overall status of the subject.

4.2. Part 1: Berotralstat Treatment

After 12 weeks on SOC, subjects will return to the site for the Day 1 (baseline) visit. Prior to the Day 1 visit, subjects must discontinue all prophylaxis for prevention of HAE attacks; use of on-demand medication to manage acute HAE attacks may continue throughout the study. At the Day 1 visit, the site will confirm concomitant medications, review subject diary entries, and discuss any AEs that occurred during the SOC treatment period. If study activities were not completed satisfactorily during this time (eg, diary entries were incomplete or the P/C was not reachable to assess AEs at the prescribed intervals), the subject may be discontinued from the study prior to the berotralstat treatment period at the sole discretion of the investigator. Beginning on Day 1, subjects will take berotralstat orally once each day, with food, for 12 weeks. Additional study visits in Part 1 will occur at Weeks 2, 6, and 12. All safety assessments will be assessed at each visit. In addition to the clinic visits, the site will contact the P/C at Week 9 to assess safety and subject status.

At the Week 12 visit, the subject will move from Part 1 into Part 2. The subject will be weighed, and the dose of berotralstat will be adjusted according to the current weight of the subject.

4.3. Part 2: Berotralstat Treatment

Beginning at the Week 12 visit, all subjects will be provided continued access to open-label berotralstat through Week 48 (a total of 36 weeks). Study visits in Part 2 will occur every 12 weeks (Weeks 24, 36, and 48). Also, during Part 2, sites will contact the P/C at 4-week intervals between study visits (ie, at Weeks 16, 20, 28, 32, 40, and 44) to assess the subjects' overall wellbeing. The contact should be an arranged tele-contact; however, it may become an on-site visit if the investigator or P/C considers an in-person visit necessary for medical management of the subject. At the Week 48 visit, the site will collect all subject diaries.

4.4. Part 3: Berotralstat Treatment

After Week 48, subjects may continue to receive open label berotralstat in Part 3 (Weeks 48 through 144; a total of 96 weeks). Visits in Part 3 will occur every 24 weeks: Weeks 72, 96, 120, and 144. Also, during Part 3, sites will contact the P/C at 12-week intervals between study visits (ie, at Weeks 60, 84, 108, and 132) to assess the subjects' overall wellbeing. The contact should be an arranged tele-contact; however, it may become an on-site visit if the investigator or P/C considers an in-person visit necessary for medical management of the subject. Berotralstat will be provided in Part 3 through Study Week 144 or until another mechanism is available to provide drug to the subject (eg, market access, separate study) or the sponsor discontinues development of the product for the prevention of angioedema attacks in children < 12 years of age.

Subjects who discontinue berotralstat at Week 144 or earlier will be required to attend an EOS follow-up visit 3 weeks after study drug discontinuation. Subjects who discontinue the study but will continue to receive berotralstat via another mechanism will have EOS assessments performed at their last regularly scheduled visit. After Week 48, subjects who discontinue study drug but continue to receive berotralstat via another mechanism will be considered study completers.

4.5. Subject Stopping Rules

A subject will be permanently discontinued from study drug for any of the following reasons:

- Emergence of any laboratory abnormality or AE that in the judgment of the investigator compromises the ability of the subject to continue study-specific procedures or it is considered not to be in the subject's best interest to continue in the study due to an altered risk/benefit profile.
- Subsequent determination that inclusion/exclusion criteria were not met.
- Intercurrent illness or emergence of a new illness/medical condition that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject noncompliance with study drug or to the protocol.
- The subject has a confirmed corrected QT interval using Fridericia's formula (QTcF) >500 msec (if there is an associated maximum plasma concentration (C_{max}) exceeding the adult range the dose may be interrupted and/or reduced, as described in Sections 11.2.1 and 11.2.2 of the protocol).
- The subject has a confirmed QTcF increase of more than 60 msec from the mean QTcF value calculated from the triplicate ECGs recorded at baseline and a simultaneous absolute QTcF > 460 msec (if there is an associated C_{max} exceeding the adult range, the dose may be interrupted and/or reduced, as described in Sections 11.2.1 and 11.2.2 of the protocol).
- Pregnancy in a female subject.

Subjects are not eligible to receive berotralstat in Parts 2 or 3 if they discontinue prior to completing Parts 1 or 2, respectively.

4.6. Definition of Study Drugs

Berotralstat (BCX7353) is an oral small-molecule inhibitor of plasma kallikrein.

The investigational active pharmaceutical ingredient (API) is BCX7353 and is supplied as either 150 mg capsules (identical to commercial product) or granules for oral administration. All ingredients are considered safe for use in the targeted pediatric population.

Additional details for the chemical and physical characteristics of berotralstat may be found in the investigator's brochure (IB).

4.7. Sample Size Considerations

The study is designed to evaluate the PK and safety/tolerability of oral administration of berotralstat in pediatric subjects ages 2 to <12 years of age who have HAE. A sample size of

approximately 30 subjects enrolled in 4 or more cohorts is adequate to evaluate these PK and to describe safety and tolerability. The sample size was selected based on feasibility considerations, however, with 30 subjects enrolled in the study, there is approximately a 96% chance of observing at least 1 treatment-emergent adverse event (TEAE) that occurs 10% of the time. Formal inferential testing of effectiveness and safety endpoints is not planned.

4.8. Randomization and Blinding

This is a single-arm, open-label study; as such, randomization and blinding are not applicable.

4.9. Clinical Assessments

See Table 2 for the schedule of assessments.

Table 2: Schedule of Assessments

	Standard of Care Therapy			Open-label Berotralstat Treatment										Post Treatment Follow-up
				Part 1					Part 2 (Wks)		Part 3 (Wks)			
				Clinic Visits and Contact					Site Contact	Visits	Site Contact	Visits	EOT	EOS Visit[a]
Assessment	Scr./ Enr.[b]	Wks 4 & 8 ±1Wk	Washout [prior to Day 1]	Baseline (Day 1)[c] ±4 days	Wk 2 +4 days	Wk 6 ±3 days	Wk 9[d] ± 1 Wk	Wk 12 ± 3 days	16, 20, 28, 32, 40, 44 ±1 Wk	24, 36, 48 ± 1 Wk	60, 84, 108, 132 ± 1 Wk	72, 96, 120 ±1 Wk	Wk 144 ±1 Wk	3 wks (±3 days) after the last dose
Informed consent[e]	X													
Inclusion/exclusion criteria (including confirmation of C1-INH HAE diagnosis)	X			X[f]										
Medical and medication history	X			X										
Height/weight/BMI[g]	X			X	X	X		X		X		X	X	X
Physical examination[h]	X			X	X	X		X		X		X	X	X
Vital signs[i]	X			X	X	X		X		X		X	X	X
Clinical chemistry/hematology[j]	X			X	X	X		X		X			X	X
Urinalysis[k]	X			X	X	X		X		X			X	X
Pregnancy testing[l]	X			X		X		X		X		X	X	X
Discontinuation of therapy[m]														
Oral androgen[n]			≥ Day -28											
CYP2D6 or CYP3A4 substrates			≥ Day -7											
ACE-inhibitor			≥ Day -7											
Lanadelumab			≥ Day -28											
SOC prophylaxis[o]			≥ Day -1											
ECG[p,q]	X			X	X	X		X		X			X	X

				Open-label Berotralstat Treatment										Post Treatment Follow-up
				Part 1					Part 2 (Wks)		Part 3 (Wks)			
	Standard of Care Therapy			Clinic Visits and Contact					Site Contact	Visits	Site Contact	Visits	EOT	EOS Visit[a]
Assessment	Scr./ Enr.[b]	Wks 4 & 8 ±1Wk	Washout [prior to Day 1]	Baseline (Day 1)[c] ±4 days	Wk 2 +4 days	Wk 6 ±3 days	Wk 9[d] ± 1 Wk	Wk 12 ± 3 days	16, 20, 28, 32, 40, 44 ±1 Wk	24, 36, 48 ± 1 Wk	60, 84, 108, 132 ± 1 Wk	72, 96, 120 ±1 Wk	Wk 144 ±1 Wk	3 wks (±3 days) after the last dose
Telephone/telemedicine contact[r]		X[s]					X		X[t]		X[t]			
PK: single, random plasma sample[u]								X		X				
PK: multiple samples[v]					X									
Diary instructions and/or review[w]	X	X		X	X	X		X	X	X				
HAE therapy														
SOC	X	X												
Berotralstat				X	X	X	X	X[x]	X	X	X	X	X	
Palatability/acceptability assessment[y]				X										
AEs	X	X		X	X	X	X	X	X	X	X	X	X	X[z]
Concomitant medications	X			X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ACE=angiotensin-converting enzyme; AE=adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI=body mass index; C1-INH=C1 esterase inhibitor; C_{max} = maximum plasma concentration; CRF=case report form; CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4; ECG=electrocardiogram; Enr. =enrollment; EOS=end of study; EOT=end of treatment; GGT = gamma-glutamyl-transpeptidase; HAE=hereditary angioedema; LDH = lactate dehydrogenase; P/C = parent/caregiver; PK = pharmacokinetic(s); QTc=corrected QT interval; Scr.=screening; SOC=standard-of-care; Wk(s)=week(s).

[a] Subjects who discontinue berotralstat either at the Week 144 visit or earlier will be required to attend an EOS follow-up visit 3 weeks (± 3 days) after study drug discontinuation. Subjects who discontinue the study but will continue to receive berotralstat via another mechanism will have EOS assessments performed at their last regularly scheduled visit.

[b] Screening assessments will be conducted at the screening visit although, if necessary, the assessments may take place over a screening period not to exceed 14 days without prior consent of the sponsor. Subjects will be considered enrolled into the study as of the date of the screening visit if all available results satisfy the inclusion and exclusion criteria as of that date. If, after the screening visit, screening results are returned that indicate the subject no longer meets

the inclusion and exclusion criteria, the subject will be considered a screen failure. The investigator will provide the P/C with study materials (eg, subject's diary) at the end of the screening visit and request the P/C to record diary data starting at the date of the screening visit and for the next 12 weeks (ie, the SOC treatment period). The P/C will be subsequently contacted via tele-contact once all screening results are available to confirm eligibility or screen failure.

[c] The Day 1/baseline visit should occur 12 weeks ± 4 days after enrollment. If extenuating circumstances prevail, this timeframe may be extended with medical monitor approval (see Section 9.3.1 of the protocol).

[d] At Week 9, the site should contact the P/C to assess subject status including AEs and concomitant medications.

[e] The informed consent form must be signed by the parent or child's legal representative prior to conducting any study-related procedures. Based on the child's age and local regulatory requirements, subject assent will be collected as appropriate.

