BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-304

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

Version 7.0: 05 November 2024

EU Clinical Trial No. 2024-511257-22-00

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

CONFIDENTIAL

INVESTIGATOR'S AGREEMENT

Protocol No: BCX7353-304

Protocol 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

Date: Version 7.0: 05 November 2024

I have received and read the Investigator's Brochure for berotralstat. I have read the Study BCX7353-304 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol: Study BCX7353-304.

_____

Investigator's Signature Date

_____

Name (Print)

1. SYNOPSIS

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
Berotralstat, BCX7353

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

Protocol Number: BCX7353-304	**Phase: 3**	**Countries: Multiple study centers in North America, Israel, and Europe**

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

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

Primary Objective:

- 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 Objectives:

- 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 Objective:

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

Primary Endpoint:

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

Secondary Endpoints:

- 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 Endpoint:

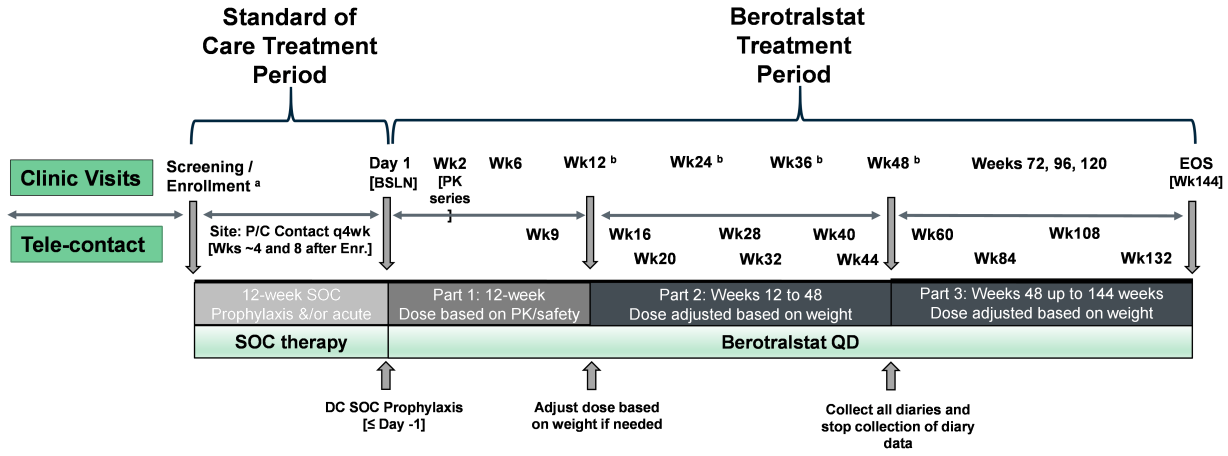
- Age-appropriate questionnaire for palatability/acceptability of berotralstat oral granules as assessed by the site following the first dose

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 cohort will occur prior to dosing subjects in Cohorts 3 and 4 with berotralstat. Additional dose cohort(s) may be enrolled 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.

The study schema is as follows:



Abbreviations: BSLN = Baseline; DC = discontinue; Enr = enrollment; 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 a single, random, plasma sample is collected for PK.

Pediatric patients who are considered good candidates for the study will report to the site for a screening visit. After P/C have provided informed consent, and, where appropriate, children have provided assent, screening assessments may be initiated. 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).

To monitor effectiveness, the P/C must begin recording HAE attacks in the subject's diary at the time of subject enrollment, and continue recording through Week 48 (ie, end of Part 2).

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. At the Week 48 visit, the site will collect all subject diaries.

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 exposures fall 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 should be drawn if the berotralstat dose is adjusted.

Number of subjects (planned):

Approximately 30 subjects are planned to be enrolled.

Main criteria for inclusion:

- Age 2 to < 12 years of age and weighing ≥ 12 kg
- Parent/caregiver willing and able to provide written, informed consent (with assent from the child where appropriate).
- Subjects with a clinical diagnosis of HAE. A clinical diagnosis of HAE is defined as:
  a. Screening results that document 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 lower limit of normal.

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

- In the opinion of the investigator, the subject would benefit from long-term oral prophylaxis.
- 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 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, with food. The doses for Cohorts 1, 2, 3, and 4 are shown in the table. Based on safety assessments and available PK data, 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 one or more of the cohorts or additional dose cohort(s) may be added. Subject enrollment in any one 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 (PK):

Plasma PK concentrations will be used in the population PK analysis.

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) or standard error of the mean (SEM), median, minimum, and maximum for continuous data, and frequency and percentages for categorical data. 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 performed 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 (PK):

Plasma PK data from Cohorts 1 and 2 will be used to confirm/determine weight bands for any subsequent cohorts using population PK modeling. The results of the PK analyses will be reported in a separate pharmacometric report.

Safety:

Analysis of safety and tolerability will be descriptive. For treatment-emergent adverse event (TEAE) data, both the number of subjects and 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.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BK	bradykinin
BMI	body mass index
C1-INH	C1 esterase inhibitor
C4	complement component 4
CDC	Centers for Disease Control and Prevention
CL	clearance
CL_{CR}	creatinine clearance
C_{max}	maximum plasma concentration
C_{trough}	concentration at the end of the dosing interval
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CYP	cytochrome P450
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end-of-study
EOT	end-of-treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltranspeptidase
GI	gastrointestinal
HAE	hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Explanation
HK	high-molecular-weight kininogen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product (study drug)
INR	international normalized ratio
IRB	institutional review board
ITT	intent to treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
P/C	parents and/or caregivers
P-gp	P-glycoprotein efflux pump
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PKK	prekallikrein
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SmPC	Summary of Product Characteristics
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UK	United Kingdom
US	United States

4. INTRODUCTION

4.1. Background

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

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

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.

4.2. Nonclinical Findings for Berotralstat

The principal findings of nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies of berotralstat are described in the berotralstat Investigator's Brochure (IB) and approved product labeling for Orladeyo.

4.3. Clinical Findings for Berotralstat

4.3.1. Pivotal Studies

The principal results of clinical pharmacology, PK, and clinical safety and efficacy studies of berotralstat are described in the berotralstat IB and approved product labelling for Orladeyo.

4.3.2. Data from Adolescent Patients Enrolled in Berotralstat Clinical Trials

Orladeyo has been approved in the US, EU, UK, Japan, and other countries for prophylaxis to prevent attacks of HAE in adult and pediatric patients 12 years of age and older. To support expanding the Orladeyo label to include patients aged ≥ 2 years, BioCryst is conducting this study in pediatric patients aged 2 to < 12 years and weighing ≥ 12 kg.

A detailed overview of data obtained as part of the berotralstat clinical development program in adolescent subjects is presented in the berotralstat IB. A total of 28 adolescent subjects ≥ 12 years of age who weighed at least 40 kg were enrolled in 2 studies: 6 adolescent subjects enrolled in Study 302, and 22 adolescent subjects enrolled in Study 204. The safety and efficacy/effectiveness data generated from these studies was part of the submissions for marketing authorization and supported the approval in pediatric subjects aged 12 and older.

4.4. Rationale for Study

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, Castaldo 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 approved only 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 PK of berotralstat in pediatric patients aged 2 years and older in order to expand the label and provide an oral therapeutic option for young children who suffer from this debilitating rare disease.

4.4.1. Rationale for Study Design

The European Medicines Agency (EMA) (European Medicines Agency 2006), US Food and Drug Administration (FDA) (FDA 2022), and International Council for Harmonisation (ICH) (ICH 2018) (ICH E11(R1), 2018) provide guidelines for development of therapeutics in the pediatric population. Use of berotralstat in the treatment of type 1 and 2 HAE meets the criteria specified in the FDA guidance for a PK and safety approach to extrapolation for development of drugs in the pediatric population (FDA 2022). The criteria include a sufficiently similar disease course and response to intervention compared to adult and adolescent patients to allow for exposure matching to establish efficacy. The extrapolation approach also takes into consideration safety and efficacy data obtained in studies conducted as part of the berotralstat clinical program. Therefore, Study 304 is a PK and safety study designed to satisfy the clinical study requirements for the extrapolation approach as set forth in the guidance documents.

The Paediatric Committee of the EMA formulated a positive opinion on a Paediatric Investigation Plan (PIP) for berotralstat in accordance with Regulation (EC) No 1901/2006; Study 304 is defined as a measure in the agreed PIP.

4.4.2. Rationale for Berotralstat Doses

The doses for berotralstat were determined using a population PK modelling and simulation approach. A population PK model was based on 13 berotralstat studies conducted in 771 adult and adolescent subjects. Thirteen Phase 1 to 3 studies were used to generate exposures in pediatric subjects. The weights of the simulated pediatric subjects were randomly selected from the uniform distribution with the four proposed weight ranges. For the weight group 40 kg and above, the maximum weight was 62 kg which was in the 97th percentile of body weight in pediatric subjects 12 years of age in the Centers for Disease Control and Prevention (CDC) growth charts.

Steady-state PK profiles of simulated pediatric subjects were generated for proposed weight groups of 12 to < 24 kg, 24 to < 32 kg, 32 to < 40 kg, and ≥ 40 kg. The doses for each weight group were then selected to match exposures (steady-state maximum plasma concentration [C_{max}] and concentration at the end of the dosing interval [C_{trough}] in adults).

4.4.3. Rationale for Age and Weight Range

Orladeyo is approved for patients aged 12 years and above in the US, EU, UK, Japan, and other markets. It has been noted in the EU, UK, Canada, and Switzerland labels that no subjects weighing < 40 kg were enrolled into the pivotal studies. The age and weight range for the population enrolled into this study is proposed to be 2 to < 12 years and weighing ≥ 12 kg, respectively.

