EUROPEAN UNION RISK MANAGEMENT PLAN FOR ORLADEYO® (BEROTRALSTAT)

Name: Orladeyo (**berotralstat)**

Dosage form:	Capsules and film-coated granules for oral administration
Drug class:	Plasma kallikrein inhibitor
Approved indication:	Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Proposed indication:	Orladeyo granules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to less than 12 years.
Version, date:	4.0, 22 Jun 2026

European Union (EU) Risk Management Plan (RMP) for Orladeyo (Berotralstat)

RMP version to be assessed as part of this application:

RMP version number: 4.0

Data lock point for this RMP: 02-Dec-2024

Date of final sign-off: 22 Jun 2026

Rationale for submitting an updated RMP: This EU RMP version 4.0 is prepared to support the extension of the indication of Orladeyo to include paediatric patients aged 2 to < 12 years with HAE and introduce film-coated granules (hereinafter referred to as granules) as an age-appropriate dosage form. The data lock point for the interim analysis for Study BCX7353-304 (Study 304) is 11-Sep-2024.

Summary of significant changes in this RMP:

Part/Module	Major changes
Part I	Information on the proposed indication, dosage, and pharmaceutical form relating to the use of the granules formulation in the paediatric population (aged 2 to < 12 years) was added.
Part II/Module SI	Updated indications for capsule and granules formulation were added. Information on the prevalence; the main existing treatment options; World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines; and the natural history of the indicated conditions in the untreated population, including mortality and morbidity relating to the paediatric population, was added.
Part II/Module SII	Results for the assessment of BCX7353 toxicity in juvenile rats were added. Safety data from Study 304 for the paediatric population was added to Table SII.1: Safety Concerns from Nonclinical Studies.
Part II/Module SIII	An introduction to Study 304, designed to enrol subjects 2 to < 12 years old, was added. It was clarified that in the previous version of the RMP, the first 7 subjects enrolled into Study 304 were included in the integrated data tables (Table SIII.2, Table SIII.3, Table SIII.4, and Table SIII.5) which were prepared in 2023. Rather than integrate the subsequently enrolled 304 population into these tables, it was explained that the Study 304 exposure data are being presented separately and not being integrated with data from other clinical studies in the current version of the document due to differences in study design and subject population. Therefore, the exposure summary from the interim analysis for all 4 cohorts of Study 304 subjects (29 subjects) is presented as a separate table. The previously presented tables were not amended as the clinical trial exposures for adults and adolescents were not significantly changed. The initial exposure information on those 7 paediatric subjects also remains in those tables but are now presented in their entirety as of the cutoff date in Table SIII.1. Information on race, sex, ethnicity, and exposure data for Study 304 was added. Information was also added on the countries where Study 304 is being conducted.

	Updated information on number of studies conducted in adults and adolescent patients aged 12 years and older in the berotralstat clinical development programme.
	Updated information on exposure of subjects across the berotralstat clinical development programme.
Part II/Module SIV.1	Added clarification on exclusion criteria that were relevant for adult and adolescents and paediatric population aged 2 to < 12 years.
	Added age specification of "≥ 12 years" to the language describing clinically significant abnormal electrocardiogram (ECG) criteria at screening. Criteria of corrected QT interval using QTcF > 450 msec for paediatric subjects aged < 12 years was added.
	Updated the criteria for use of berotralstat in patients with varying degrees of renal impairment to align with the summary of product characteristics (SmPC).
	Added a note to clarify that concomitant medications with narrow therapeutic index that are metabolised by cytochrome P450 (CYP) 2D6 and CYP3A4 were prohibited in Study 304.
Part II/Module SIV.3	Updated Table SIV.1 with the following: Exposure data from pregnant or breastfeeding women, a note stating patients with hepatic and renal impairment were not enrolled in the paediatric development programme, percentage of patients that were White in Study 302 Parts 2 and 3.
	Added a Study 304 limitation in respect to populations typically underrepresented in the clinical trial development programme that all enrolled subjects who reported race in the paediatric development programme were White.
Part II/Module SV.1.2	Clarification was added that post-marketing exposure data are not available for patients aged 2 to < 12 years as berotralstat is not yet approved for this age group.
	Updated cumulative exposure in patient-years for adults and adolescent patients based on sales data.
Part II/Module SVII.1.2	Added Study 304 and Study 312 for assessment of safety of long-term use of berotralstat in paediatric patients.
Part II/Module SVII.2	Added language explaining that the safety profile in paediatric patients 2 to < 12 years is consistent with observations from prior studies of berotralstat in the adult and adolescent population.
Part II/Module SVII.3.1	Updated post-marketing reporting data and any treatment-emergent adverse events (TEAEs) reported in the paediatric development programme for important potential risks hepatotoxicity, hypersensitivity, QT prolongation, drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4, phospholipidosis, and carcinogenicity.
	Information on recommended doses using Monte Carlo simulations for paediatric patients aged 2 to < 12 years was added.