[f] At the baseline visit, the site will review prohibited medications (see Section 8.7 of the protocol), subject diary entries, and discuss any AEs that occurred during the SOC treatment period. If any activities were not completed satisfactorily (eg, diary entries were incomplete or the P/C could not be contacted to assess AEs at the prescribed intervals) or the use of prohibited medications is discovered, the subject may be discontinued from the study and not enrolled into Part 1 at the sole discretion of the investigator. If subjects are discontinued at Day 1, subject diaries should be collected, and subjects should be instructed to remain on their SOC therapy. No additional visits are required for subjects who discontinue after the SOC treatment period and never receive berotralstat.

[g] Weight will be recorded at each visit. Height will be recorded, and BMI calculated at screening, baseline/Day 1, Weeks 12, 24, 36, 48, 72, 96, 120, 144, and the EOS visit. At 8 weeks after enrollment, where possible the subject should assess their weight at home in light clothing with shoes and heavier items removed. The site will obtain the results of the home weight assessment by telephone and record the results in source documents.

[h] Full physical examinations will be performed at screening, Day 1/baseline, and Week 12; symptom-directed physical examinations will be performed only as necessary at all other visits.

[i] Vital signs will include blood pressure, pulse rate, and body temperature. Respiratory rate will only be captured at screening, Day 1/baseline, and Week 12.

[j] See Table 3 of the protocol for a list of analytes to be assessed.

[k] Urine samples will be collected from all children old enough to provide a reasonable clean-catch sample. If very young children are not able to provide a urine sample, the lack of a sample should be noted in the source documents; lack of sample collection in small children will not be considered a protocol deviation.

[l] For all girls of childbearing potential, a serum pregnancy test will be administered at screening. Urine pregnancy tests will be assessed at all subsequent visits as indicated in the table. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test. In addition, girls of childbearing potential will be dispensed urine pregnancy tests to complete at home approximately every 4 weeks, where dictated by local requirements; participants will receive the appropriate number of pregnancy tests to complete testing at the intervals above during in-person clinic visits as needed. Sites will obtain the home test results during planned site contacts and record the results in source documents.

[m] To qualify for entry into Part 1, subjects must discontinue use of listed medications at the times indicated. Note that the times are relative to the Day 1/baseline visit. Refer to exclusion criteria (Protocol Section 7.2.2) for further explanation.

[n] Subjects should have ALT, AST, ALP, LDH, GGT, and total and direct bilirubin measured 2 weeks (+ 7 days) after androgen discontinuation.

[o] The final dose of SOC prophylaxis must be administered no later than the day before the Day 1/baseline visit. Subjects may continue to take medication to treat acute attacks throughout the study.

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

[q] If AEs commonly associated with prolonged QTc interval (eg, unexplained intermittent or continuous lightheadedness, syncope, palpitation, chest pain) are reported or the dose is modified, additional ECGs should be recorded.

[r] The site should contact the P/C by the method agreed upon at the screening visit; the contact may be by telephone or may be a telemedicine visit.

[s] The contact should occur at 4 ± 1 and 8 ± 1 weeks following the enrollment visit and should be as evenly spaced out over the SOC therapy period as is reasonable. The tele-contact must be interactive, eg, a telephone call or telemedicine visit. An in-person clinic visit would also satisfy this requirement (see Section 9.2.2 of the protocol for further explanation).

[t] The contact must be interactive and may include a telephone call, telemedicine visit, or in-person visit if requested by the P/C and/or investigator. If there is a safety concern or if required for medical management of the subject, an in-person visit should be conducted.

[u] A single plasma PK sample is to be collected at Weeks 12, 24, 36, and 48. Additional plasma PK samples may be collected as described in Section 10.9 and 10.9.1 of the protocol. The date and time of the PK blood draw and the last dose of berotralstat taken prior to the blood draw will be captured in the CRF. PK sample collection may be discontinued following the interim data cut used to finalize the population PK model and pharmacometric analysis report at the discretion of the sponsor.

[v] In Cohorts 1, 2, and 3, plasma samples for PK analysis should be collected pre-dose and at 1 ± 0.5, 2 ± 0.5, 4 ± 1, and 6 ± 1 hours post dose (exact timing of the dose and each blood draw must be recorded). PK samples should be collected as close to the nominal collection timepoint as possible, but all scheduled PK samples should be collected even if they are outside the sampling window. The date and time of the PK blood draws and the last dose of berotralstat taken prior to the blood draw will be captured in the CRF. In Cohort 4, plasma samples for PK analysis should be collected pre-dose, 1 to 2 hours post dose and 4 to 6 hours post dose. Of note, in younger and/or smaller subjects, the number of samples and/or volume of blood drawn for each sample may be reduced to ensure volumes collected fall within acceptable ranges. See Protocol Section 10.9 for additional details.

[w] Diaries will be given to the P/C for each subject at screening. If the child does not qualify based on the results of the pending laboratory tests, the child will be considered a screen failure. For eligible subjects, P/Cs will complete the diary, recording HAE attacks through Part 2 (Week 48) of the study. At each visit, the P/C should bring the completed diary with them for review by site personnel. Diaries will be collected at each visit through Week 48, and new diaries will be dispensed at each visit prior to Week 48. Any issues with diary entries will be discussed with the P/C and corrections will be made by the subject or P/C as required. All diaries will be collected at the Week 48 visit.

[x] Subjects will remain on the dose of berotralstat assigned at the Day 1 visit until the subject reports to the clinic for the Week 12 visit unless PK results from Week 2 indicate that the C_{max} levels fall outside the protocol-specified range or there is a safety concern. At the Week 12 visit and continuing throughout Parts 2 and 3, the dose of berotralstat will be adjusted based on the weight of the subject.

[y] Palatability/acceptability will be assessed using an age-appropriate hedonic scale for the granule formulation by those subjects who receive the granule formulation; presumably, those in Cohorts 2, 3, and 4.

[z] If an AE is ongoing at the EOS visit, additional clinic visit(s) or telephone contact(s) may be warranted (see Protocol Section 11.1.2.1).

5. PLANNED ANALYSES

5.1. Interim Analyses

Data summaries will be provided to the Data Monitoring Committee (DMC) as specified in the DMC Charter. Interim analyses of PK, safety and effectiveness data may be conducted after at least 15 subjects complete 48 weeks of treatment (through Part 2) using interim locked data as defined in the protocol to support the New Drug Application (NDA) submission. An additional interim analysis may be done when all subjects complete end of Part 2/48 weeks of treatment. Effectiveness data are not collected after the Week 48 visit. Safety and dosing tables for the end of 48-week analysis will only include data through the Week 48 visit; for all other analyses, all available data will be reported unless otherwise specified. Additional analyses may be conducted to support regulatory filings, safety updates, and publications.

5.2. Final Analysis

The final analysis of disposition, dosing, and safety data collected in Parts 1, 2, and 3 will be conducted once the last subject completes or discontinues his or her respective parts, the resulting clinical database has been cleaned and quality checked, the analysis populations have been finalized, and database lock has occurred. Disposition, dosing, and safety data will be summarized through the end of study (Week 144).

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

This section addresses the definitions, algorithms, imputations, and conventions that will apply to the analysis and handling of the data in general. Rules that are data specific will be addressed in the detailed discussions of individual summary tables.

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will include "footers" providing:

1. Date of output generation.
2. SAS program name that generates the output.
3. File path(s) to datasets used in the SAS program, including names of datasets.
4. Any abbreviations used in the body of the table.
5. Any other output-specific details that require elaboration.

Version 9.4 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 to permit uninvolved outside statistical experts to replicate all the analyses specified in this statistical analysis plan (SAP).

The date of output generation links the output to the locked and archived database to allow replication of the results.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Tables and listings will be numbered to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with up to 2 digits per level (eg, Table XX.Y.Z.).

The first level number should be consistent with the corresponding clinical study report (CSR) appendix in which the tables, figures or listings will appear. Following the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E3 (ICH-E3), all post text tables and figures should have first level 14 and data listings should have 16.2.

Subject accounting and final disposition, baseline, and demographic profile will appear as the first sub-level (Table 14.1 series). Analysis of berotralstat concentration and non-compartmental PK analysis will be included in Section 14.2, however, analysis results of population PK modeling will be provided in a separate pharmacometric report. Effectiveness data will also be included in Section 14.2. Safety data will be included in Section 14.3. Analysis of palatability

data will be in Section 14.4. For subject data listings, 16.2.1.x and 16.2.2.x includes subject accounting, 16.2.3.x includes analysis populations and enrollment by country and site, 16.2.4.x includes demographics and medical/medication histories, 16.2.5.x includes dosing, drug accountability and compliance, and PK concentration, 16.2.6.x includes effectiveness, 16.2.7.x includes adverse events, 16.2.8 includes laboratory results, and 16.2.9.x includes palatability.

The title of the output should be complete, accurate, and concise. If convenient, the parameter and unit of measurement can appear in parentheses to conserve space in the body of the table. For example, the summary of vital signs title could read "Summary of Sitting and Standing Blood Pressure (mmHg) and Heart Rate (bpm)." Whether in the title or body of a table or listing, units must always be specified for all appropriate data. The last line of the title should provide the analysis group being summarized (eg, Safety Population or PK Population).

If possible, variables being summarized, and statistics reported should appear in the leftmost column of a table. The next columns for treatment groups should report the data from left to right for all treated subjects with the investigational drug, by cohort. Any row with all zeros will not appear except with reasons for not completing the study. Summary tables clearly indicate the number of subjects to which the data apply, and unknown or not performed are distinguished from missing data. PK tables are addressed in Section 10.

In general, the listings should be sorted and presented by cohort, subject number, and study day or time of assessment. From left to right, the cohort number, subject number, visit number, and visit date / relative day should appear.

All tables and listings must have explanatory notes that give the definition of all derived variables and decodes for coded data. Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.

6.3. Data Management

A data management plan will be developed and approved prior to commencement of data entry.

Data will be captured using the Medidata electronic data capture system. Electronic validation steps (edit checks) will be utilized, and data cleaning will occur in conjunction with each site. Prior to transfer of data provided by vendors (eg, laboratory data), a data transfer agreement including specifications for the type of file, definitions of variables, and contact information for the sending and receiving parties will be developed and finalized. The standard operating procedures (SOPs) of PharPoint, the selected data management, statistics, and programming vendor for this study, will be used.

Data will be mapped to Study Data Tabulation Model (SDTM)-compliant datasets prior to creation of Analysis Data Model (ADaM)-compliant derived datasets for use in the creation of summary tables. All analyses will be generated using SAS® v9.4 or above and in accordance with PharPoint SOPs.

6.4. Data Presentation Conventions

Continuous data will be summarized using the number of subjects with available data, mean, standard deviation (SD) or standard error of the mean (SEM), median, minimum, and maximum. Categorical data will be summarized using counts/frequencies and percentages. Percentages will be calculated using the total number of subjects per cohort unless otherwise specified.