Since the dose of berotralstat will be weight-based, it was necessary to select a minimum weight for study participants. The lower weight limit of 12 kg was selected based on PK modelling of the berotralstat dose in conjunction with estimated age ranges for the selected weight. Specifically, using the pediatric growth charts published by the CDC, it is expected that the target weight range (≥ 12 kg) will include pediatric patients across the target age range of 2 to < 12 years, including down to approximately 2 years (50th percentile for boys 12 kg; for girls 11 kg). It should be noted that 40 kg is approximately the 50th percentile for girls at 12 years of age; thus, it is anticipated that the number of enrolled children who weigh ≥ 40 kg will be small.

The upper age limit of < 12 years was chosen based on currently approved ages, ie, pediatric subjects who do not qualify for commercial product are eligible to participate in this study. The lower age limit was selected based on appearance of first HAE symptoms (Bork, Meng et al. 2006, Farkas 2010, Christiansen, Davis et al. 2016). Importantly, no other prophylactic therapy is approved for children from 2 to < 6 years of age. The only therapies approved for pediatric patients aged 6 to < 12 years are injectables, so having an oral prophylactic therapy available as an option for young children would represent a needed advancement in the treatment of HAE patients. While HAE attacks are rarer in young children, an increase in the number of attacks is often seen around the ages of 3 to 6 years and at puberty (Farkas 2010). Including children as young as 2 years old such that the label would include patients at that age allows for treatment to be available for young children at an age where the attack frequency and severity may increase. Of note, enrolling subjects from birth to < 2 years old is not feasible nor justifiable given that the earliest possible HAE diagnosis is at 1 year of age and patient recruitment difficulties due to the extremely low prevalence of HAE and HAE symptoms in this age group. Nevertheless, the therapeutic need is recognized for the targeted indication and therefore all other pediatric subsets (2 to < 12 years of age) will be included.

4.4.4. Rationale for Open-label Design

Several options for control groups were considered in the design of Study 304. A placebo control was not considered appropriate for this PK study, which is designed to fulfill the obligations of the full extrapolation model. An active control was also considered and was included as a question in a feasibility assessment conducted by BioCryst. In addition, BioCryst sought expert advice from Key Opinion Leaders (KOLs) to define current use of prophylaxis medications in this HAE pediatric population. Those investigations found that the use of prophylaxis in the proposed study population was extremely limited due to numerous factors, one of which was lack of an orally administered option. That is, all approved options for the prophylaxis of HAE are injectables, which are more difficult and stressful to administer to children and none of which are approved for children below the age of 6 years. As a result, use of an active control group in this study was not considered feasible. Therefore, this study is designed as an open-label study with a 12-week standard-of-care (SOC) treatment period followed by a 12-week treatment period with berotralstat (Part 1). The SOC treatment period will serve as a control for safety assessments as well as provide additional data regarding baseline attack rates in this population.

4.4.5. Berotralstat Risk Analysis

Potential risks and findings from nonclinical and clinical studies of berotralstat are discussed in Section 6 of the IB (Summary of Data and Guidance for the Investigators). Adverse reactions seen during clinical trials with berotralstat at 150 mg once daily (QD) include abdominal pain, vomiting, diarrhea, and gastroesophageal reflux disease. In the prescribing information, a warning and precaution is noted for an increase in QT prolongation which can occur at dosages higher than the recommended adolescent and adult dose of 150 mg QD.

4.4.6. Benefits of Trial Participation

Orladeyo has been approved for prophylaxis of HAE attacks in adult and pediatric patients aged 12 years and older. Therefore, subjects in this study may benefit by experiencing a reduction in the number of HAE attacks. In addition, study subjects will receive regular medical care for the duration of the study.

4.4.7. Overall Benefit-Risk Assessment

The risks from daily oral administration of berotralstat seen to date in both nonclinical and clinical studies were primarily mild, monitorable, and reversible. Based on the utility of other kallikrein inhibitors such as C1-INH and the pharmacology of berotralstat, there is an expectation of benefit to the individual subject. The information obtained from this study will support expanding the approved indication for Orladeyo down to patients aged 2 years and weighing a minimum of 12 kg. The overall benefit-risk balance is therefore considered to be acceptable.

5. TRIAL OBJECTIVES AND OUTCOME MEASURES

5.1. Objectives

5.1.1. Primary Objective

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

5.1.2. Secondary Objectives

- 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.

5.1.3. Exploratory Objective

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

5.2. Endpoints

5.2.1. Primary Endpoints

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

5.2.2. Secondary Endpoints

The secondary endpoint of safety will be measured by 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 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 frequency of attacks, duration of symptoms, anatomical location, on-demand treatment required, 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.

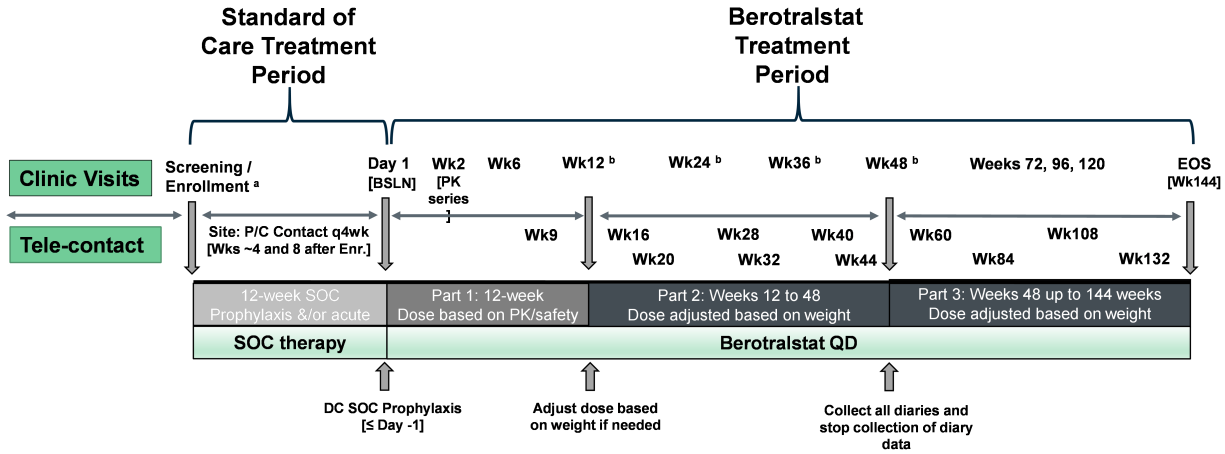
5.2.3. Exploratory Endpoints

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).

6. OVERALL STUDY DESIGN AND PLAN

This is a sequential, three-part, open-label study. A subject's participation in this study is expected to be a minimum of 24 weeks in the SOC treatment period through Part 1 of the study and up to an additional 132 weeks in Parts 2 and 3. A schematic of study visits is shown in Figure 1.

Figure 1: Study Schema



Abbreviations: BSLN = Baseline; DC = discontinue; Enr = enrollment; 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.

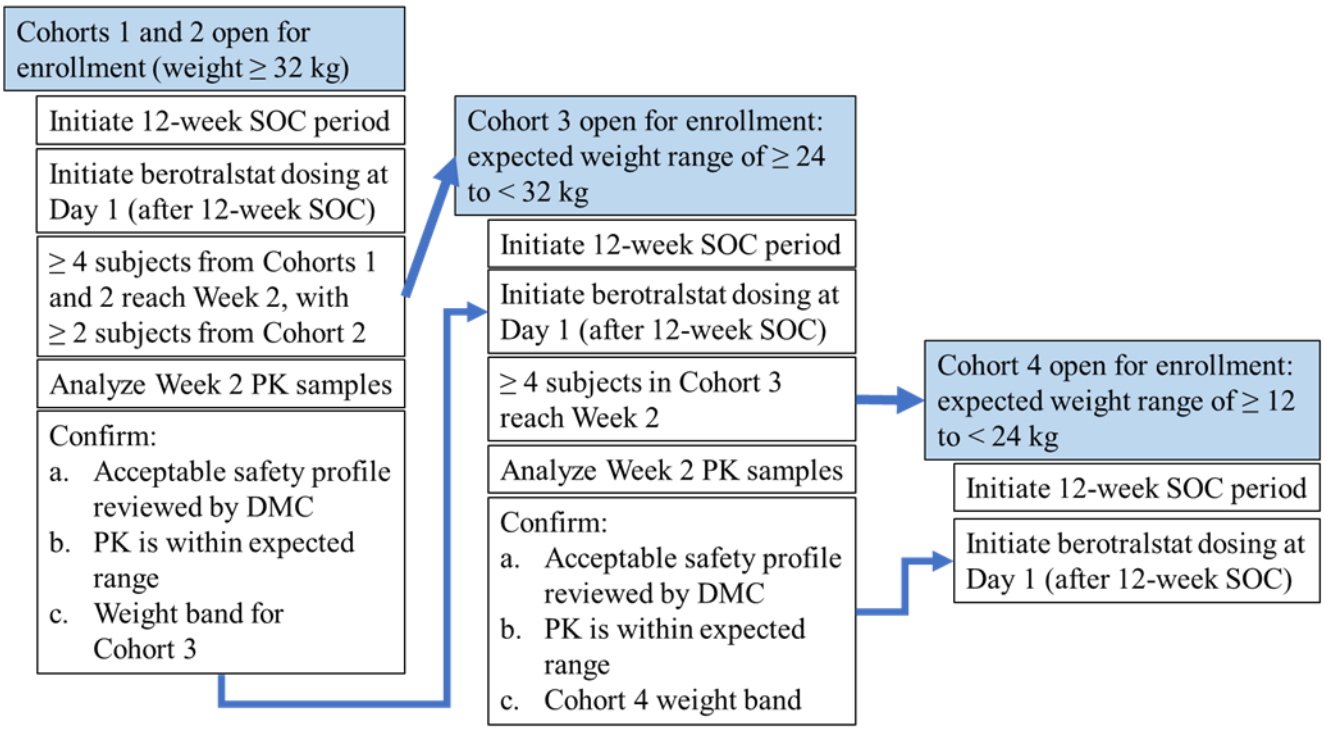
The study will enroll subjects into 4 or more dose cohorts. Subjects will be assigned into each cohort based on subject weight on Day 1/baseline. The subject weight bands for each cohort were determined based on PK modelling and simulation as discussed in Section 4.4.2 and presented in Table 1.