	Table SVII.2 and text providing a summary of QTcF assessments with potentially clinically significant QTcF values in Study 304 subjects with Type 1 or 2 HAE was added. A dosing recommendation of 108 mg granules once daily (QD) for paediatric patients aged > 12 years and weighing < 40 kg was added.
Part II/Module SVII.3.2	Updated post-marketing reporting data for missing information: safety profile in pregnancy and breastfeeding and long-term safety in paediatric patients. Added a summary of safety conclusions from Study 304. Added age range for Study 304.
Part III.2	Updated dates for Study BCX7353-401 (Study 401) milestones. Study 304 and Study 312 added as Category 3 studies.
Part III.3	Updated the information on number of progress reports that have been submitted. Study 304 and Study 312 added as Category 3 studies.
Part V.1	Following updates made to Table Part V.1: Added/updated package leaflet (PL) and SmPC section numbers for each of the safety concerns.
Part V.2	Following updates made to Table Part V.2: Added/updated PL and SmPC section numbers for each of the safety concerns.
Part V.3	Study 304 and Study 312 added as Category 3 studies. Added specific adverse reaction follow-up questionnaires for paediatric patients (2 to < 12 years of age).
Part VI. I	Updated the proposed indication for the capsule and granules formulation.
Part VI.II.B	Added/updated PL and SmPC section numbers for each of the important potential risks. Study 304 and Study 312 added as additional pharmacovigilance activities.
Part VI.II.C.2	Study 304 and Study 312 added.
Annex 2	Updated milestones for Study 401 in Table 1. Study 304 and Study 312 added.
Annex 3	Study 304 and Study 312 added.
Annex 7	Updated references.
Annex 8	Added approval date and procedure number for Version 2.0; updated the summary of changes for Version 2.1. Study 304 and Study 312 added as Category 3 studies.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 4.0

Approved with procedure: EMA/X/0000268892

Date of approval (opinion date): 25-Jun-2026

Name[1]: Luke Lawlor

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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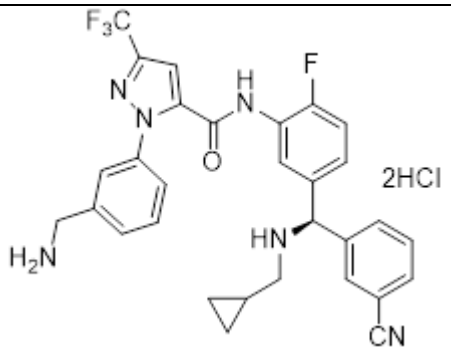
Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (International Non-proprietary Name [INN] or common name)	Berotralstat (as dihydrochloride)
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Other haematological agents, drugs used in hereditary angioedema, ATC code: B06AC06
Marketing Authorisation Holder	BioCryst Ireland Ltd Block 4, Harcourt Centre, Harcourt Road Dublin 2, DO2HW77 Ireland
Medicinal products to which this Risk Management Plan (RMP) refers	01
Invented name(s) in the European Economic Area (EEA)	Orladeyo
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Inhibitor of plasma kallikrein
	Summary of mode of action: Berotralstat is an inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high-molecular-weight kininogen (HMWK), releasing bradykinin (BK), a potent vasodilator that increases vascular permeability. In patients with hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired, which leads to uncontrolled increases in plasma kallikrein activity and BK release, resulting in HAE attacks consisting of swelling (angioedema).
	Important information about its composition: The chemical name of berotralstat is (*R*)-1-(3-(aminomethyl)phenyl)-*N*-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride. The molecular formula is $C_{30}H_{26}F_4N_6O$ • 2HCl, and the molecular weight is 635.48 g/mol (dihydrochloride). The chemical structure is:

	
Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/orladeyo-epar-product-information_en.pdf
Indication(s) in the EEA	Current: Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
	Proposed: Orladeyo granules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to less than 12 years.
Dosage in the EEA	Current: The recommended dose for adults and adolescents aged 12 years and older weighing ≥ 40 kg is 150 mg berotralstat once daily.
	Proposed: The recommended doses for paediatric patients aged 2 to < 12 years (based on body weight) are 72 mg, 96 mg, 108 mg, or 132 mg berotralstat once daily. In patients aged 12 years and older and weighing < 40 kg, a dose of 108 mg granules may be considered.
Pharmaceutical form(s) and strengths	Current: Hard capsule (capsule) 150 mg Capsule (19.4 mm × 6.9 mm) with white opaque body imprinted with "150" and light blue opaque cap imprinted with "BCX".
	Proposed: Oral film-coated white to off-white granules (approximately 2 mm in diameter) in unit-dose sachets
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Orladeyo capsules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Orladeyo granules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to less than 12 years.

Incidence: Not applicable.

Prevalence: HAE is a serious, life-threatening, rare genetic life-long disorder. The prevalence of HAE in the EEA is estimated based on the worst-case, i.e., the highest prevalence observed in an individual analysis. The highest prevalence was observed in Italy at approximately 1:65,000 (Zanichelli et al. 2015). Thus, it can be estimated that HAE affects approximately 0.15 in 10,000 inhabitants of the EU/EEA. Based on a population of 449 million, it can be estimated that there are about 7000 people currently affected with HAE in the EU (Eurostat 2025). Of interest, the prevalence of HAE in paediatric patients aged < 12 years was reported as 2.51:100,000 in a recently conducted study in Germany (Prenzel et al. 2023). Based on a population of 44 million individuals aged 2 to < 12 years in the EU, the estimated number of patients aged < 12 years with HAE in the EU is approximately 1100 (Eurostat 2025).

Because HAE is genetically determined, prevalence of HAE in the paediatric population is anticipated to be similar to adults. Attacks of HAE often begin in childhood, with 50% of female and male patients experiencing their first attack before the age of 12 and 13 years, respectively (Maurer et al. 2022).

Demographics of the population in the authorised indication age, gender, racial and/or ethnic origin and risk factors for the disease: There are no known differences in HAE prevalence due to sex, ethnicity, or race (Zuraw 2010).

Demographics of the population in the authorised indication of C1-INH deficient HAE (C1-INH-HAE) and clinical characteristics for the disease were determined by Mendivil and colleagues in a non-interventional web-based survey of 242 patients with HAE in Austria (n=13), France (n=58), Germany (n=7), Spain (n=39), Australia (n=28), Canada (n=32), Switzerland (n=8), and the United Kingdom (n=57) (Mendivil et al. 2021). Mean patient age (range) was 43.8 (18 to 92) years, and 67.4% of patients were female. Racial/ethnic data were not provided. The majority of patients (81.8%) had type 1 versus type 2 HAE. The mean (standard deviation [SD]) age of onset of symptoms and age at diagnosis were 11.5 (8.9) and 20.8 (13.2) years, with a mean (SD) delay in HAE diagnosis of 9.3 (11.0) years. Most patients (79.3%) had a family history of HAE.

HAE is a genetic condition inherited in an autosomal dominant pattern with nearly 100% penetrance (Agostoni and Cicardi 1992). Approximately three-quarters of cases are familial, and one-quarter arise from spontaneous new mutations in *SERPING1*. There are no other known risk factors (Mendivil et al. 2021).

The main existing treatment options:

The existing treatment options for the prevention of HAE attacks in adults and adolescent patients aged 12 years and older are shown in Table SI.1.

Table SI.1: Therapies Approved for the Prevention of HAE Attacks in ICH Regions (Europe, US, and Japan)

Drug, route	Europe (date of approval)	US (date of approval)	Japan
Danazol PO	Approved in some member states	Approved (1976)	Not approved
Stanozolol PO	Withdrawn	Not approved Discontinued (1984)	Not approved
Tranexamic acid PO	Approved in some EU member states (1969) CHMP advised member states to delete this indication (2012)[a]	Not approved	Not approved
Orladeyo® PO	Approved (2021)	Approved (2020)	Approved (2021)
Berinert® IV	Approved in some EU member states	Not approved	Approved (2017)
Cinryze® IV	Approved (2011)	Approved (2008)	Not approved
Berinert® 2000/3000 (Haegarda® SC)	Approved in some EU member states (2018)	Approved (2017)	Approved (2022)
Takhzyro® SC	Approved (2018)	Approved (2018)	Approved (2022)
Andembry® SC	Approved (2025)	Not approved	Approved (2025)

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; EU = European Union; HAE = hereditary angioedema; ICH = International Council for Harmonisation; IV = intravenous; PO = oral; SC = subcutaneous; US = United States; WAO/EACCI = World Allergy Organization / European Academy of Allergy and Clinical Immunology.
Note: Androgens are not recommended for long-term prophylaxis in adolescents prior to Tanner Stage V per WAO/EACCI HAE guidelines (Maurer et al. 2022).
[a] Source: EMA/680967/2012.