Means and medians will be formatted to 1 more decimal place than the measured value, SDs and SEMs to 2 more decimal places, and minimum and maximum values to the same number of decimal places. For categorical variables, the number and percentage of responses will be presented in the form XX (XX.X%) where the percentage is in the parentheses, except that 100% will be presented to 3 digits with no decimal. Adverse event data will be presented in the form XX (XX.X%) [XXX] where the number of subjects with at least 1 event (incidence) is the first number and the number of occurrences of an event is in "[ ]". Dates will be formatted as DDMMMYYYY and times will be formatted in 24-hour time as HH:MM. Partial dates will be handled as described in Section 8.5.

Berotralstat concentration data will be listed and summarized as part of the statistical analysis for this study and included in the Clinical Study Report. Noncompartmental PK parameters will be calculated as described in Section 10.1.2 and included in the Clinical Study Report. PK parameters from population PK modeling will be calculated and summarized as described in the Population PK Analysis Plan and included in the Population PK report.

Wherever possible, data will be decimal aligned.

A table of contents at the end of this SAP provides the expected titles and numbers of the tables, listings, and figures of the final report. Changes to titles or numbering in the final report will not necessitate a revision to the SAP, nor will they be considered deviations from planned analyses. Additional data listings supporting the tables will not be considered a deviation from planned analyses.

6.5. Analysis Populations

6.5.1. Screen Failures

Subjects for whom informed written consent is provided by their P/C and assent is provided (where appropriate), but are not allocated to study treatment, and are noted as screen failures in electronic case report form (eCRF) are considered screen failures. This includes subjects who withdraw consent during the SOC period of the study. Subjects who are "preliminary enrollees" awaiting final confirmation of eligibility will also be considered screen failures if found to be ineligible for study participation. These subjects will not be treated with study drug and will not be summarized other than on the disposition table. Data collected from screen failures may be presented on corresponding data listings.

6.5.2. Intent to Treat Population

The intent to treat (ITT) population will include all subjects who satisfy all entry criteria, who enroll into the study, and are not considered to be screen failures. As this study focuses on safety and PK of berotralstat, analysis using the ITT population will be limited, with the majority of analyses done using the Safety population.

6.5.3. Completer Populations

Week 12 and Week 48 completers will include subjects from the Safety Population and will be analyzed for effectiveness endpoints and are defined below.

- A Week 12 completer is defined as a subject who completes dosing through the Week 12 visit.
- A Week 48 completer is defined as a subject who completes dosing through the Week 48 visit.

These definitions ignore missed doses and treatment interruptions due to AEs.

6.5.4. Safety Population

The safety population will include all subjects who received at least 1 dose of berotralstat. This population will be used for all analyses of accountability, demographics, berotralstat drug dosing, effectiveness, compliance, and safety.

6.5.5. Pharmacokinetic Population

The PK population will include subjects in the safety population who had at least 1 evaluable and quantifiable post-dose PK sample obtained. The PK population will be the primary population for noncompartmental and population PK analyses.

6.6. Baseline Definition

For a given subject and assessment, the baseline result generally will be the latest non-missing result prior to administration of the first dose of berotralstat. The baseline ECG values will be the average of the 3 triplicate readings obtained pre-dose on Day 1. For many effectiveness endpoints, the baseline value will be based on events during the SOC period.

6.7. Derived and Transformed Data

6.7.1. Study Day

Day 1 is defined as the date of the first dose of berotralstat. If the date of interest occurs on or after the Day 1, then study day will be calculated as (date of interest – date of Day 1) + 1. If the date of interest occurs prior to the date of first dose of berotralstat (eg, during the SOC period), then study day will be calculated as (date of interest – date of first dose). There is no Day 0.

6.7.2. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result). If either the baseline or the post-baseline result is missing, the change from baseline is set to missing as well. For laboratory values, if the baseline laboratory value is missing but a screening laboratory value exists, then the screening laboratory value may be used as the baseline value.

6.7.3. Percent Change from Baseline

Percent change from baseline is calculated as (100 × change from baseline/baseline result). If either the baseline or the post-baseline result is missing, the percentage change from baseline is set to missing as well.

6.7.4. Treatment-Emergent Adverse Events

TEAEs are defined as AEs that occurred on or after first dose of study treatment through 30 days post-discontinuation of study treatment. Additionally, it is assumed that an AE which was reported to have started on Day 1 without an associated onset time may have occurred after the initiation of berotralstat. Hence, AEs occurring on Day 1 with no associated onset time will be assumed to be treatment emergent.

6.7.5. Prior and Concomitant Medications

Any medication taken within 30 days of screening and ended before study enrollment is considered a prior medication.

Any medication that is ongoing, started, or ended after enrollment is considered concomitant. It is assumed that a medication that was reported to have ended on the date of study enrollment without an associated end time may have been stopped after enrollment. Hence, medications occurring on the date of study enrollment with no associated end time will be assumed to be concomitant.

6.7.6. Treatment-Emergent Laboratory Toxicity

In general, the treatment-emergent laboratory toxicities will be graded according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading Adverse Events for Adults and Pediatrics (Corrected Version 2.1, July 2017). Any graded clinical laboratory abnormality that occurs following the initiation of berotralstat and represents at least 1-grade increase (according to the DAIDS) from the baseline assessment is defined as treatment-emergent. However, for creatinine, the following modification will be used to target meaningful changes in creatinine in pediatric subjects with low baseline creatinine values:

- Grade 1 mild: 1.1 to 1.3 x upper limit of normal (ULN) OR increase ≥ 0.2 mg/dL from participant's baseline
- Grade 2 moderate: > 1.3 to 1.8 x ULN OR increase (≥ 1.3 x baseline AND increase ≥ 0.3 mg/dL from baseline)
- Grade 3 severe: > 1.8 to 3.5 x ULN OR (increase ≥ 1.5 x baseline AND increase ≥ 0.5 mg/dL from baseline)
- Grade 4 potentially life threatening: > 3.5 x ULN OR (increase ≥ 2 x baseline AND increase ≥ 0.7 mg/dL from baseline.)

In addition, since triglyceride values may vary depending on if the sample was taken after fasting or not, only triglyceride samples taken after fasting will be graded. Values for all other samples will have a missing grade. Non-fasting and fasting cholesterol values will be graded according to the DAIDS criteria for fasting cholesterol.

6.7.7. Derived Effectiveness Endpoints

6.7.7.1. Subject-Reported Attack

A subject-reported attack is any attack reported on the HAE Attack Details eCRF page. Each reported attack will count as a separate attack, even if the time periods for the attacks are overlapping.

6.7.7.2. Adjusted Attack

Subject-reported attacks reported must meet the following criteria (applied in order) for inclusion in effectiveness analyses:

- Attack must include at least 1 symptom of swelling;
- Subject response to diary question, “In retrospect, could there be an alternative explanation for your symptoms other than an HAE attack (ie, allergic reaction, viral cold etc.)?” must be “no”.
- Attack must be unique (attack began > 24 hours from the end of the prior attack);
- Any attack that begins within 24 hours from the end of a prior attack will be combined with the prior attack;

- If the entire adjusted attack is untreated, it must have a duration > 24 hours.

Using the above criteria, adjusted attacks will be determined programmatically. For adjusted attacks that span 2 or more subject-reported attacks, attack triggers, locations, symptoms, duration, and other characteristics will be based on the information from each component subject-reported attack. Additionally, the start date/time of the adjusted attack will be the start date/time from the first attack and then end date/time of the adjusted attack will be the end date/time from the last attack being collapsed programmatically.

6.7.7.3. Baseline Attack Rate

The baseline attack rate will be calculated using data from the SOC period and standardized to number of attacks per month, where 1 month is defined as a 28-day (4 week) period. It is calculated as:

$$\frac{\text{Number of HAE attacks during the SOC period Screening} * 28}{\text{Study Day 1 Date} - \text{Screening Date} + 1}$$

where the number of HAE attacks during SOC period includes any attacks starting after informed consent through the time of first dose. The screening day is the first day of the SOC period. Note that the SOC period starts upon signing the informed consent form. A similar method will be used to calculate other baseline rates (eg, baseline HAE attacks treated with rescue medication).

6.7.7.4. Attack Rate in Parts 1 and 2

The observed attack rate will be computed as the number of attacks per month, where 1 month is defined as a 28-day (4-week) period.

In general, the formula for computing an attack rate is the number of attacks meeting the attack criteria divided by the duration of the reporting period of interest.

$$Attack\ Rate\ (\frac{attacks}{month}) = \frac{\text{Number of Attacks} * 28}{\text{Duration of Treatment Period of Interest}}$$

For subjects who complete the reporting period of interest, duration of reporting period of interest is defined as the last day in the reporting period – first day in reporting period + 1. For subjects who discontinue treatment prematurely in the reporting period of interest, the duration of reporting period of interest is defined as (last day of treatment +1) – first day in reporting period + 1. For example, if a subject receives the last treatment on Day 13 of Month 3 with 2 attacks between Day 1 and Day 14, that subject will be considered to have had a rate of 4 attacks/month (2 × 28/14 = 4) for Month 3. Both the reporting period and the treatment period have been adjusted to include an additional day as the subject prematurely discontinued dosing in Month 3.

Subject-Reported Attack Rate

Subject-reported attack rates will be computed through Week 12 and through Week 48 (eg, 0-12 weeks and 0-48 weeks).

Adjusted Attack Rate

Adjusted attack rates will be computed for the following reporting periods of interest and expressed in units of attacks/month where 1 month = 28 days:

- During SOC
- By month
- Through Week 12 (eg, 1-12 weeks)
- Through Week 48 (eg, 1-48 weeks)

Adjusted attack rates will be calculated during the SOC period as well as study Parts 1 and 2. For on-study adjusted attack rates by month, months will be defined in blocks of 28 days, beginning on Day 1, after the first dose of berotralstat. If an attack occurs on Day 1, and the time of both the attack and berotralstat administration are recorded, then an attack prior to berotralstat should be counted in the SOC period and an attack after berotralstat administration should be counted in Week 1 (Month 1). Should a subject prematurely discontinue treatment at the end of the monthly reporting period (ie, Day 28), any attacks that occur within 24 hours after last dose will be counted in the calculation of attack rate of the prior month and the additional 24-hour period will be included in the duration of the reporting period. For example, if a subject has 1 attack from Day 1 to 28, discontinues drug on Day 28, and has an attack on Day 29, the Month 1 (Day 1 to Day 28) attack rate will be 0.55 attacks/month ($2 \times 28/29 = 0.55$). Since HAE attack data are only to be collected during SOC, Part1, and Part 2, an attack that numerically falls beyond Week 48 will be included with data in Week 48 (Month 12) if it occurs on or prior to the Week 48 visit (also see Table 5).

No imputation will be done for missing data.