As shown in Figure 2, Cohorts 1 and 2 will enroll in parallel. Subjects will be dosed based on their weight at the Day 1 visit. After 4 subjects from either Cohort 1 and/or 2 have completed the Week 2 visit, population PK modeling will be used to verify doses for subsequent cohorts.

Cohort 3 will open for enrollment and initiate the 12-week 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 (or any subsequent cohorts) 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 cohort will occur prior to dosing subjects in Cohorts 3 and 4 (or any subsequent cohorts) with berotralstat.

Based on emerging safety data and analysis of PK, additional cohorts with doses ranging from 60 mg to < 150 mg may be added with DMC endorsement.

Figure 2: Cohort Enrollment Scheme



Abbreviations: DMC = Data Monitoring Committee; PK = pharmacokinetic; SOC = standard of care.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Number of Subjects

Approximately 30 subjects are planned to be enrolled in the study with a minimum of 15 subjects who complete the study through Week 48 and are evaluable for the PK and safety endpoints.

7.2. Subject Selection

7.2.1. Inclusion Criteria

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

1. Male and non-pregnant, non-lactating females 2 to < 12 years of age and weighing ≥ 12 kg.
2. Parent/caregiver (P/C) 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 document immunogenic 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 lower limit of normal.

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 one 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 HAE prophylaxis.
7. Females who had started their menses and males must either:
   a. Be sexually abstinent. Abstinence in this study is defined as true abstinence: when this is in line with the preferred and usual lifestyle of the subject.
   b. Use contraception. The following represents the minimum contraception that should be used by subjects who could be sexually active. Additional contraceptive requirements, such as highly effective methods, may be required by local site practice and/or governing institutional review board/ethics committee. It is anticipated that not all contraceptive methods may be available in all countries/regions, so the list should be modified accordingly.

      Male subjects should use condoms while enrolled in the study.

      Female subjects should use one or more of the following methods during the study and 30 days after the last dose of berotralstat:

      – Intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
      – Progesterone-only (implantable or injectable only) or oral (norethindrone based only) hormonal contraception
      – Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
        Note: Angioedema attacks may be precipitated by estrogen.

- Male or female condom with or without spermicide
- Use of an occlusive cap (diaphragm, or cervical/vault caps) with spermicide (foam/gel/film/cream/suppository)

7.2.2. Exclusion Criteria

Subjects must meet none of the numbered exclusion criteria below to be eligible for participation in this study. Medications prohibited for use during the study are addressed in Section 8.7.

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 (CL_{CR}) using the Modified Schwartz formula of ≤ 30 mL/min/1.73 m^2 or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value $\geq 3 \times$ 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 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.

7.3. Subject Withdrawal from the Study and from Study Drug

7.3.1. Subject Withdrawal from the Study

Participation in the study is strictly voluntary; the parents and/or caregivers (P/C) may withdraw consent for their child or, where appropriate, the child may withdraw assent to contribute additional study information at any point. A subject who has had consent withdrawn by the P/C or assent withdrawn will be requested to attend an early termination visit to complete all end-of-study evaluations as appropriate for the study part. Although a subject may be withdrawn from the study at any time without specifying a reason for withdrawal, if known, the reason for withdrawal will be recorded in the subject's medical records (source documents) and in the case report form (CRF). If the reason for subject withdrawal is not known, the subject must be contacted to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 11. If at any point in the study the clinic is unable to contact the P/C after appropriate attempts have been made, the subject will be considered lost to follow-up.

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

7.3.2. Subject Discontinuation from Study Drug

A subject will be permanently discontinued from study drug for any of the following reasons, which will be recorded in the source documents and CRF:

- 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 benefit-risk 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 QTcF > 500 msec (if there is an associated C_{max} exceeding the adult range, the dose may first be interrupted and/or reduced; see Sections 11.2.1 and 11.2.2).
- The subject has a confirmed QTcF increase of more than 60 msec from the mean QTcF value calculated from triplicate ECGs recorded at the Baseline visit and a simultaneous absolute QTcF > 460 msec (if there is an associated C_{max} exceeding the adult range, the dose may first be interrupted and/or reduced; see Sections 11.2.1 and 11.2.2).

- Pregnancy in a female subject.

Discontinuation of study drug should be considered for a subject if any of the following thresholds are met and confirmed by repeat measure

- ALT or AST > 8× upper limit of normal (ULN)
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN and (total bilirubin > 2× ULN or international normalized ratio [INR] > 1.5)
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

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

7.3.3. Criteria for Study Termination

The following study rules will be used to stop the study (permanent termination or suspension of enrollment/treatment) or the participation of a particular site:

- Emergence of unacceptable risk, toxicity, or negative change in the benefit-risk assessment
- Request of the relevant competent authority/ethics committee/institutional review board
- Non-compliance with the study protocol, including inaccurate or incomplete recordkeeping, that jeopardizes the scientific integrity of the study or subject safety

BioCryst reserves the right to discontinue the study prior to inclusion of the planned number of subjects but intends to exercise this right only for valid scientific or administrative reasons. If BioCryst does discontinue the study, the investigator must contact all participating subjects immediately after notification of study termination.

7.4. End of Study Definition

The end of study will be defined as when the last subject completes the last protocol-scheduled visit or sponsor-defined last visit should study be terminated early.

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.

8. TREATMENT OF SUBJECTS

Subjects in will remain on their SOC regimen for the first 12 weeks of the study (SOC treatment period). These SOC medications, including on-demand therapy for attacks, must be obtained by the subject's P/C, presumably via the normal method. BioCryst will not supply SOC medications

(prophylaxis during the SOC treatment period or acute medications for use throughout the study). All SOC medications taken during the study must be recorded on the CRF.

Beginning on Day 1/Baseline, subjects will take open-label berotralstat for 12 weeks in Part 1, for 36 weeks in Part 2 (Weeks 12 to 48), and for up to an additional 96 weeks in Part 3 (ie, through study Week 144).

8.1. Berotralstat Formulation

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 IB.

8.2. Berotralstat Packaging, Labeling, and Storage

Berotralstat capsules will be packaged in bottles while granules will be packaged in unit-dose packets as described in the investigational medicinal product (IMP) manual. Subjects will be dispensed a sufficient amount of berotralstat to cover the dosing period until the next study visit.

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

Berotralstat must be stored between 15°C and 25°C (controlled room temperature).

Details on packaging, labeling, shipment, storage, and dispensing of berotralstat will be provided in the IMP manual.

8.3. Dose and Administration of Berotralstat

8.3.1. Berotralstat Dose

Subjects will be enrolled into 4 or more cohorts of decreasing dose of berotralstat as shown in Table 1.

Table 1: Cohort Dose and Weight Bands

Cohort	Dose	Minimum Target Enrollment[a]	Weight Band (from PK Modelling)
1	150 mg capsule[b]	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

Abbreviation: PK = pharmacokinetic.
Note: Additional dose strength(s) ranging from 60 to < 150 mg (including 60 and/or 66 mg) and/or cohorts may be utilized as indicated based on safety and/or PK results.
[a] The n represents the minimum number who will be enrolled into each cohort. Since the total target enrollment is planned to be approximately 30 subjects, additional subjects will be enrolled into one or more of the cohorts or additional dose cohort(s) may be added. Subject enrollment in any one or more cohorts may be suspended to ensure sufficient enrollment of subjects in each cohort.
[b] The 150 mg capsule is identical to commercial product (Orladeyo) which is approved for adolescents and adults ages ≥ 12 years and weighing ≥ 40 kg.

The weight bands for Cohorts 1 and 2 were determined based on PK modelling and simulation (Section 4.4.2). These dose cohorts will be enrolled in parallel.

The weight bands for subsequent cohorts are extrapolated from previous study data and will be finalized based on available safety and/or PK data as discussed in Section 6.

Cohort 3 will open for enrollment and initiate the 12-week 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 (and any subsequent cohorts) are open for enrollment. Safety assessments by the DMC and PK modelling from all available PK data to confirm the weight band for the cohort will occur prior to dosing subjects in Cohorts 3 and 4 (and any subsequent cohorts) with berotralstat.

8.3.2. Administration of Berotralstat

Subjects should take berotralstat orally QD at approximately the same time each day with food as follows:

- From Day 1 until the Week 2 Visit: Subjects will take their first dose on Day 1 in the clinic. This dose should be given with food. Beginning at Day 2 and up to the Week 2 visit, subjects should take their daily dose of berotralstat at home in the morning with food, presumably breakfast. At the Week 2 visit, subjects should take their daily dose of berotralstat in the clinic with food. A series of blood draws for PK analysis will be collected at this visit (see Section 10.9 and the Schedule of Assessments).
- After Week 2 to the End of Treatment (EOT): Subjects should take berotralstat at approximately the same time each day with whichever meal is typically the largest meal of the day, or up to 30 minutes after consuming that meal. No adjustment of dosing time is needed prior to or on clinic visit days, even those where a PK sample is planned to be collected unless the dose is modified (see Section 10.9.1).

It is recommended that berotralstat be administered with food to help minimize GI effects. If GI-related symptoms are noted as an AE, the site should query the subject and record whether the drug is being taken as instructed (ie, with a meal).

Subjects taking the granule formulation must take all of the granules in the packet at the same time in accordance with instructions provided by the site.

After each dose, the P/C should ensure that all of the granules were dispensed and that all of the granules were consumed by the subject.

As much as possible, subjects should keep the same daily dosing interval between berotralstat doses. If a subject forgets to take berotralstat at the correct time, the dose may be taken later in the day; however, no more than 1 dose of berotralstat should be taken on any calendar day. The subject should resume their regular dosing schedule on the next day. Dosing may not be split across a day.

8.4. Study Drug Dose Modification

Emerging PK data will be incorporated into a population PK analysis on an ongoing basis, and simulations of pediatric exposure will be compared to those in adults. Adjustments to the berotralstat dose regimen and/or cohort weight bands may be made: to ensure that exposures fall into the acceptable safety range, due to a safety finding, or due to changes in subject weight; this may result in a dose increase or a dose reduction. If the dose is adjusted, additional plasma PK samples will be collected as described in Section 10.9.1.When dose modifications are made, the sponsor must be contacted prior to any dose adjustment to verify drug supply is readily available.

Study drug interruptions and reductions are discussed in Section 11.2.1 and Section 11.2.2, respectively.

8.5. Accountability of Berotralstat

Accountability of the amount of berotralstat dispensed and returned (as applicable) will be performed starting at Day 1 and throughout Parts 1, 2, and 3 or until the subject withdraws from the study. Therefore, subjects should bring all bottles/kits, used and unused, with them to each study visit beginning in Part 1 through the Week 144 visit. Accountability and adherence will be reviewed at these visits. Returned bottles and/or kits must be retained by the site and will be reviewed during monitoring visits by the clinical research associate (CRA).

The investigator/pharmacist must maintain accurate records of the disposition of berotralstat, issued to the subject (including date), and any drug accidentally destroyed. At the end of the study, information describing supplies of berotralstat (eg, kit numbers) and disposition of supplies for each subject must be provided, signed by the investigator or designee, and collected by the CRA. If any errors or irregularities in any shipment of berotralstat to the site are discovered at any time, the sponsor (and or designee) must be contacted immediately.

At the end of the study or at other times as agreed by all involved parties, all berotralstat not dispensed or administered will either be collected under the supervision of the CRA and returned to the sponsor or destroyed on site as dictated by the appropriate Standard Operating Procedure at the participating institution.

8.6. Concomitant Medications

All SOC prophylactic medication used in the SOC treatment period and all medication used for treatment of acute attacks throughout the study must be recorded in the CRF.

Any regularly administered concomitant medication not listed as prohibited must be anticipated to be continued at a stable dose and regimen throughout SOC treatment and Part 1 of the study, and, preferably throughout Parts 2 and 3 of the study as well.

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

Clinics will instruct the P/C to contact the site when starting any new concomitant medications.

Note that berotralstat is a P-glycoprotein efflux pump (P-gp) inhibitor at a dose of 300 mg. Therefore, close monitoring with potential dose titration is recommended for P-gp substrates (eg, digoxin, loperamide) when co-administered with berotralstat during the course of the study.

The sponsor will provide a spreadsheet outlining potential drugs with interactions with berotralstat to sites.

8.7. Prohibited Medications

All subjects in the study must refrain from taking prohibited medications throughout the entire course of the study.

During the 12-week SOC treatment period, subjects will remain on their normal SOC regimen, either prophylaxis and/or treatment for acute attacks. Subjects will stop prophylaxis for HAE no later than the day before Day 1/baseline. At the Day 1/baseline visit (the beginning of Part 1), subjects will start open-label treatment with berotralstat. Any other long-term prophylaxis to prevent HAE attacks is prohibited during berotralstat treatment (Parts 1, 2, and 3 of the study).

The following medications are excluded during the study (Section 7.2.2):

- Angiotensin-converting enzyme inhibitors within 7 days of the baseline visit or planned initiation during the study (potential for exacerbation of HAE).
- Another investigational drug within 30 days of the screening visit or initiation during the study.
- Daily use of concomitant medications with a narrow therapeutic index that are metabolized by cytochrome P450 (CYP)2D6 (eg, thioridazine, pimozide) or CYP3A4 (eg, cyclosporine, fentanyl) within 7 days of the baseline visit or planned initiation of such medications during the study.
- Chronic administration of P-gp or breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine).
- Any use of P-gp inducers (eg, rifampin, St. John’s wort).

Androgens for prophylaxis of HAE attacks within the 28 days prior to the Day 1 (baseline) visit or initiation during the study. Androgens must not be used at all during Parts 1, 2, or 3 of the

study. Note: Use of testosterone replacement therapy is allowed. The following medications are excluded in the time frame specified prior to Day 1 and for the duration of the study:

- Concurrent chronic administration of P-gp or BCRP inhibitors (eg, cyclosporine) within 7 days of the Day 1 visit.
- Use of P-gp inducers (eg, rifampin, St. John's wort) within 7 days of the Day 1 visit.
- Use of oral androgens for treatment of HAE (prophylaxis or acute) within 28 days of the Day 1 visit or planned initiation during the berotralstat treatment period (Parts 1, 2, and 3).
- Daily use of concomitant medications with a narrow therapeutic index that are metabolized by CYP2D6 (eg, thioridazine, pimozide) or CYP3A4 (eg, cyclosporine, fentanyl) within 7 days of the baseline visit or planned initiation of such medications during the berotralstat treatment period (Parts 1, 2, and 3).
- Use of an angiotensin-converting enzyme inhibitor within 7 days of the Day 1 visit or planned initiation during the berotralstat treatment period (Parts 1, 2, and 3).
- Use of lanadelumab, where available, within 28 days prior to the Day 1 visit.

9. STUDY CONDUCT

9.1. Schedule of Assessments

The study schedule of assessments is shown in Table 2; study procedures are described in Section 10.

Table 2: Schedule of Assessments

Assessment	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]
	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										
Weight/height/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] • CYP2D6 or CYP3A4 substrates • ACE-inhibitor • Lanadelumab • SOC prophylaxis[o]			≥ Day -28 ≥ Day -7 ≥ Day -7 ≥ Day -28 ≥ Day -1											
ECG[p,q]	X			X	X	X		X		X			X	X
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				

Assessment	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]
	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
HAE therapy														
• Standard of care (SOC)	X	X												
• Berotralstat				X	X	X	X	X[x]	X	X	X	X	X	
Palatability/acceptability assessment[y]				X										
Adverse events	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; BMI = body mass index; C1-INH = C1 esterase inhibitor; CRF = case report form; ECG = electrocardiogram; Enr. = enrollment; EOS = end of study; EOT = end of treatment; HAE = hereditary angioedema; hr = hour; LLN = lower limit of normal; 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).

[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 (Section 8.7), 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 other 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 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 (Section 7.2.2) for further explanation.

[n] Subjects should have alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl-transpeptidase (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 adverse events 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 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 Section 10.9.1. 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 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 Section 11.1.2.1).

9.2. Study Visits – Standard of Care Treatment Period

For all visits and site contacts, assessments will be performed as indicated in the Schedule of Assessments (Table 2).

9.2.1. Screening and Enrollment

Pediatric patients who are considered good candidates for the study will report to the site for a screening visit. After the P/C have provided informed consent, and, where appropriate, children have provided assent, screening assessments may be initiated. 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.

Subjects will be dosed based on their weight at the Day 1 visit. Therefore, subjects who are targeted for Cohorts 1, 2, or 3 may be enrolled into the study if they are minimally below the required weight at screening as long as the investigator feels with great certainty that the subject would be at the required weight after 12 weeks in the SOC treatment period. Of note, all subjects targeted for Cohort 4 must weigh ≥ 12 kg before being enrolled into the study.

A subject with an exclusionary value may be rescreened if the investigator believes the exclusionary value obtained was not an accurate reflection of the subject's status (eg, out of range laboratory value due to compromised sample). With prior sponsor approval, subjects with an exclusionary C1-INH test result may be retested during the SOC treatment period if the results are incongruent with clinical history or considered by the investigator to be confounded by recent C1 inhibitor use.

Once enrolled, subjects will begin the SOC treatment period. During this 12-week period, subjects will continue taking their SOC therapy for HAE (either short-term or long-term prophylaxis, and/or acute treatment for HAE attacks). No additional in-person visits are required during the SOC treatment period.

9.2.1.1. Sexual Counseling

Competent adolescents should receive age-appropriate sexual counseling by a qualified health care professional to determine the adherence to inclusion criterion #7 in Section 7.2.1.

There are insufficient data in pregnant women available to inform drug-related risks with berotralstat use in pregnancy. If a female subject becomes pregnant during the study, study drug/IMP will be discontinued per Section 7.3.2 and pregnancy reporting and follow-up will be conducted as described in Section 11.1.3.2.

9.2.2. Weeks 4 and 8 after Enrollment

At approximately 4 ± 1 and 8 ± 1 weeks after the date of enrollment (Section 9.2.1), the site must have an interactive contact with the P/C to assess AEs and status of HAE attacks. Subjects may be included in the contact at the discretion of the investigator. Site contact may be a telephone call, telemedicine visit, or an in-person clinic visit if such a visit was otherwise planned or if the investigator believes it would be in the best interest of the subject to return to the clinic. The contact may also be an in-person consultation between site staff and the P/C if requested by either the investigator or P/C. At 8 weeks after enrollment, where possible, the subject should assess their weight at home in light clothing with shoes and other heavier items removed. The site will obtain the results of the home weight assessment by telephone and record the results in source documents.