6.7.7.5. Number and Proportion of Days with Angioedema Symptoms

The number of days with angioedema symptoms is the number of the days during the reporting period for which at least 1 symptom is reported during an adjusted HAE attack based on the start date and resolution date of an attack. The definition of the reporting period will be specified for subjects who discontinue in the same manner as for the attack rate calculation (see Section 6.7.7.4). with angioedema symptoms is derived as the number of days with angioedema symptoms divided by the duration of the reporting period of interest. The calculation will be performed similarly to the calculation of the attack rate (see Section 6.7.7.3).

6.7.7.6. Attack Duration

The duration of each subject-reported attack will be calculated in hours, based on the start, and stop date and time of the subject-reported attack (time the attack finished). For an adjusted attack that includes more than 1 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 that has been combined into 1 adjusted attack. Similarly, the duration of the attack from start of the attack to time that "the worst was over" will also be calculated.

All subject-reported attack durations will be included in listings and those included in adjusted attacks will be denoted. Adjusted attack duration will be summarized.

6.7.7.7. Medications to Treat HAE Attacks

The following medications reported taken as acute treatment in the subject diary will be classified in the analyses as targeted medications to treat subject-reported HAE attacks: Berinert®, Cinryze®, Kalbitor®, Firazyr®, Ruconest®, and fresh frozen plasma.

All other medications also recorded in the subject diary as HAE treatments, will be classified as non-targeted medications: pain or anti-cramping medication, nausea medication, intravenous fluids, other.

6.7.7.8. Attack Symptoms

Symptoms reported for adjusted attacks will be included in summaries of attack characteristics. In addition, listings of diary data will show symptoms for all subject reported attacks.

6.7.7.9. Attack Location

The anatomical location of each subject-reported and adjusted attack will be determined based on the symptoms indicated in the diary as shown in Table 3.

Table 3: Determination of Attack Location Using Symptoms Collected in the Diary

Abdominal-Only Attack	**Mixed Attack**	**Non-abdominal Attack (Inclusive of Skin and Airway Swelling)**
Symptoms checked must only come from this box: Internal swelling or symptoms of internal swelling in the abdomen: Nausea Abdominal discomfort Cramps (colicky pain) Vomiting Abdominal pain Diarrhea	Must have at least 1 symptom from left and right box (from abdominal and non-abdominal attack characterization)	Symptoms checked must only come from this box: **Peripheral (Non-laryngeal) Events:** Visible swelling: face/head neck (outer swelling) legs buttocks/genitals eyes arms feet stomach (outside) hands chest/back joints

Abdominal-Only Attack	Mixed Attack	Non-abdominal Attack (Inclusive of Skin and Airway Swelling)
		Pink rings (erythema marginatum) with other swelling **Laryngeal Events:** Internal swelling or symptoms of internal swelling of the airways: mouth/tongue/lips lump in throat/tightness change in voice difficulty swallowing difficulty breathing

Note: Symptoms of headache and substantial fatigue may be checked by the subject but play no role in the characterization of the location of a subject-reported attack.

6.7.7.10. Laryngeal Events

Laryngeal events are those events that have visible swelling in the mouth/tongue/lips or any of the following internal swelling symptoms: lump in throat (tightness), change in voice, difficulty swallowing, or difficulty breathing, as recorded in the subject diary. Note that swelling of the lips may not indicate a true laryngeal event but is an artifact of the data collection tool.

6.7.7.11. Peripheral (non-abdominal, non-laryngeal) Events

Peripheral events are those events that have visible swelling of the face/head, neck (outer welling), legs, buttocks/genitals, eyes, arms, feet, stomach (outside), hands, chest/back, and joints. This also includes erythema marginatum (pink rings) in the presence of any other swelling.

6.7.7.12. Attack Triggers

Attack triggers for adjusted attacks will be summarized with the attack characteristics for adjusted attacks. In addition, attack triggers for each subject-reported attack will be included in the listings.

6.7.7.13. Average Number of Hospitalizations and Clinic Visits Due to HAE

The average number of hospitalizations due to HAE is derived as the number of hospitalizations due to HAE divided by the duration of the reporting period of interest. The calculation will be performed similarly to the calculation of the attack rate (see Section 6.7.7.4).

The average number of clinic visits due to HAE is derived as the number of clinic visits due to HAE divided by the duration of the reporting period of interest. The calculation will be performed similarly to the calculation of the attack rate (see Section 6.7.7.4).

6.7.8. Age at Time of Adverse Events

Age at time of AE is calculated as age at screening date plus the difference in years between screening date and the AE date, rounded down to the nearest whole number.

6.8. Presentation of Visits

For by visit displays, scheduled visits will be summarized nominally as collected on the case report form (see Table 4); unscheduled and early termination visits will not be analyzed. Data captured from unscheduled and early termination visits will be utilized in the determination of baseline values and worst post-baseline assessments. All visits will be displayed in the listings.

Table 4: Visit Windows (Days)

Visit Description	Relative Target Day	Protocol-Specified Visit Window	Analysis Visit Window
Screening visit	-84	-88 to -80	-88[a] to -80
SOC period	-88 to -1	-88 to -1	-88[a] to -1
Baseline visit	1	1	1
Week 2 (Day 15)	15	15 - 19	2 - 29
Week 6 (Day 43)	43	40 - 46	30 - 54
Week 9 (Day 64)*	64	57 - 71	55 - 75
Week 12 (Day 85)	85	82 - 88	76 - 99
Week 16 (Day 113)*	113	106 - 120	100 - 127
Week 20 (Day 141)*	141	134 - 148	128 - 155
Week 24 (Day 169)	169	162 - 176	156 - 183
Week 28 (Day 196)*	196	189 - 203	184 -210
Week 32 (Day 225)*	225	218 - 232	211 - 239
Week 36 (Day 253)	253	246 - 260	240 - 267
Week 40 (Day 281)*	281	274 - 288	268 - 295
Week 44 (Day 309)*	309	302 - 316	296 - 323
Week 48 (Day 337)	337	330 - 344	324 - 379
Week 60 (Day 421)*	421	414 - 428	380 - 463
Week 72 (Day 505)	505	498 - 512	464 - 547
Week 84 (Day 589)*	589	582 - 596	548 - 631
Week 96 (Day 673)	673	666 - 680	632 - 715
Week 108 (Day 757)*	757	750 - 764	716 - 799
Week 120 (Day 841)	841	834 - 848	800 - 883
Week 132 (Day 925)*	925	918 - 932	884 - 967
Week 144 (Day 1009)	1009	1002 - 1016	≥ 968

Abbreviation: SOC = standard of care.
Weeks with * will have telephone call or telemedicine visit.
[a]-88 days or earlier if the informed consent date is prior to day -88; this day is relative to the day the first dose of study drug is given.

In certain presentations, the HAE attack rates are summarized by month. The HAE attack will be assigned to an analysis month according to the study day of the actual HAE attack using the following conventions in Table 5:

Table 5: Attack Days Windows (Days)

Attack Day	Analysis Month for Display*
Date/Time of Consent to -1	SOC or Baseline
1 – 28	Month 1 (Day 1 – 28)
29 – 56	Month 2 (Day 29 – 56)
57 – 84	Month 3 (Day 57 – 84)
85-1112	Month 4 (Day 85-112)
113-140	Month 5 (Day 113-140)
141-168	Month 6 (Day 141-168)
169-196	Month 7 (Day 169-196)
197-224	Month 8 (Day 197-224)
225-252	Month 9 (Day 225-252)
253-280	Month 10 (Day 253-280)
281-308	Month 11 (Day 281-308)
309 to Week 48 visit	Month 12 (Day 309 to Week 48 visit)

Abbreviation: SOC = standard of care.
*28-day month blocks through the end of Part 2 (Week 48 visit) of the study. The values in "( )" may or may not be used on the actual display depending on space availability.

Note that an attack on Day 1 with the time recorded prior to the first dose of berotralstat will be included in the SOC period. Alternatively, an attack on Day 1 with the time after the first dose of berotralstat or an attack with no time will be included as an on-study attack starting on Day 1. Also note that since effectiveness data are only to be collected through the end of Part 2 (Week 48 visit); an attack that falls beyond Day 336 will be included in Week 48 (Month 12).

6.8.1. Multiple Assessments

Where multiple scheduled measurements are recorded for a given time point (ie, triplicate ECGs or repeated blood pressure assessments), the mean of the measurements will be calculated and used in any derivation of summary statistics. All available data will be listed.

When multiple visits occur within the same window, the scheduled visit will be used in the analysis if available. If no scheduled visit occurs within the window and unscheduled visit(s) and/or an early termination visit occur within the window, the analysis visit closest to the target day will be selected for use in analysis. If deemed appropriate by the sponsor (eg, in the case of a

retest), unscheduled visits may be chosen for analysis given documentation of the desired visit from the sponsor.

Results from unscheduled visits will be eligible for inclusion in analyses of worst post-baseline results regardless of their use for 'by visit' displays.

Listings will display all visits as recorded on the eCRF, including the date and study day. All available data including any totals, domains, or subscales of scale assessments summarized will be listed.

7. TREATMENT COMPARISONS

7.1. Data Display Treatment and Other Sub-Group Descriptors

Planned groups to be displayed on the summary tables are based on the cohort corresponding to initial dose as determined by subject weight/weight band at study baseline:

Cohort	Dose	Weight Band (at baseline)
1	150 mg capsule	≥40 kg
2	108 mg granules	32 to <40 kg
3	96 mg granules	24 to <32 kg
4	78 mg granules	12 to <24 kg
All Cohorts	All Doses	12 to ≥40 kg

Unless otherwise noted, tables will be arranged by cohort, and listings will be sorted by cohort, subject number, and date. Subjects will be analyzed by their original assigned cohort. Subjects who have their dose changed (decreased or increased) may be footnoted in Tables and Figures (eg, 1 subject in Cohort 1 had a dose decrease to xxx mg in Part x or Week xx). In addition, a listing of subjects with dose increases or decreases will be generated.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All statistical analyses will be conducted with the SAS® software package version 9.4 or higher. All analyses will be subject to formal verification in accordance with PharPoint's SOPs. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical reports. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

All data collected during the study will be included in data listings.

The following considerations do not apply to the population PK analyses. Considerations for those analyses will be presented in the population PK analysis plan.

8.1. Multicenter Studies

This study will enroll subjects across multiple study centers in North America, Israel, and Europe.

8.2. Other Strata and Covariates

No stratification or adjustment for covariates is planned.

8.3. Examination of Subgroups

No subgroup analyses are planned.

8.4. Multiple Comparisons and Multiplicity

No adjustment for multiple comparisons is planned.

8.5. Data Handling Conventions

8.5.1. Premature Withdrawal and Missing Data

For subjects who prematurely discontinue the study, all available data will be included for the key safety and effectiveness analyses. No imputation for missing data will occur.