9.3. Study Visits – Berotralstat Treatment Period: Part 1

9.3.1. Baseline Visit (Day 1)

Subjects will return to the clinic 12 weeks ± 4 days after the date of enrollment (Section 9.2.1) for the Day 1 (baseline) visit. If extenuating circumstances would result in the baseline visit being delayed, the site must get prior approval from the medical monitor for the visit to occur outside of the defined visit window and for the subject to continue in the study. Prior to the Day 1 visit, subjects must discontinue prophylaxis for HAE as well as other specific medications.

At the baseline visit, the site will review prohibited medications (Section 8.7), 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. After final eligibility for entry into Part 1 is confirmed, subjects will receive their first dose of berotralstat in the clinic and those taking berotralstat granules for oral administration will complete the palatability/acceptability hedonic scale assessment as appropriate for the subject's age. Reference Section 8.3 for berotralstat dosing procedures. The dose of berotralstat will be determined based on the subject's weight at Day 1 and will not be adjusted during Part 1 due to weight changes. If required for medical management, any changes in berotralstat dose during Part 1 should be discussed with the BioCryst medical monitor prior to implementation. Details can be found in Section 8.4.

9.3.2. Weeks 2, 6, 9, and 12

All subjects will return to the clinic for visits during Weeks 2, 6, and 12 following baseline and the site will contact the P/C (tele-contact) during Week 9.

At the Week 2 visit, a series of blood samples will be collected for PK analysis (Section 10.9). To ensure the trough sample provides accurate PK information, the Week 2 visit should be scheduled as close as possible to the regularly scheduled time of dosing for the subject. The dose of berotralstat should be given in the clinic with food (a snack or light meal should be provided). A blood sample for PK analysis will be collected before dosing and at the times post dosing as shown in the Schedule of Assessments.

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 (Table 1).

9.4. Study Visits – Berotralstat Treatment Period: Part 2

9.4.1. Week 16, 20, 28, 32, 40, and 44 Contacts

The investigator (or designee) must contact the P/C at the weeks shown in the Schedule of Assessments via an interactive method, eg, telephone discussion or telemedicine visit. During the contact, the investigator (or designee) will assess the subject's overall wellbeing, collect information on any AEs that may have been experienced by the subject, discuss compliance, and proper recording of attack details (if applicable). If warranted for medical management of the subject or if requested, the contact may be an in-person visit. In this case, visit information should be recorded in the CRF according to directions provided in the CRF completion instructions.

9.4.2. Week 24, 36, and 48 Visits

All subjects will return to the clinic during study Weeks 24, 36, and 48 for appropriate assessments.

A plasma sample for PK analysis will be collected at these visits. The date and time of the preceding dose of berotralstat must be captured and recorded in the source documents and CRF.

9.5. Study Visits – Berotralstat Treatment Period: Part 3

9.5.1. Week 60, 84, 108, and 132 Contacts

The investigator (or designee) must contact the P/C at the weeks shown in the Schedule of Assessments via an interactive method, eg, telephone discussion or telemedicine visit. During the contact, the investigator (or designee) will assess the subject's overall wellbeing, collect information on any AEs that may have been experienced by the subject, concomitant medications taken by the subject, and discuss compliance (if applicable). If warranted for medical management of the subject or if requested, the contact may be an in-person visit. In this case, visit information should be recorded in the CRF according to directions provided in the CRF completion instructions.

9.5.2. Week 72, 96, and 120 Visits

Following the Week 48 visit, subjects should return to the clinic every 24 ± 1 weeks for clinic visits.

9.5.3. Week 144 / End of Treatment (EOT)

Subjects will return to the clinic for the EOT visit at Week 144 (± 1 week). Any subject who discontinues the study during Part 3 should return to the site as soon as possible to complete the Week 144 (EOT) assessments.

If an AE is ongoing at the last study visit, additional clinic visit(s) or telephone contact(s) may be warranted (see Section 11.1.1.4).

9.6. End-of-Study (EOS) Follow-up Visit

Subjects who discontinue berotralstat either at the Week 144 visit or earlier will be required to attend a follow-up visit 3 weeks (21 ± 3 days) after study drug discontinuation. Subjects will be discontinued from the study at this visit. Subjects who discontinue the study but will continue to receive berotralstat via another mechanism will have end-of-study 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 completers.

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

10. ASSESSMENTS

The schedule of procedures and assessments to be conducted throughout the study are outlined in the Schedule of Assessments (Table 2).

To the extent possible, the following chronology of events should be adhered to during the scheduled visits:

- ECGs: obtain prior to vital signs and blood specimen collection
- Vital signs: obtain prior to blood specimen collection
- Study drug dispensing/dosing: end of the visit

10.1. Demographics

Demographic information, including month and year of birth, sex, race, and ethnicity (as applicable or as permissible by country requirements) will be captured for each subject participating in the study at the screening visit. Medical and medication history will be captured at the screening visit and updated at enrollment (if different from the screening visit).

10.2. HAE Medical and Medication History

An HAE medical history questionnaire provided by the sponsor will be completed at screening. All questions should be completed by the investigator (or designee) from historical source documentation when available, with P/C or subject input as necessary to complete the remaining questions. The completed HAE Medical History Questionnaire will be considered a source document and must be entered in the CRF.

10.3. Physical Examination

A full physical examination will be conducted at screening, baseline (Day 1), and at Week 12 (beginning of Part 2). Targeted or symptom-directed examinations will be performed only as necessary at all other visits.

Genitourinary and breast examinations may be omitted when not required by normal site practice. With female subjects past the age of menarche, the age of menarche should be determined.

10.4. Weight/Height/Body Mass Index

Subject weight is important for this study as the dose of berotralstat will be based on subject weight. Therefore, the site should be diligent in accurately taking and recording subject weight. Subjects should be weighed in light clothing with shoes and other heavier items (eg, belts or phones) removed. Heavier outer clothing (eg, jackets or sweaters) should also be removed.

Height should be recorded at the indicated visits. Body mass index (BMI) should be calculated at all visits where weight and height are measured using the following formula:

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

10.5. 12-lead Electrocardiograms

A standard bedside or routine 12-lead ECG machine that calculates heart rate and measures the PR, QRS, QT, RR, and QTc intervals will be used. Prior to obtaining an ECG, subjects should rest quietly for at least 10 minutes. Resting may be in a supine position or other position (eg, on the P/C's lap) as age appropriate for the subject.

Qualified site personnel should review the ECGs and automated findings in real time for gross abnormalities and interval measurements of concern (absolute readings and for post-baseline ECGs, a change from baseline). For all ECGs, the clinical interpretation of the ECG and calculated QTc should be recorded directly on a hard copy of the ECGs. Copies of the ECGs may be requested by the sponsor. All subject identifiers will be masked prior to provision to the sponsor.

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

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

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. ECGs obtained due to dose modification should be taken approximately 2 to 6 weeks after dose modification and should be aligned with PK blood sample timelines described in Section 10.9.1 to the extent possible.

10.6. Vital Signs

Blood pressure (systolic and diastolic) and pulse rate should be taken after the subject has rested in the supine position for at least 5 minutes. For younger subjects who cannot rest for 5 minutes in a supine position, sitting quietly on the P/C's lap is an acceptable alternative. Blood pressure measurements must be obtained with an age-appropriate cuff size and with the subject's arm supported at the level of the heart. It is acceptable to obtain a pulse rate from the blood pressure or ECG machine. Respiratory rate will be captured at screening, baseline, and Week 12 (beginning of Part 2) only.

10.7. Clinical Laboratory Evaluations

Blood samples will be obtained per the schedule of events. Numbing options (eg, numbing cream or ice spray) may be used per site standard practice. Blood sample volume limits should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time (European Commission 2008). Further details and guidance on maximum blood draws will be provided in the laboratory manual. 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. Individual laboratory tests to be performed are provided in Table 3.

All laboratory samples will be collected using kit supplies provided by the central laboratory, which will also analyze all samples. The use of a local laboratory is permitted in specific circumstances with the permission of the sponsor medical monitor. If any results are obtained from both central and local laboratories for the same assessments at a single study time point, only the central laboratory results will be used for study purposes. A laboratory reference manual will be provided to the site detailing kit contents, reordering instructions, sample collection, handling, storage, and shipment.

Results from the laboratory values should be reviewed as received by the investigator. Evidence of this review should be provided in the source records and may include printing of the laboratory reports with a signature attesting to a review. For out-of-range laboratory findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings in the opinion of the investigator should be recorded as an AE and handled as described in Section 11.

Table 3: Clinical Laboratory Evaluations

Chemistry	**Coagulation**
• Albumin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Bilirubin (total and direct) • Blood glucose • Blood urea nitrogen (BUN) • Electrolytes (calcium, sodium, potassium, chloride, bicarbonate [CO_2], phosphorus) • Lipid panel (total cholesterol, triglycerides) • Creatine kinase • Creatinine and calculated creatine clearance (CL_{CR}) • Gamma-glutamyl transferase (GGT) • Lactate dehydrogenase (LDH) • Total serum protein • Uric acid • *If amylase is > 2 × upper limit of normal (ULN), reflex to* lipase	• Prothrombin time (PT) and international normalized ratio (INR) • Activated partial thromboplastin time (aPTT)
Urinalysis	**Pregnancy Test**
• Specific gravity • Blood • Bilirubin • Glucose • Leukocytes • Ketones • Nitrites • pH • Protein • Urobilinogen • Microalbumin to creatinine ratio • Reflex microscopy if dipstick is abnormal	Only for girls who have begun to menstruate: Serum (screening) and urine (other specified visits) beta-human chorionic gonadotropin (βHCG) for girls of childbearing potential only[a]
	Hematology
	• Hemoglobin • Hematocrit • Erythrocytes • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) • Platelets
	Additional Tests
	• C1 esterase inhibitor (C1-INH) level and function[b] • C4[b] • SERPING-1 analysis [b]

[a] A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test.
[b] Only if required to confirm HAE diagnosis.