Dropouts will not be replaced.

8.5.2. Missing Start and Stop Dates for Prior and Concomitant Medication

For analysis of medications, a complete date should be established to identify whether a medication was taken during the study treatment period or not. The following algorithm will be applied to handle partially reported start and stop dates for medications:

- Missing start day, but month and year present:

If study medication had been taken in the same month and year as the occurrence of the medication, then the start day of the event/medication will be assigned to the day of first dose of study medication.

Otherwise, the start day will be set to the first day of the month.

- Missing start day and month, but year present:

If study medication had been taken in the same year as the occurrence of the medication, then the start date of the medication will be assigned to the date of first dose of study 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 study termination.

However, if study termination year is greater than the year of the event/medication, then the day and month will be set to 31 December.

- Completely missing start date:

For HAE medications collected on subject diaries, the date will be set to the corresponding HAE attack date. For all other concomitant medications, a completely missing start date will be set to the treatment start date (if prior to the medication end date) or otherwise will be set to the medication end date.

In subject data listings, start and stop date of medication will be displayed as reported on the eCRF.

8.5.3. Missing Start and Stop Dates for Adverse Events

The same conventions for addressing incomplete dates for prior and concomitant medications will also be used for AEs.

8.5.4. Missing Assessment Time for Laboratory, Vital Sign, PK, or ECG Measurement

For assessments with missing times, the timepoint, if available, will be utilized to determine if the assessment occurs pre- or post-dose. For Day 1 assessments without a planned post-dose evaluation, any assessment with no associated time will be considered as obtained prior to the initiation of berotralstat (ie, pre-dose).

8.5.5. Missing AE Start Time or End Time

For AEs with missing start or end times the duration will be calculated using only dates. As noted above, AEs with missing start times that occur on Day 1 will be considered as treatment emergent.

8.5.6. Missing Time of First and Last Dose

In case of missing time for first dose, it will be assumed that baseline pre-dose measures that were to be taken prior to first dose according to the protocol were in fact taken prior to dosing.

In case the time of the last dose is not reported on the diary, time of dose will be assigned as the median dosing time from all prior doses for the subject, as subjects are to dose once per day at approximately the same time each day.

8.5.7. Incomplete Date and Time for a Subject-Reported Attack

For HAE attacks reported with a missing start/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 diary 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, and the stop time will be set to 11:59PM.

8.5.8. Missing Severity or Relationship of Adverse Events

Should an event have a missing severity code then the event will be considered to be a Grade 3 (severe) event. If an event has a missing relationship, it will be classified as being related to study treatment.

8.6. Values of Clinical Concern

QTcF intervals >500 msec or a change from baseline in QTcF > 60 msec and a simultaneous absolute QTcF > 460 msec are of clinical concern.

9. STUDY POPULATION

Tables describing the study population as noted below will present summaries by cohort unless otherwise specified.

9.1. Disposition of Subjects

Subject disposition will be presented for all subjects. The number and percentage of subjects included in the ITT, completer, safety, and PK populations will be presented by cohort. The number and percentage of subjects who complete each study part as well as the entire study and those who discontinue from the study will be provided. The reasons for early discontinuation will be presented.

A consolidated standards of reporting trials (CONSORT) diagram will be created based on the summary tables for the study report.

These data will also be listed by cohort and subject.

9.1.1. Screen Failures

The number of screen failures and percent of screened subjects who are screen failures will be summarized along with reasons for screen failure on the disposition table. A listing of demographic information for screen failures will be provided.

9.2. Protocol Deviations

Protocol deviations will be identified and displayed in data listings by cohort, subject, study day, and (where applicable) date of deviation.

9.3. Demographic and Baseline Characteristics

Demographic data and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), and HAE history will be summarized using descriptive statistics for the safety population, presented by cohort and overall. Age, height, weight, and BMI will be summarized as continuous variables. If not collected, baseline BMI will be calculated as:

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

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Demographic data, baseline characteristic data, and medical history will be listed by cohort, subject and medical history event diagnosis start date. Note that race/ethnicity is not collected from participants in France.

9.4. Listing of Subject Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be listed for each subject.

9.5. Prior and Concomitant Medications

Medications will be classified as prior or concomitant, coded using the World Health Organization Drug Dictionary (WHODrug Global B3 March 2022), and summarized by Anatomic Therapeutic Classification 4 term, preferred Term (PT), and cohort. Medications will be listed by cohort, subject, medication start date, medication stop date, and medication name.

9.6. HAE Medical and 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

A summary of the HAE Medical History information as provided on the HAE Medical History page will be provided. A summary of screening complement 4 (C4), C1-INH antigen level, and functional C1 esterase inhibitor (C1-INHf) will be provided in categories showing how subjects met the inclusion criteria confirming diagnosis of HAE. Confirmation by SERPING1 gene mutation analysis, if required, will be included in the summary. Categories for C4 will be C4 < lower limit of normal (LLN) and C4 ≥ LLN and for C1-INHf will be < 50%, 50% to < 74%, and ≥ 74%. Where the C4 test has been repeated, the test result for the repeat will be used in this summary.

Past prophylactic treatments will include those medications that were taken as prophylaxis and discontinued prior to the initiation of study treatment as recorded on the HAE Medication History Page. Past prophylactic medications will include Cinryze, Berinert, tranexamic acid, Takhzyro, HAEGARDA, and androgens. Androgens could include oxandrolone, danazol, and stanozolol.

Past on-demand treatments will include those medications that were taken as needed and discontinued prior to the initiation of study treatment as recorded on the HAE Medication History Page. Current on-demand medications will include those that are noted at screening as currently used for on-demand treatment as recorded on the HAE Medication History Page. Summaries of on-demand medications will include a grouping of any C1-INH medication as well as displays of individual medications. The C1-INH grouping will include plasma-derived C1-INH replacement (Firazyr, Cinryze on-demand, Berinert on-demand, Kalbitor) and recombinant C1-INH replacement (Ruconest). Fresh frozen plasma, a source of C1-INH, will also be considered an on-demand treatment and included with the plasma derived C1-INH replacements.

In addition, detailed SERPING data (laboratory confirmed or historically obtained) will be listed if provided.

9.7. Baseline Physical Examination

Physical examination findings, including baseline, will be listed.

9.8. Baseline Effectiveness Evaluations

All HAE attacks (subject-reported and adjusted) will be summarized on the corresponding effectiveness.

9.9. Exposure

The number and percentage of subjects exposed to berotralstat, and the duration of exposure (days) will be summarized by cohort. Individual dosing data will be listed by cohort, subject, and study day. Subjects who change doses over time will be noted.

Treatment adherence, dose interruptions, and reason for dose interruptions will be provided as summaries or listed as appropriate.

10. CLINICAL PHARMACOLOGY DATA ANALYSES

10.1. Pharmacokinetic Analyses

10.1.1. PK Concentrations

Analyses of concentration data will be performed using the PK population. All BCX7353 concentration data will be listed by subject, cohort, and time. The PK concentration data collected during the Week 2 visit will be summarized by cohort and overall, by nominal time. Concentration data from timed samples following dose modifications will also be summarized by cohort and overall, by nominal collection window. Concentration data from untimed samples will not be summarized as the nominal time of PK blood sample collection was not pre-specified; however, these concentrations will be included in the concentration listing.

For calculation of summary statistics for BCX7353 concentration data, concentrations that are below the limit of quantification (BLQ) will be treated as zero. Individual BLQ concentrations may alternatively be set to missing if deemed appropriate by the clinical pharmacologist (eg, BLQ result is implausible based on the totality of available data). If any values are set to missing for concentration analyses, this will be described in the CSR along with the rationale for doing so. These values will be reported as "BLQ" in individual-subject summaries (including listings) with a flag to denote the rationale for excluding in calculation of summary statistics.

If ≥ 33% of the available concentration values at a given timepoint (or interval) are BLQ, only the number of samples, minimum, and maximum will be included in the summary tables. All other descriptive statistics parameters will be reported as "NC" (not calculable).

10.1.2. PK Parameter Calculation

PK parameters will be calculated using noncompartmental and population PK methods.

Standard noncompartmental methods will be used to calculate the following individual subject PK parameters from observed plasma concentrations: C_{max}, area under the concentration-time curve from time 0 to the last measurable concentration ($AUC_{0\text{-}last}$), area under the concentration-time curve from time 0 to 6 hours post-dose ($AUC_{0\text{-}6}$), time to C_{max} (T_{max}), last measurable concentration (C_{last}), and time to C_{last} (T_{last}) as data permit. Noncompartmental analyses will not be conducted for subjects in Cohort 4 due to the limited PK sampling in this group. Descriptive statistics will be calculated for each parameter and may be stratified by cohort and dosing regimen as appropriate.

Population PK modeling approach will be used to estimate the following PK parameters: AUC over the dosing interval (AUC_{tau}) at steady state, C_{max} at steady state, T_{max}, average plasma concentration (C_{avg}) at steady state, concentration at the end of a dosing interval (C_{trough}) at steady state, apparent clearance (CL/F), and apparent total volume of distribution (Vss/F). Detailed methods for the population PK modeling approach can be found in the population PK analysis plan. The results of these analyses will be reported in the stand-alone pharmacometric report.

10.2. Pharmacodynamic and Biomarker Analyses

Not applicable.

11. SAFETY AND TOLERABILITY ANALYSES

Tables in this section will present summaries by cohort unless otherwise specified.

11.1. Adverse Events

AEs will be assessed and recorded from the time of signing of the informed consent through the last follow-up visit or until the AE is resolved or the subject is in a clinically stable condition with regards to the AE. AEs will be assigned as pre-treatment, treatment-emergent, or post-treatment according to the start date of the event. Events occurring prior to the start of study drug (ie, berotralstat) will be considered pretreatment and any AE reported as related to treatment will be attributed to SOC treatment and not berotralstat. Events starting on or after the initiation of study drug (ie, berotralstat) in Part 1 will be considered treatment-emergent or post-treatment and any AE reported as related to treatment during these periods will be assigned to berotralstat.

AEs will be mapped to system organ classification and PT using MedDRA version 25.0. Relationship to study drug will be assessed as not related or related. AEs will be graded according to the DAIDS table for grading the severity of adult and pediatric AEs (Publish date July 2017, see Protocol Appendix Section 15.1). AEs not covered by the DAIDS table will be assessed and classified into 1 of 5 severity categories: mild, moderate, severe, life-threatening, and death, corresponding to toxicity Grades 1 through 5. Should an event have a missing relationship or severity, these events will be classified as ‘related’ or ‘severe’.

The duration of AEs in days will be derived and presented in all listings; this value is calculated as (AE stop date/time – AE start date/time). Both start and stop dates must be present to calculate a duration. Duration will not be calculated if either the start or stop date is imputed.

No events of special interest have been identified in this protocol.

TEAEs are defined as AEs that occurred on or after first dose of berotralstat through 30 days post discontinuation of study treatment. All AEs that occurred prior to the initiation of berotralstat or those recorded after 30 days after the last dose of berotralstat will be excluded from the tables but will be included in the listings. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

An overall summary of AEs will be produced to summarize the number and percentage of subjects reporting:

- Any TEAE
- Any treatment-emergent SAE (TESAE)
- Any drug related TEAE
- Any drug related TESAE

- Any Grade 3 or Grade 4 TEAE
- Any drug-related Grade 3 or Grade 4 TEAE
- Any TEAE leading to interruption of study drug (berotralstat)
- Any TEAE leading to discontinuation of study drug (berotralstat)
- Any TEAE leading to death.

TEAEs will be summarized by system organ class, PT, and cohort. TEAEs will also be summarized by system organ class, PT, severity, and cohort. TEAEs considered to be related to study drug will be summarized by system organ class, PT, and cohort. TESAEs will be summarized by system organ class, PT, and cohort. In addition, tables and listings of subjects who reported a TEAE with a preferred term that is included in the Hypersensitivity (narrow terms), Anaphylactic Reaction (narrow and broad terms) or Severe Cutaneous Reactions (narrow terms) standardized MedDRA queries (SMQs) will be generated. In addition, a table and listing will be generated for subjects who report either a TEAE with a preferred term that is included in the Torsade de Pointes (TdP)/QT prolongation SMQ or a TEAE with the preferred term Palpitation.

AEs, SAEs, and TEAEs considered to be related to study drug will be listed separately by treatment group, cohort, subject, and start date, showing system organ class, PT, and verbatim term.

An overall summary of AEs reported in the SOC period will be produced to summarize the overall number and percentage of subjects reporting:

- Any AE
- Any SAE
- Any drug related AE
- Any Grade 3 or Grade 4 AE
- Any AE leading to death.

A summary table of AEs reported in the SOC period will be presented overall by system organ class and PT. All AEs reported during the SOC will be listed.

11.2. Exposure to Study Treatment and Treatment Compliance

The number of subjects exposed to study treatment and the number of subjects who discontinue treatment early will be presented on the disposition table. A summary of exposure to study treatment will also be presented. Listings of exposure to study treatment and of drug accountability will be provided by subject and treatment. Kaplan-Meier plots of duration of study

treatment (eg, time to discontinuation) will be provided. Subjects who discontinue study drug but continue to receive berotralstat via another mechanism will be considered completers.

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

For compliance (%) for the study period of interest based on the drug accountability page of the eCRF: $Number\ of\ Capsules\ or\ Packets\ Taken$

$= Number\ of\ Capsules\ or\ Packets\ Dispensed -$
$Number\ of\ Capsules\ or\ Packets\ Returned -$ *Number of Lost Capsules or Packets*

$$Expected\ Number\ of\ Tablets\ or\ Packets\ Taken$$
$$= \sum_{i=1}^{k} (\text{CEILING}[dose_i\ x \times (Date\ of\ the\ Last\ Dose\ of\ Dose\ i - Date\ of\ the\ First\ Dose\ of\ Dose\ i + 1)] - [Interrupted_i])$$

$$= (\text{CEILING}[dose_1 \times (Date\ of\ the\ Last\ Dose\ of\ Dose\ 1 - Date\ of\ the\ First\ Dose\ of\ Dose\ 1 + 1\ )] - [Interrupted_1]) + \cdots + (\text{CEILING}[dose_k \times (Date\ of\ the\ Last\ Dose\ of\ Dose\ k - Date\ of\ the\ First\ Dose\ of\ Dose\ k + 1)] - [Interrupted_k])$$

where i refers to the dosing period, $dose_i$ is the per day dosing frequency for Period i, $Interrupted_i$ is the number of dose interruptions for Period i, and k is the last period that dose changed. Subjects dose may change between visits; in this case the current dosing period will be split where the day before dose change will be the end of the prior period (and will retain the original frequency as specified at the start of the period) and a new period will begin the day of the change and $dose_i$ will be adjusted to the new dosing frequency based on the case report form (CRF) specified frequency change. In the event a subject has not taken a dose on date of change or interruption (as specified in the CRF) and the frequency changed from a daily regimen ('Once daily' or '2 packets daily') to 'Every other day', the prior dosing period will end the date before the date of change and the new dosing period will begin the day following the date of dose change. In the case of missing interruptions for a given period, the number of dose interruptions for that period will be imputed as zero. In the case of missing values for number of capsules or packets returned or number of lost capsules or packets for a given period, data for that dosing period will be considered missing and will be excluded in the calculation of compliance.

Treatment compliance based on dispensing information will be calculated for each study treatment that the subject received as follows:

$$\text{Treatment Compliance (Dispensed)} = \frac{Number\ of\ Capsules\ or\ Packets\ Taken}{Expected\ Number\ of\ Capsules\ or\ Packets\ Taken} \times 100$$

Treatment compliance will be listed and summarized for Part 1, defined as Day 1 to Week 12; Part 2, defined as Week 13 to 48; and overall.

A categorical summary of treatment compliance will be produced with the following categories shown in Table 6.

Table 6: Definition of Compliance Categories

Compliance	Range of Compliance (%)
Poor compliance	<80%
Acceptable compliance	80% – <90%
Good compliance	90% – 110%
Over-dosing	> 110%

Treatment compliance will also be calculated between scheduled visits (or between the final dispense date and the final return date) like above with the following changes for Part 1 only. The expected number of capsules or packets will be computed as the number of capsules or packets expected between scheduled dispense dates. Drug will be assumed to have been taken during the period after the drug was dispensed, if the bottle or empty packet is returned, regardless of the return date. Visits for which no bottles or empty packets are returned at any time are considered missing data and compliance is not calculated in these cases. Note that this calculation does not consider any protocol allowable study drug interruptions.

11.3. Clinical Laboratory Evaluations

Non-PK blood and urine samples will be obtained per the schedule of assessments in Table 2.

Laboratory test results and change from baseline will be summarized by panel, parameter, time point, and cohort. Laboratory results, including laboratory normal ranges, will be listed by cohort, subject, parameter, and time point.

11.3.1. Analysis of Abnormal Laboratory Values

Laboratory abnormalities will be graded according to the DAIDS (also see Section 6.7.6). Treatment-emergent graded toxicities are defined in Section 6.7.6 (including exceptions) and the number and percentage of subjects who experience treatment-emergent graded toxicities will be summarized by panel, parameter, time point, and cohort.

Laboratory toxicity shifts from baseline to worst post-baseline grade will be summarized by panel, parameter, toxicity grade, and cohort.

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments (where “and” indicates elevations occurring at the same visit). Within each treatment group and laboratory parameter grouping, a subject may be counted once per elevation criteria using the worst-case result. That is, a subject with a worst-case alanine transaminase (ALT) elevation >3 × the ULN for a given treatment group would be counted once in the ALT > 1.5 × ULN category and once in the ALT > 3 × ULN

category, regardless of how many ALT elevations the subject had that met the > 3 × ULN and > 1.5 × ULN elevation criteria.

- ALT and/or aspartate transaminase (AST) > 3 × ULN and total bilirubin > 1.5 or 2 × ULN
- AST > 1.5, 3, 5, 10, and 20 × ULN
- ALT > 1.5, 3, 5, 10, and 20 × ULN
- Total bilirubin > 1, 1.5, or 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN

Profiles of liver enzymes and bilirubin over time will be graphically displayed for subjects with any Grade 3 or 4 abnormality in these analytes. In addition, a listing of all liver function test (ALT, AST, bilirubin, ALP, gamma-glutamyl transferase) results for subjects experiencing a treatment-emergent Grade 3 or 4 liver function test will be provided.

In addition, a Hy's law plot, a shift plot showing liver safety panel tests over time (baseline vs. on-study), and distribution plots of ALT, AST, ALP, bilirubin, cholesterol, and triglycerides over time will be produced using the format recommended by the Food and Drug Administration (FDA)/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). Note that triglyceride data will be summarized separately for fasted and non-fasted values. The plots to be included are the scatter plot of maximum transaminase versus maximum bilirubin, the liver test safety panel over time and the distribution of ALT by time and treatment. The distribution plots for AST, ALP, bilirubin, cholesterol, and triglycerides will use the same format as is used for ALT.

11.3.2. Complement Factors and HAE Diagnosis

Laboratory results related to HAE diagnosis, including complement factors C1-INHAg, C1-INHf, and C4 will be included in summaries of laboratory data. Criteria used to confirm diagnosis of HAE Type I or II will be summarized and listed as described in Section 9.6.

11.4. Pregnancy

A listing of positive pregnancy test results, if applicable, will be provided.

11.5. ECGs

A standard bedside or routine 12-lead ECG will be obtained as scheduled in Table 2. Baseline (pre-dose) ECGs will be obtained in triplicate and all other ECGs will be single assessments. For the purposes of deriving baseline values, any triplicate ECGs collected prior to dosing on Day 1 will be averaged, by using the arithmetic mean.

Descriptive summaries of ECG parameters (PR, QRS, QT, QTc, QTcF, QTcB, RR, heart rate) will be presented by parameter, time point, and cohort. ECG interpretations (normal, abnormal, abnormal clinically significant) will be presented by time point and cohort.

The number and percentage of subjects with QTcF values will be summarized by category for ranges (≤ 450, >450 and ≤470, >470 and ≤500, and > 500 msec) and increase-from-baseline ranges (< 30, 30 to 60, and > 60 msec) by time point and treatment group. In addition, QTcF and PR change over time will be plotted over time.

ECG results will be listed by cohort, subject, parameter, and time point.

11.6. Vital Signs

Descriptive summaries of vital signs (blood pressure, temperature, pulse, respiratory rate, height, weight, BMI) and change from baseline vital signs will be presented by parameter, time point, and cohort. Vital signs and physical examination results will each be listed by cohort, subject, and time point.

12. EFFECTIVENESS ANALYSES

12.1. Analysis of the Effectiveness Endpoints

The effectiveness analysis is comprised of multiple endpoints (Section 3.2.2) and will be conducted on the safety population. Some endpoints will also be summarized using the 12-week or 48-week completer populations. All effectiveness analysis will be performed for observations that occur from Day 1 (first dose of berotralstat) through Week 12 and, separately and for Day 1 through Week 48, unless otherwise noted. Rate of HAE attacks will also be calculated at steady state (after Week 2) through the Week 12 visit and through the Week 48 visit. In general, summaries will be provided by cohort and for all subjects.

12.1.1. HAE Attack Rate

The number of subject-reported and adjusted HAE attacks will be analyzed by cohort using appropriate descriptive statistics. The adjusted attack rate (expressed as attacks/month) will be presented by month as well as by study part.