CL_{CR} will be calculated using the Modified Schwartz formula and actual body weight as shown in the laboratory manual.

10.8. Confirmation of HAE Diagnosis

Subjects must have confirmed HAE to be eligible for study participation. Several methods may be used to confirm an HAE diagnosis.

- C1-INH functional level and C4 level: If necessary to satisfy eligibility criteria, blood samples for C1-INH functional level and C4 will be drawn at the screening visit; samples should not be drawn within 3 days of C1-INH administration (eg, use for treatment of an HAE attack).
  - Immunogenic C1-INH antigenic level results below the LLN or functional C1-INH results < 50%, and a C4 level below the LLN reference range.
  - 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
- Laboratory documentation of historical C1-INH functional level below the assay LLN.
- Historical or new laboratory documentation of a SERPING-1 mutation known or likely to be associated with HAE.
- For subjects currently receiving C1-INH based prophylactic therapies, a confirmed family history of C1-INH deficiency. The investigator should document this based on either the investigator's personal knowledge (ie, if a relative of the screening subject is also a patient of the same investigator/practice) or interaction with medical staff of the treatment facility where the relative receives HAE care, who confirms the diagnosis. No historical laboratory documentation on the relative should be collected in the source documents.

10.9. Pharmacokinetics

All plasma samples for determination of berotralstat will be analyzed using a validated liquid chromatography-mass spectrometry assay.

Blood samples for analysis of PK parameters will be drawn on all subjects as indicated in the Schedule of Assessments. At the Week 2 visit, a series of samples will be collected for PK analysis to allow for determination of PK parameters including C_{max}.

Actual date and time of sample collection will be recorded in the CRF. Sites will ensure that the time of the dose of berotralstat taken prior to the blood draw is recorded in the source documents and CRF. Sites should communicate to the P/C the importance of providing the most accurate time of dosing prior to the PK sample collection.

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

In Cohorts 1, 2, and 3, at the Week 2 study visit where multiple PK samples are to be collected, 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). 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. 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. 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. If plasma samples for PK analysis cannot be collected as described above at Week 2, sites are required to document the reason in source notes and collect samples for PK analysis prior to or during the Week 6 visit.

A single plasma PK sample is to be collected at Weeks 12, 24, 36, and 48. Additional plasma PK samples may be collected during the study if prescribed by the principal investigator as indicated for clinical management of the subject or if a previously scheduled sample was not collected and/or evaluable. The date and time of the PK blood draw, the last dose of berotralstat taken prior to the blood draw, and if the dose was taken with food will be captured in the CRF. As noted above, accuracy of the previous dose time of berotralstat is important.

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.

10.9.1. Plasma Pharmacokinetic Samples for Dose Modifications

Adjustments to the berotralstat dose may be required during the study based on safety and/or PK findings. If the berotralstat dose is adjusted due to an AE or high exposure level, the subject will be required to provide blood samples for analysis of PK parameters as follows:

- Subjects in Cohorts 1 and 2 will provide a PK sample 20 to 24 hours after their previous dose of berotralstat, and another sample 2 to 4 hours after taking their daily dose of berotralstat.
- Subjects in Cohorts 3 and 4 will provide a PK sample 20 to 24 hours after their previous dose and, if possible, another sample at 2 to 4 hours after taking their daily dose of berotralstat.

These samples will be collected approximately 2 to 6 weeks after the dose adjustment. If a telephone call or telemedicine appointment is scheduled for the next visit, an in-person clinic visit may be conducted instead. Note: home health collection may be an option if available per country requirements.

Subjects with dose adjustment will be asked to take their daily dose in the morning for a minimum of 2 weeks before the PK draw will be completed. On the day of PK draw, subjects should take their daily dose during the visit with food.

The date and time of berotralstat dosing and PK sample collection, as well as whether the dose was taken with food, will be recorded in the source documents and the CRF.

Subjects with dose adjustments based on weight in Part 2 or Part 3 of the study should provide PK samples approximately 2 to 6 weeks after the dose adjustment, as described in the bulleted

list above. If samples cannot be collected in this timeframe, they must be collected at the next visit.

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.

10.10. Adverse Events

AEs will be assessed and recorded from the time that the informed consent form (ICF) is signed through the last follow-up visit or until the AE is resolved or the subject is in a clinically stable condition with regard to the AE. Full details on recording and reporting AEs are provided in Section 11.1.1.4.

10.11. HAE Attack Diary

The sponsor will supply paper diaries to sites to be distributed to the P/C for recording the subject's HAE attacks. The P/C will fill out the HAE attack diary whenever an attack (or suspected attack) occurs. If the subject reports an attack or if the P/C suspects that an attack has occurred, additional details should be entered into the diary including start and stop time of the attack, attack symptoms, anatomical location of swelling (if applicable), severity, treatment(s) administered and times of administration, and whether additional medical care was sought for the attack. Subjects will complete the diaries from enrollment through the end of Part 2 (ie, Week 48).

The P/C will be instructed to bring the subject's diary with them to each study visit. Diaries will be collected at each visit through Week 48, and new diaries will be dispensed at each visit prior to Week 48.

Subjects who withdraw from the study should continue to record the occurrence of HAE attacks in their diary until they return to the site for the appropriate EOS visit.

Once a subject completes or discontinues the study, the site must collect all diaries from the P/C.

Study staff are not permitted to make any entries into the diary.

11. ADVERSE EVENT MANAGEMENT AND REPORTING

11.1. Adverse Events

11.1.1. Definitions

11.1.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject. No causal relationship with the study drug/IMP or with the clinical study itself is implied. An AE may be an unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the clinical study. Clinically significant results of diagnostic procedures including abnormal laboratory findings (eg, requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be AEs. If the diagnostic procedure prompts no additional treatment, visits, or monitoring, it will not meet the definition of an AE.

AEs include the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 11.1.1.4).
- Findings from protocol-mandated interventions. This can include laboratory assessments performed in the clinical study. AEs should be reported only if the abnormalities are adverse changes from baseline and clinically significant as described above.
- Pre-existing medical conditions (other than HAE) judged by the investigator to have worsened in severity or frequency or undergone an adverse change in character during the protocol-specified AE reporting period. When recording such events on an AE/SAE CRF page, it is important to convey the concept that the preexisting condition has adversely changed by including applicable descriptors (eg, "more frequent headaches" or "worsened headache").
- Untoward and unintended responses resulting from medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported as an AE.

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

For the purposes of this protocol, HAE attacks and their associated symptoms will not be defined as AEs, even if the subject requires hospitalization. HAE attacks and associated symptoms are reported in the subject's diary and are a reflection of the disease under study. Events that trigger an HAE attack and meet the definition of an AE, such as an infection or trauma, should be reported as AEs.

AEs are designated as "nonserious" or "serious".

11.1.1.2. Serious Adverse Event

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

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

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

In addition, abortion (spontaneous or induced), fetal demise, and still birth along with congenital abnormalities in the newborn should be reported as separate SAEs (see Section 11.1.3).

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

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

Overdose will be considered an SAE only if any of the seriousness criteria are met. Any clinical complication in association with the overdose should be reported as an AE or SAE (as applicable) along with the overdose (see Section 11.2.3). Details of signs or symptoms, clinical management, and outcome should be reported, if available. Overdose without associated signs or symptoms should not be recorded as AEs but should be recorded as protocol deviations.

11.1.1.3. Adverse Events of Special Interest

For this protocol, no events of special interest have been identified.

11.1.1.4. Definition of Severity

All AEs and SAEs will be assessed (graded) for severity by the investigator and classified using the Division of AIDS (DAIDS) table for grading the severity of adult and pediatric AEs (Publish date July 2017). Any AEs not covered by the DAIDS table will be assessed and classified into 1 of 5 clearly defined categories as follows:

Mild: (Grade 1): Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.

Moderate: (Grade 2): Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.

Severe:	(Grade 3): Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
Life-threatening:	(Grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
Death:	(Grade 5): Indicates death related to the AE.

The investigator should report the highest severity experienced during the course of the event. It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, defined above, whereas seriousness is defined by the criteria under Section 11.1.1.4. An AE of severe intensity may or may not be considered serious. An example would be a severe headache that does not result in any serious outcome is a non-serious AE; conversely, a mild event that results in hospitalization is a serious AE.

11.1.1.5. Definition of Relationship to Study Drug

Using the following guidelines, an investigator who is qualified in medicine must make the determination of relationship to berotralstat or SOC HAE medication used for prophylaxis and/or acute therapy for each AE (not related or related). The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by berotralstat or SOC HAE medication. If no valid reason exists for suggesting a relationship, then the AE should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between berotralstat or SOC HAE medication and the occurrence of the AE, then the AE should be considered "related."

Because multiple study drugs are being administered in this study, the investigator should assess causality individually to berotralstat or SOC HAE medication, taking into consideration the timing of the AEs in relation to berotralstat or SOC HAE medication dosing as well as the known safety profile of berotralstat or SOC HAE medication.

The degree of certainty with which an AE is attributed to berotralstat or SOC HAE medication (or alternative causes, eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of berotralstat or SOC HAE medication
- Reactions of a similar nature have been previously observed with berotralstat or SOC HAE or these classes of drugs
- The experience being related by time to berotralstat or SOC HAE medication, terminating with their withdrawal or recurring on re-challenge
- Alternative cause

The investigator should assess causality by determining whether the AE/SAE is suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgement as follows:

Not Related: The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Related: The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.