12.1.2. Number and Proportion of Days with Angioedema Symptoms

The number and proportion of days with angioedema symptoms reported from subject-reported and adjusted attacks will be summarized by study part using descriptive statistics.

12.1.3. Discontinuations Due to Lack of Efficacy

The number of subjects who discontinue due to lack of efficacy will be provided in the Subject Disposition table and will be summarized and noted as part of the CONSORT diagram when generated.

12.1.4. Attack Characteristics

Characteristics of subject-reported and adjusted attacks, including location of attack, duration of attacks from start to finish and from start to the time the worst symptoms of the attack were over, triggers, swelling, other symptoms, whether the attack was treated, parent or caregiver assessment of severity by the subject's ability to do daily activities, appearance affected, professional care sought, and location of professional care will be summarized by study part as well as across the study and provided as a listing.

A summary of duration of abdominal, non-abdominal, and mixed attacks will also be provided for subject-reported and adjusted HAE attacks.

12.1.5. Use of HAE Medications

Use of targeted HAE medications as noted in the subject diary will be summarized separately from concomitant medications as noted in Section 6.7.7.7. In addition, summaries of the number of subject-reported HAE attacks requiring treatment will be provided.

The subject-reported and adjusted attack rates of attacks requiring treatment with targeted HAE medications will be summarized as noted in Section 6.7.7.7.

12.1.6. Hospitalizations and Clinic Visit due to HAE

The average number of hospitalizations and clinic visits due to HAE from Week 1 through Week 12 and Week 1 through Week 48 will be summarized.

13. EXPLORATORY ANALYSES

The TASTY Scale is being used to assess the palatability of berotralstat granules formulation (108 mg, 96 mg, 78 mg), specifically for subjects enrolled in Cohorts 2 to 4. The TASTY Scale should be administered at the Baseline (Day 1) visit. The scale is from 0 to 6, with 0 being the lowest level ("dislike" the taste) and 6 being the highest level ("tasty").

The number and percentage of subjects for each scale level will be summarized by cohort and for all subjects. These data will be listed.

14. ATTACHMENTS

14.1. Table of Contents for Data Display Specifications

This table of contents provides the expected titles and numbers of the tables, listings, and figures of the final report. Changes to titles or numbering in the final report, additional data listings supporting the tables, or displays being split into multiple smaller displays for clarity will not necessitate a revision to the SAP, nor will they be considered a deviation from planned analyses.

Table 7: Data Displays

Tables and Figures

X= included in analysis

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X	X	X	14.1.1.1	Subject Disposition	All Subjects
X	X	X	14.1.1.2	CONSORT Diagram	All Subjects
X			14.1.2.1.1.1	Summary of Subjects by Country and Site	All Subjects
X			14.1.2.1.1.2	Summary of Subjects by Country and Site	Safety
X	X		14.1.2.1.2	Analysis Populations	All Subjects
X			14.1.2.2	Confirmation of Clinical Diagnosis of HAE	All Subjects
X			14.1.2.3.1	Inclusion/ Exclusion Criteria	All Subjects
X			14.1.2.3.2	Inclusion/Exclusion Criteria Violations	Screen Failures
X		X	14.1.3.1.1	Demographic and Baseline Characteristics	Safety
X			14.1.3.1.2	Demographic and Baseline Characteristics for Screening Failures	Screen Failures
X			14.1.3.2	Summary of Subject-Reported HAE Baseline Characteristics - HAE Medical History	Safety
X	X	X	14.1.3.3.1	Past Prophylactic Medications for HAE	Safety

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X			14.1.3.3.2	Reasons for Discontinuation of Past Prophylactic Medications for HAE	Safety
X	X	X	14.1.3.4.1	Summary of Current On-Demand Treatments of HAE	Safety
X			14.1.3.4.2	Summary of Adjusted Attack Baseline HAE Characteristics - Retreatment of Acute HAE Medications	Safety
X			14.1.4.1	Summary of Medications Taken within 30 Days of Screening and Discontinued Prior to Dosing	Safety
X	X	X	14.1.4.2	Summary of Concomitant Medications	Safety
X	X	X	14.1.4.3	Summary of Concomitant Medications for HAE	Safety
X	X		14.1.4.4.1	Summary of Concomitant Medications for Acute Treatment of Angioedema Attacks – Attack Level	Safety
X	X*		14.1.4.4.2	Summary of Concomitant Medications for Acute Treatment of Angioedema Attacks – Attack Level During Weeks 1-12	Week 12 Completer
X	X		14.1.4.4.3	Summary of Concomitant Medications for Acute Treatment of Angioedema Attacks – Attack Level During Weeks 1-48	Week 48 Completer
X	X	X	14.1.5.1.1	Treatment Exposure and Compliance	Safety
X	X*		14.1.5.1.2	Treatment Exposure and Compliance During Weeks 1-12	Week 12 Completer
X	X		14.1.5.1.3	Treatment Exposure and Compliance During Weeks 1-48	Week 48 Completer
X	X	X	14.1.5.2	Plot of Duration of Exposure to Study Drug	Safety
X			14.2.1.1.1	Summary of Plasma BCX7353 Concentrations (ng/mL) at Week 2	PK
X			14.2.1.1.2	Summary of Plasma BCX7353 Concentrations (ng/mL) Following Dose Modifications	PK
X			14.2.1.2.1	Summary of BCX7353 PK Parameters (New table to be specified by PK group)	PK
X	X		14.2.2.1.1	Summary of HAE Adjusted Attack Rate	Safety
X	X		14.2.2.1.2	Summary of HAE Adjusted Attacks Rate After Week 2	Safety
X	X		14.2.2.1.3	Summary of HAE Adjusted Attack Rate, During Weeks 1-12	Safety
X	X		14.2.2.1.4	Summary of HAE Adjusted Attack Rate, During Weeks 1-48	Safety

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X	X		14.2.2.1.5	Summary of HAE Adjusted Attack Rate, During Weeks 1-12	Week 12 Completer
X	X		14.2.2.1.6	Summary of HAE Adjusted Attack Rate, During Weeks 1-48	Week 48 Completer
X			14.2.2.1.7	Summary of HAE Adjusted Attack Rate during the SOC Period	Safety
X			14.2.2.2.1	Summary of HAE Adjusted Attacks	Safety
X	X		14.2.3.2.1	Mean HAE Adjusted Attack Rate by Month	Safety
X	X*		14.2.3.2.2	Mean HAE Adjusted Attack Rate by Month, During Weeks 1-12	Week 12 Completer
X	X		14.2.3.2.3	Mean HAE Adjusted Attack Rate by Month, During Weeks 1-48	Week 48 Completer
X	X		14.2.3.3.1	Summary of Duration of Adjusted Attacks (hours)	Safety
X	X*		14.2.3.3.2	Summary of Duration of Adjusted Attacks (hours), During Weeks 1-12	Week 12 Completer
X	X		14.2.3.3.3	Summary of Duration of Adjusted Attacks (hours), During Weeks 1-48	Week 48 Completer
X			14.2.3.4.1	Summary of Attack Characteristics for Adjusted Attacks During the SOC Period	Safety
X	X		14.2.3.4.2	Summary of Attack Characteristics for Adjusted Attacks	Safety
X	X*		14.2.3.4.3	Summary of Attack Characteristics for Adjusted Attacks, During Weeks 1-12	Week 12 Completer
X	X		14.2.3.4.4	Summary of Attack Characteristics for Adjusted Attacks, During Weeks 1-48	Week 48 Completer
X			14.2.3.5.1	Summary of Attack Locations for Adjusted Attacks During the SOC Period	Safety
X	X		14.2.3.5.2	Summary of Attack Locations for Adjusted Attacks	Safety
X	X*		14.2.3.5.3	Summary of Attack Locations for Adjusted Attacks During Weeks 1-12	Week 12 Completer
X	X		14.2.3.5.4	Summary of Attack Locations for Adjusted Attacks During Weeks 1-48	Week 48 Completer

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X			14.2.3.6.1	Summary of HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications during the SOC Period	Safety
X	X		14.2.3.6.2	Summary of HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications	Safety
X	X*		14.2.3.6.3	Summary of HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications During Weeks 1-12	Week 12 Completer
X	X		14.2.3.6.4	Summary of HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications During Weeks 1-48	Week 48 Completer
X	X		14.2.3.7.1	Mean HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications by Month	Safety
X	X*		14.2.3.7.2	Mean HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications by Month During Weeks 1-12	Week 12 Completer
X	X		14.2.3.7.3	Mean HAE Adjusted Attack Rate for Attacks Requiring Treatment with Targeted HAE Medications by Month During Weeks 1-48	Week 48 Completer
X	X		14.2.4.1.1	Summary of Number and Proportion of Days with Angioedema Symptoms from Adjusted Attacks	Safety
X	X*		14.2.4.1.2	Summary of Number and Proportion of Days with Angioedema Symptoms from Adjusted Attacks During Weeks 1-12	Week 12 Completer
X	X		14.2.4.1.3	Summary of Number and Proportion of Days with Angioedema Symptoms from Adjusted Attacks During Weeks 1-48	Week 48 Completer
X	X		14.2.5.1	Plot of Mean and Median Adjusted HAE Rate by Month	Safety
X	X*		14.2.5.2	Plot of Mean and Median Adjusted HAE Rate by Month During Weeks 1-12	Week 12 Completer
X	X		14.2.5.3	Plot of Mean and Median Adjusted HAE Rate by Month During Weeks 1-48	Week 48 Completer
X	X		14.2.5.4	Plot of Mean and Median Subject Reported HAE Rate by Month	Safety
X	X*		14.2.5.5	Plot of Mean and Median Subject Reported HAE Rate by Month During Weeks 1-12	Week 12 Completer

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X	X		14.2.5.6	Plot of Mean and Median Subject Reported HAE Rate by Month During Weeks 1-48	Week 48 Completer
X			14.2.6.1	Summary of Average Number of Hospitalizations and Clinic Visits During the SOC Period	Safety
X	X		14.2.6.2	Summary of Average Number of Hospitalizations and Times Subject Sought Medical Care	Safety
X	X*		14.2.6.3	Summary of Average Number of Hospitalizations and Times Subject Sought Medical Care During Weeks 1-12	Week 12 Completer
X	X		14.2.6.4	Summary of Average Number of Hospitalizations and Times Subject Sought Medical Care During Weeks 1-48	Week 48 Completer
X	X	X	14.3.1.1.1	Overall Summary of Treatment-emergent Adverse Events	Safety
X			14.3.1.1.2	Summary of Treatment-emergent Adverse Events, Part 1	Safety
X	X	X	14.3.1.2.	Subjects Reporting Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.3	Subjects Reporting Treatment-emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Severity	Safety
X	X	X	14.3.1.4	Subjects Reporting Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.5.1	Subjects Reporting Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.5.2	Subjects Reporting Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term, Part 1	Safety
X	X	X	14.3.1.5.3	Subjects Reporting Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term, Part 1 and 2	Safety
X	X	X	14.3.1.6	Subjects Reporting Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.7	Subjects Reporting Treatment-emergent Grade 3 or Grade 4 Adverse Events by MedDRA System Organ Class and Preferred Term	Safety