The sponsor may upgrade causality if deemed appropriate.

11.1.2. Recording Adverse Events

Information about AEs and SAEs will be collected from the signing of the ICF until the end of the study and will be recorded during the study at the investigational site in the CRF according to the instructions provided in the CRF completion guidelines.

The AE term should be recorded using standard medical terminology (not lay language). The investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually. Once a diagnosis is made during evaluation or treatment, the investigator will update the AE record by replacing the individual signs and symptoms with this diagnosis.

11.1.2.1. Time Period for Follow-up of Adverse Events

All AEs that are ongoing at the time of the last study follow-up visit must be followed until they are resolved, or the subject is in a clinically stable condition with regard to the AE.

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

11.1.3.1. Initial and Follow-up Reports

The investigator must report all SAEs immediately and in no case later than within 24 hours of their knowledge of the event. Investigators should adhere to their country or region requirements for the reporting timeframe which may not allow any delay. The initial and follow-up SAE reports will identify subjects by the unique subject numbers assigned to ensure that the sponsor will have the necessary information to continuously assess the benefit-risk profile of the study drug in the clinical study.

SAEs should be reported to the medical monitor and via the AE and SAE electronic CRFs (eCRFs). The SAE eCRF is an additional form to the AE eCRF that provides important details on the SAE. All additional follow-up evaluations of the SAE must be reported to BioCryst or its designee as soon as they are available. A notification of the SAE should be sent to the following email addresses:

Email: safety@biocryst.com

In the event the eCRF system is not functioning, the reporting of an SAE must not be delayed. Sites will have SAE report forms (electronic Word document) that can be completed and emailed to the above recipients. As soon as the eCRF system is functioning, that particular SAE must be entered into the AE eCRF.

11.1.3.2. Pregnancy

Any female subject who becomes pregnant during the course of the study must have study drug/IMP discontinued immediately and must be followed through the end of the pregnancy. While pregnancy is not considered an AE, all cases of fetal drug exposure via the parent as a study participant (including partners of study participants) are to be reported immediately to BioCryst or its designee.

The Pregnancy Notification Form and Pregnancy Outcome Form should be sent to the following email address:

Email: safety@biocryst.com

Consent from partners of study participants who become pregnant will be obtained prior to reporting any details of the pregnancy. Information related to the pregnancy must be given on a "Pregnancy Notification Form" and "Pregnancy Outcome Form" that will be provided by BioCryst so that the pregnancy may be followed, and an outcome determined. Any AEs or SAEs experienced by a pregnant subject are to be reported as directed in Section 11.1.2 and Section 11.1.3. Any complications reported in a subject's pregnant partner should be reported on the "Pregnancy Notification Form" and "Pregnancy Outcome Form". All pregnancies must be followed to outcome, which occurs when an infant is delivered (live or still born), there is fetal demise, or there is an abortion (spontaneous or induced). Abortion (spontaneous or induced), fetal demise, and still birth, along with congenital abnormalities in the newborn, should be reported as separate SAEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented, even if the subject was discontinued from the study.

11.1.3.3. Record Retention and Reporting to Regulatory Authorities

Investigators or designees at each site are responsible for retaining copies of all suspected unexpected serious adverse reaction (SUSAR) reports (initial and follow-up) and other safety information (eg, revised IB or Summary of Product Characteristics [SmPC]) in their investigator site files.

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

BioCryst or its designee shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to all relevant competent authorities, and to the independent ethics committee (IEC)/institutional review board (IRB) in any case no later than 7 calendar days after knowledge by BioCryst of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned and to the IEC/IRBs, as applicable according to local regulations, as soon as possible but in no case later than 15 calendar days of first knowledge by BioCryst. BioCryst or its designee shall also inform all investigators in accordance with local regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.

11.1.4. Unanticipated Problems

11.1.4.1. Definition of Unanticipated Problems

Any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

The investigator is responsible for ensuring that the IEC/IRB is also informed of the unanticipated problem, in accordance with local regulations.

11.2. Toxicity Management

The investigator (or qualified designee) will grade clinically significant events and laboratory abnormalities (if considered AEs) as described in Section 11.1.1.4. Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing and before any contemplated study drug discontinuation, unless such a delay is not consistent with good medical practice.

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

11.2.1. Treatment Interruptions

Treatment interruptions as a result of investigator management of AEs potentially related to berotralstat are permissible. Resumption of berotralstat is also permissible upon resolution of the event, as assessed by the investigator, with a plan for stringent monitoring of the subject for recurrence of the AE as appropriate. In addition, other extenuating circumstances may lead to treatment interruptions such as vomiting during an abdominal HAE attack or required fasting for medical procedures; in these cases, berotralstat should be resumed once the extenuating circumstance is resolved. The sponsor medical monitor should be notified in the event of a treatment interruption due to an AE. Any treatment interruption will be recorded in the CRF and source documents, including the reason for the interruption.

Treatment interruptions due to confirmed QTcF > 500 msec or increase more than 60 msec from baseline associated with C_{max} exceeding the adult range are permissible. If interrupted, subjects may resume berotralstat at a reduced dose at the investigator's discretion. Subjects may remain on the reduced berotralstat dose if they no longer meet QTcF stopping criteria at steady state (see Section 7.3.2).

Other treatment interruptions may be permissible following consultation with the medical monitor.

11.2.2. Dose Reductions

Dose reductions are allowed based on emerging PK and/or safety data (see Section 8.4).

Dose reductions due to confirmed QTcF > 500 msec or increase more than 60 msec from baseline associated with C_{max} exceeding the adult range are permissible. Subjects may remain on the reduced berotralstat dose if they no longer meet QTcF stopping criteria at steady state (see Section 7.3.2).

If the berotralstat dose is reduced, see Section 10.9.1 for collection of PK samples.

Other dose reductions may be permissible following consultation with the medical monitor. The previous dose of berotralstat may be resumed upon resolution of the safety event at the discretion of the medical monitor based on PK and/or safety review (see Section 8.4).

11.2.3. Overdose

To date, there is no experience with overdose of oral berotralstat. Single doses of up to 1000 mg, 7 days of dosing up to 500 mg/day, and 14 days of dosing with 350 mg/day revealed no clinically significant safety concerns in healthy subjects. Safety data generated in Study BCX7353-203 with 28-day dosing of up to 350 mg/day revealed no clinically significant safety concerns in subjects with HAE. Subsequently, subjects enrolled in Study BCX7353-106 were exposed to berotralstat 450 mg QD for 14 days without any unanticipated AEs or increased AE severity.

In the event that study personnel become aware of an overdose of berotralstat (> 1 dose per calendar day) that is associated with an AE, both the overdose and the resultant event should be reported as AEs. An overdose without associated signs or symptoms should not be recorded as an AE but should be reported as a protocol deviation.

If an overdose occurs with or without associated AEs, subjects should undergo clinical and laboratory monitoring as appropriate for their clinical condition and, if indicated, should receive clinically indicated supportive therapy.

Overdose will be considered an SAE only if any of the seriousness criteria are met. Any clinical complication in association with the overdose should be reported as an AE and, where applicable, SAE along with the overdose (see Section 11.1.3). Details of signs or symptoms, clinical management, and outcome should be included in the AE report, if available.

Additional information about overdose as an AE or SAE is discussed in Section 11.1.1.2.

11.3. Data Monitoring Committee

An independent DMC will be established for interim safety monitoring. The specific responsibilities and composition of the DMC are outlined in a separate DMC charter. The charter will include, at a minimum, a description of DMC membership, roles, timing of DMC review and responsibilities of DMC members. In addition, the details of outputs provided for the meetings will be referenced in this charter.

The DMC will be convened according to FDA guidelines. In general, the DMC will review safety data on an ongoing basis and SAEs considered related to berotralstat as they occur. Prior to initiating dosing with berotralstat (ie, initiation of Part 1) in Cohorts 3 and 4 (and any subsequent cohorts), the DMC will meet and review safety data and endorse opening of all subsequent cohorts.

11.4. COVID-19

The study will be conducted in accordance with relevant local, regional, and national guidance around coronavirus disease 2019 (COVID-19). In order to minimize the risk of COVID-19 transmission, additional procedures or assessments (which may include but are not limited to symptom assessment, temperature assessment, and viral ribonucleic acid testing) may be implemented at the discretion of the investigator beyond those required in this protocol. Study visits or procedures may be modified in accordance with relevant local, regional, and national guidance as necessary to preserve subject safety during trial conduct. All protocol deviations resulting from COVID-19 will be identified as such. All study activities will be conducted in accordance with relevant local, regional, and national guidance around COVID-19.

12. STATISTICS

12.1. 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 the 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 an approximately 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.

12.2. Statistical Methods

A detailed statistical analysis plan (SAP) will be developed to describe the methods of analyses and summaries, including all endpoints, time points, populations, missing data, prior to the review of any data. Deviations from the analyses outlined in the SAP will be described in the clinical study report.

12.2.1. Analysis Populations

The analysis populations are defined in subsections that follow.

12.2.1.1. Intent to Treat Population

The intent to treat (ITT) population will include all subjects who satisfy all entry criteria and who enroll into the study. As this study focuses on safety and PK of berotralstat, analyses of the ITT population will likely be limited.

Note that subjects for whom their P/C provided written informed consent but who are not enrolled in the study will be considered screen failures. Subjects who are "preliminary enrollees" awaiting final confirmation of eligibility will also be considered screen failures if found to be ineligible for study participation.

12.2.1.2. Completer Population

For study Parts 1 and 2, the subset of subjects who complete the 12 and 48 weeks of dosing may be analyzed for a subset of effectiveness endpoints.