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X	X	X	14.3.1.8	Subjects Reporting Drug-related Treatment-emergent Grade 3 or Grade 4 Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.9	Subjects Reporting Treatment-emergent Adverse Events Leading to the Interruption of Study Drug by System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.10	Subjects Reporting Treatment-emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety
X	X	X	14.3.1.11	Most Frequently Reported Treatment-emergent Adverse Events	Safety
X	X	X	14.3.1.12	Subjects Reporting Special Situation Events	Safety
X	X	X	14.3.1.13.1	Subjects Reporting Treatment-emergent Adverse Events in the Hypersensitivity SMQ	Safety
X	X	X	14.3.1.13.2	Subjects Reporting Treatment-emergent Adverse Events in the Anaphylactic Reaction SMQ	Safety
X	X	X	14.3.1.13.3	Subjects Reporting Treatment-emergent Adverse Events in the Severe Cutaneous Adverse Reaction SMQ	Safety
X	X	X	14.3.1.13.4	Subjects Reporting Treatment-emergent Adverse Events in the Hypersensitivity, Anaphylactic Reaction or Severe Cutaneous Reaction SMQs	Safety
X	X	X	14.3.1.14	Subjects Reporting Treatment-emergent Adverse Events in the Torsade de pointes/QTc Prolongation SMQ or Palpitation Preferred Term	Safety
X	X	X	14.3.1.15	Overall Summary of Adverse Events During the SOC Treatment Period	Safety
X	X	X	14.3.1.16	Subjects Reporting Adverse Events During the SOC Treatment Period by MedDRA System Organ Class and Preferred Term	Safety
X	X	X	14.3.4.1.1	Summary of Observed and Change from Baseline in Clinical Chemistry Laboratory Parameters	Safety
X	X	X	14.3.4.1.2	Summary of Observed and Change from Baseline in Hematology and Coagulation Laboratory Parameters	Safety
X	X	X	14.3.4.1.3	Summary of Observed and Change from Baseline in Quantitative Urinalysis Laboratory Parameters	Safety
X	X	X	14.3.4.2.1	Summary of Elevations in Post-Baseline Liver Function Tests	Safety
X	X	X	14.3.4.2.2	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT	Safety

NDA IA	End of Part 2 (Wk 48) IA†	Final/ EOS**	Output Number	Title	Population
X	X	X	14.3.4.2.3	Liver Test Safety Panel Over Time, Baseline vs. On-Study	Safety
X	X	X	14.3.4.2.4	Distribution of Liver Tests Over Time: ALT, AST, ALP, and Bilirubin	Safety
X	X	X	14.3.4.3	Treatment-Emergent Grade 3 and 4 Laboratory Toxicities by DAIDS Grades*	Safety
X	X	X	14.3.4.4.1	Shift from Baseline to Worst Post-baseline Assessment: Clinical Chemistry	Safety
X	X	X	14.3.4.4.2	Shift from Baseline to Worst Post-baseline Assessment: Hematology and Coagulation	Safety
X	X	X	14.3.4.4.3	Shift from Baseline to Worst Post-baseline Assessment: Urinalysis	Safety
X	X	X	14.3.5.1.1	Observed and Change from Baseline in 12-Lead ECG	Safety
X	X	X	14.3.5.1.2	12-Lead ECG Interpretation	Safety
X	X	X	14.3.5.1.3	12-Lead ECG QTcF Interval Categories	Safety
X	X	X	14.3.5.2.1	Observed and Change from Baseline in Vital Signs	Safety
X	X	X	14.3.5.3.1.1	Plot of Mean (SD) QTcF Observed Changes Relative to Baseline Over Time	Safety
X	X	X	14.3.5.3.1.2	Distribution Plots for QTcF Observed Changes Relative to Baseline Over Time	Safety
X	X	X	14.3.5.3.1.3	Distribution Plots for QTcF Observed Changes Relative to Baseline – All Observations	Safety
X	X	X	14.3.5.3.2.1	Plot of Mean (SD) PR Interval Observed Changes Relative to Baseline Over Time	Safety
X	X	X	14.3.5.3.2.2	Distribution Plots for PR Interval Observed Changes Relative to Baseline Over Time	Safety
X	X	X	14.3.5.3.2.3	Distribution Plots for PR Interval Observed Changes Relative to Baseline – All Observations	Safety
X	X	X	14.3.5.3.3.1	Plot of Mean (SD) QRS Observed Changes Relative to Baseline Over Time	Safety
X	X	X	14.3.5.3.3.2	Distribution plots for QRS Changes Relative to Baseline Over Time	Safety
X	X	X	14.3.5.3.3.3	Distribution plots for QRS Changes Relative to Baseline – All Observations	Safety
X			14.4.1.1	Acceptability/Palatability of the Berotralstat Oral Granules (limited to Cohort 2, 3, 4)	Safety

Listings:

NDA IA	End of Part 2 (Wk 48) IA	Final (Safety)	Listing Number	Title	Population
X	X	X	16.2.1.1	Informed Consent	All Subjects
X			16.2.1.2	Screen Failures	Screen Failures
X			16.2.2.1	Inclusion Criteria Not Met/Exclusion Criteria Met	ITT
X	X	X	16.2.2.2	Protocol Deviations	ITT
X	X	X	16.2.2.3	End of Study	ITT
X	X	X	16.2.3.1	Analysis Populations	ITT
X			16.2.3.2	Enrollment by Country and Site	ITT
X	X		16.2.4.1	Demographic and Baseline Characteristics	ITT
X			16.2.4.2	Confirmation of Clinical Diagnosis of HAE	All Subjects
X			16.2.4.3.1	Medical History	ITT
X			16.2.4.3.2	HAE Medical History – HAE Baseline Characteristics	ITT
X	X	X	16.2.4.3.3	HAE Medication History – Past and Current On-Demand HAE Treatment	ITT
X			16.2.4.3.4	HAE Medication History – Past Prophylactic HAE Treatment	ITT
X			16.2.4.4.1	Medications Taken within 30 Days of Screening and Discontinued Prior to Study Drug Initiation	ITT
X	X	X	16.2.4.4.2	Concomitant Medications	ITT
X	X	X	16.2.4.4.3	Use of Concomitant Medications for HAE	ITT
X	X	X	16.2.5.1	Drug Accountability and Compliance	ITT
X	X	X	16.2.5.2	Subjects with a Change in Dosing (All Doses)	Safety
	X		16.2.5.3	Plasma BCX7353 Pharmacokinetic Concentration Time Data	ITT
X	X		16.2.6.1.1	HAE Attack Diary Detail	ITT
X	X		16.2.6.1.2	HAE Attack Level Summary – Adjusted Attacks	ITT
X	X		16.2.6.1.3	HAE Attack Rate	ITT
X	X		16.2.6.2	Days with Angioedema Symptoms from Adjusted Attacks	ITT
X	X		16.2.6.3	Subject-Level Additional Derived Effectiveness Endpoint Profile	ITT
X		X	16.2.7.1.1	Adverse Events During the SOC Treatment Period	Safety
X		X	16.2.7.1.2	Serious Adverse Events During the SOC Treatment Period	Safety

X	X	X	16.2.7.2.1	Treatment-emergent Adverse Events	Safety
X	X	X	16.2.7.2.2	Serious Treatment-emergent Adverse Events	Safety
X	X	X	16.2.7.2.3	Related Serious Adverse Events	Safety
X	X	X	16.2.7.2.4	Treatment-emergent Adverse Events Related to Study Drug	Safety
X	X	X	16.2.7.2.5	Grade 3 or 4 Treatment-emergent Adverse Events	Safety
X	X	X	16.2.7.2.6.1	Subjects Reporting Treatment-emergent Adverse Events in the Hypersensitivity SMQ	Safety
X	X	X	16.2.7.2.6.2	Subjects Reporting Treatment-emergent Adverse Events in the Anaphylactic Reaction SMQs	Safety
X	X	X	16.2.7.2.6.3	Subjects Reporting Treatment-emergent Adverse Events in the Severe Cutaneous Adverse Reaction SMQ	Safety
X	X	X	16.2.7.2.7	Subjects Reporting Treatment-emergent Adverse Events in the Torsade de pointes/QT Prolongation SMQ or Palpitation Preferred Term	Safety
X	X	X	16.2.7.2.8	Treatment-emergent Adverse Events Leading to Interruption of Study Drug	Safety
X	X	X	16.2.7.2.9	Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug	Safety
X	X	X	16.2.7.2.10	Fatal Serious Treatment-emergent Adverse Events	Safety
X	X	X	16.2.8.1.1	Laboratory Results - Clinical Chemistry	Safety
X	X	X	16.2.8.1.2	Laboratory Results – Hematology	Safety
X	X	X	16.2.8.1.3	Laboratory Results - Coagulation	Safety
X	X	X	16.2.8.1.4	Laboratory Results - Urinalysis	Safety
X	X	X	16.2.8.1.5	Grade 3 or 4 Laboratory Results	Safety
X			16.2.8.1.6	Laboratory Results – C1-INH Level, C1-INH Function and Screening C4	Safety
X			16.2.8.2	Laboratory Results - SERPING-	Safety
X	X	X	16.2.8.3	Pregnancy Tests	Safety
X	X	X	16.2.8.4	12-Lead Electrocardiogram	Safety
X	X	X	16.2.8.5	Vital Signs, Height, Weight, and BMI	Safety
X	X	X	16.2.8.6	Physical Examinations	Safety
X			16.2.9.1	Acceptability/Palatability of the Berotralstat Oral Granules	Safety

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; C1-INH = C1-esterase inhibitor; C4 = complement 4; CONSORT = consolidated standards of reporting trials; DAIDS = Division of AIDS; ECG = electrocardiogram; EOS = end of study; HAE = hereditary angioedema; IA = interim analysis; ITT = intent to treat; MedDRA = Medical Dictionary for Regulatory Activities; NDA = New Drug application; PK = pharmacokinetics; QTcF = corrected QT interval using Fridericia's formula; SD = standard deviation; SMQ = standardized MedDRA query; SOC = standard of care; Wk = week.
*Except as noted in the protocol or SAP

**These tables will also likely be included in any Safety data update required by regulatory agencies.
†Safety and dosing tables for the end of 48-week analysis will only include data through Week 48; for all other analyses, all available data will be reported unless otherwise specified.

14.2. Data Display Specifications

Mock (shell) versions of data displays for tables and listings are provided in a separate document.

15. REFERENCES

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