12.2.1.3. Safety Population

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

12.2.1.4. PK Population

The PK population will include subjects in the safety population who have at least one dose of the study medication and had at least one evaluable and quantifiable post-dose PK sample obtained.

12.2.2. General Considerations for Data Analysis

Descriptive statistics will be used to summarize the data from this study. Data will be summarized by cohort, overall, and by study day or time, if appropriate. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, standard deviation (SD) or standard error of the mean (SEM), median, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. For TEAE data, both the number of subjects and total number of events will be reported. For PK endpoints, please see Section 12.2.4 for further details.

Data summaries will be provided to the DMC as specified in the DMC Charter. Interim analysis of PK, safety, and effectiveness data 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 performed during the course of the study as needed to support regulatory filings, safety updates, and publications, as documented in the SAP. Effectiveness data are not collected after Week 48. Disposition and safety data will be summarized through the end of study (Week 144).

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 after database lock has occurred. Disposition, dosing, and safety data will be summarized through the end of study (Week 144).

Data collected during the study will be included in data listings as measured or recorded in patient diaries. Unless otherwise noted, data listings will be sorted by subject and study visit/date.

Statistical analyses will be conducted using SAS® software version 9.2 or higher (SAS Institute, Cary, North Carolina, US). All analyses will be subject to formal verification procedures. All tables and figures generated to summarize data will be reviewed by the lead statistician to ensure accuracy and consistency of analyses; the lead clinical pharmacologist will review data summarized for the PK endpoints to ensure their accuracy and consistency.

12.2.3. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race, ethnicity, height, weight, BMI, and HAE history, including medication history, will be summarized by weight cohort and for all subjects.

Subject disposition will be presented for all subjects. The number 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 tabulation of the number of subjects exposed to berotralstat and the duration of exposure will also be presented. Treatment adherence, dose interruptions, and reason for dose interruptions will be provided as summaries or listed as appropriate.

12.2.4. Pharmacokinetic Analyses

Plasma samples for determination of berotralstat concentrations are planned to be collected at times indicated in the Schedule of Assessments. All plasma concentrations that are part of the PK population will be incorporated into the population PK analyses.

The results of these analyses will be reported in a separate pharmacometric report.

12.2.5. Analysis of Safety Variables

Adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. The occurrence of TEAEs will be summarized using MedDRA preferred terms, system organ classifications, and severity (eg, Grade 3 or 4) by cohort and for all subjects. Separate summaries of treatment-emergent SAEs and AEs related to study drug will be generated, as well as AEs leading to study drug being interrupted or study withdrawal. All AEs will be listed for individual subjects showing both verbatim and preferred

terms. Adverse events that are reported during the SOC treatment period will be summarized separately.

Descriptive summaries of clinical laboratory results will be presented by study visit by cohort. Laboratory abnormalities will be graded according to the DAIDS Table for Grading Adverse Events for Adults and Pediatrics (Corrected Version 2.1, July 2017) unless otherwise specified. In addition to DAIDS requirements, creatinine increases from baseline must also meet certain minimum thresholds, to appropriately target meaningful changes in creatinine in pediatric patients with low baseline values, as summarized below:

- Grade 1 mild: 1.1 to 1.3 x 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

The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized or listed by cohort.

Effects of berotralstat on pediatric patient growth (weight, height, and BMI) will be assessed over time by cohort. Vital signs, laboratory data (eg, chemistry, hematology, and urinalysis results), and ECGs will also be summarized over time by cohort.

Previous and concomitant medications will be mapped to a World Health Organization preferred term and drug classification. The number and percentage of subjects taking concomitant medications will be summarized using preferred terms and drug classifications (including during the SOC treatment period).

12.2.6. Analysis of Effectiveness Variables

Summary statistics will be provided for the number and rate of HAE attacks, duration of symptoms, anatomical location of attacks, use of on-demand rescue medication, number of days with angioedema symptoms, P/C assessment of attack severity, and number of hospitalizations and clinic visits during Part 1 (Weeks 1 through 12) and in Parts 1 and 2 combined (Weeks 1 through 48) by cohort. The rate of HAE attacks over time will be provided. Subjects who discontinue the study due to “lack of efficacy” will be identified and provided in a listing.

12.2.7. Analysis of Exploratory Variables

Summary statistics for the exploratory endpoints related to assessment of palatability and acceptability for the berotralstat granules will be provided for subjects enrolled in Cohorts 2 to 4.

13. STUDY ADMINISTRATION

13.1. Direct Access to Source Data/Documents

13.1.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of BioCryst will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regards to protocol adherence, and the responsibilities of BioCryst or its representatives. This will be documented in a Clinical Study Agreement between BioCryst and the investigator.

During study conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow BioCryst representatives, monitors, or its designees direct access to source documents to perform this verification.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

During the study, a monitor from BioCryst or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to BioCryst.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to BioCryst and those SAEs that met criteria for reporting have been forwarded to the IEC/IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.1.2. Audits and Inspections

Authorized representatives of BioCryst, US FDA and other regulatory authorities, and/or ethics committees may visit the site to perform audits or inspections, including source data verification.

The purpose of a BioCryst audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, standard operating procedures, ICH/GCP guidelines, and any applicable regulatory requirements. The investigator will permit study-related audits mandated by the sponsor, after reasonable notice, and inspection by domestic or foreign regulatory authorities. The investigator should contact BioCryst immediately if contacted by a regulatory agency about an inspection.

It is important that the investigator and relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

13.1.3. Ethics Committee

Ethics approval for the investigation must be obtained prior to commencing the study. Initial ethics approval, and all materials approved by the ethics committee, including the ICF and any recruitment materials, must be maintained by the investigator and made available for inspection.

13.1.4. Serious Breaches of GCP

It is the responsibility of the sponsor to notify the competent authority of any serious breach of GCP that is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study. All serious breaches will be notified to the relevant competent authority in accordance with locally applicable regulations. The reporting to the sponsor will be performed by the party who suspects the serious breach.

13.2. Quality Control and Quality Assurance

During study conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed as described in Section 13.1.1.

To ensure compliance with GCP and all applicable regulatory requirements, BioCryst or its designee may conduct a quality assurance audit. Please see Section 13.3.2 for more details regarding the audit process. The investigator agrees to allow the auditors to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

13.3. Regulatory and Ethical Considerations

13.3.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to BioCryst before he or she can enroll any patient/subject into the study.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. BioCryst will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

13.3.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and BioCryst's policies.

This study will also be conducted in accordance with EU Clinical Trial Regulation 536/2014 (CTR).

13.3.3. Written Informed Consent and Assent

Signed informed consent must be obtained from each P/C prior to performing any study-related procedures. Each P/C and, where age appropriate, subject should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process should take place under conditions where the P/C has adequate time to consider the risks and benefits associated with his/her child's participation in the study. Subjects will not be screened or treated until the P/C has signed an approved ICF written in a language in which the P/C is fluent. The ICF that is used must be approved both by BioCryst and by the reviewing IRB/IEC. The ICF should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policy.

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

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

Similarly, subject assent will be obtained from each child according to local regulations/requirements. If assent is required based on the subject's age and local requirements, then the subject will not be screened or treated until the assent is received. Additionally, if required by local regulation, as the subject ages during the study and reaches an age requiring assent, then the subject will be assented to continue in the study at the next scheduled visit.

The ICF and assent forms (if applicable) must be approved both by BioCryst and the reviewing ethics committee. The ICF and assent forms should be in accordance with the current revision of the Declaration of Helsinki, current ICH/GCP guidelines, and BioCryst policy.

13.4. Data Handling and Recordkeeping

13.4.1. Inspection of Records

BioCryst will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

13.4.2. Records Retention

The investigator will maintain adequate records for the study, including the identity of all participating subjects (sufficient information to link records, CRFs, and medical/hospital records), all original signed ICFs, all original signed assents (if applicable), all CRFs, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

The investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for BioCryst or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records. It is the responsibility of BioCryst to inform the investigator/institution as to when these documents no longer need to be retained. It is the investigator's responsibility to notify BioCryst if they relocate or retire so that document storage can be addressed. The investigator must obtain BioCryst's written permission before disposing of any records and must notify BioCryst before transferring any records to another facility.

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

13.5. Confidentiality of Information and Data

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

All parties will abide by all applicable laws and regulations regarding subject privacy and confidentiality, including, the Health Insurance Portability and Accountability Act (HIPAA), where this rule is applicable and the requirements of the General Data Protection Regulation in the EU, where applicable. A valid authorization and consent must meet the specifications of the applicable laws and regulations relating to such personal data and health information. It is the

responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual. HIPAA authorizations are required for US sites only.

13.6. Study Publication

All data generated from this study are the property of BioCryst and shall be held in strict confidence along with all information furnished by BioCryst. Except as provided through written agreement with BioCryst, independent analysis and/or publication of these data by the investigator or any member of his/her staff is not permitted. Such consent will not be withheld unreasonably. BioCryst is in agreement with the principle of full disclosure of clinical trial results.

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15. APPENDICES

15.1. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events – July 2017

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

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

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Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 ≥ *3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ *7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< *7 days of age*	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171* to < *290.7*	≥ 17 ≥ *290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2* to < *324.9*	≥ 19 ≥ *324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5* to < *376.2*	≥ 22 ≥ *376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8* to < *410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

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Approval Task	[redacted] Clinical 05-Nov-2024 17:41:31 GMT+0000

Approval Task	[redacted] Clinical 05-Nov-2024 21:12:33 GMT+0000

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Approval Task	[redacted] Clinical 05-Nov-2024 17:41:31 GMT+0000

Approval Task	[redacted] Clinical 05-Nov-2024 21:12:33 GMT+0000

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