Plasma kallikrein is a proven target in the treatment of HAE. Plasma-derived purified C1-INH (Cinryze®, Berinert®) and a human recombinant C1-INH (Ruconest®) are licensed for the treatment of HAE acute attacks in the EU and United States (US).

Icatibant (Firazyr®) is also an acute attack medication option for most patients in the EU and US. Icatibant is a subcutaneously (SC) administered synthetic peptide that works distinctly from the other HAE treatments in that it functions as a BK B2 receptor antagonist. In the EU and the US, licensed therapy for prevention of HAE attacks is limited to purified plasma-derived C1-INH administered intravenously (IV; Cinryze) or SC (Haegarda® [US] and Berinert® 2000/3000 [EU]) every 3 to 4 days. Lanadelumab (Takhzyro®), a monoclonal antibody plasma kallikrein inhibitor administered by SC injection every 2 weeks, is also approved for preventative therapy in the US and Europe. More recently, Andembry® (garadacimab), a novel Factor XIIa-inhibitory monoclonal antibody administered as a once-monthly SC injection, received approval in the EU for prevention of recurrent attacks of HAE.

Ecallantide (Kalbitor®) is not approved in the EU but is approved in other regions. Kalbitor is an engineered recombinant protein non-covalent kallikrein inhibitor and is licensed in the US for treatment

of acute attacks of HAE by SC injection (Martello et al. 2012). Administration of ecallantide is associated with an approximately 4% rate of anaphylaxis.

Prophylaxis of HAE attacks with C1-INH aims to minimise the frequency and severity of attacks and prevent emergency room visits and/or hospitalisations by increasing circulating C1-INH levels. Long-term preventative therapy is typically used in patients who have frequent attacks, although prophylactic use is not based solely on attack rate but also on normalising the patient's quality of life (QoL) (Maurer et al. 2022). According to the Summary of Product Characteristics (SmPC), patients on Cinryze with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely. Indwelling ports pose a significant risk of thrombosis and infection, and their use has been discouraged (Zuraw et al. 2013). In addition, hypersensitivity to C1-INH may occur in some patients and epinephrine should be immediately available at the time of treatment. Cinryze is contraindicated for patients with hypersensitivity to the active substance or any of its excipients.

For Berinert 2000/3000, the most common adverse drug reactions (ADRs) with an incidence of ≥ 1 in 10 patients are injection site reactions and nasopharyngitis. ADRs that occur in ≥ 1 in 100 patients are hypersensitivity and dizziness.

Warnings and precautions for Takhzyro include hypersensitivity reactions. The most common ADRs with an incidence of ≥ 1 in 10 patients are injection site reactions and those ADRs that occur in ≥ 1 in 100 patients are hypersensitivity, dizziness, rash maculo-papular, myalgia, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased.

For Andembry, the most common ADRs with an incidence of ≥ 1 in 100 patients are injection site reactions, headache, and abdominal pain.

Berotralstat (BCX7353; Orladeyo) is a small-molecule inhibitor of plasma kallikrein. Warnings and precautions for Orladeyo include hypersensitivity. Patients with moderate or severe hepatic impairment may develop increased serum berotralstat concentrations that are associated with a risk of prolonged QT. Use of berotralstat in these patients should be avoided. Patients with severe renal impairment may be at risk of prolonged QT. In patients aged 12 years or older, it is preferable to avoid the use of berotralstat in patients with severe renal impairment. In children aged 2 years to < 12 years, use of berotralstat in patients with severe renal impairment should be avoided. If treatment is required, appropriate monitoring (e.g., electrocardiograms [ECGs]) should be considered.

There are no data available for the use of berotralstat in patients with independent risk factors for QT prolongation such as electrolyte disturbances, known pre-existing QT prolongation (either acquired or familial), advancing age, or concomitant use of other medicinal products known to prolong the QT. It is preferable to avoid the use of berotralstat in these patients. If treatment is required, appropriate monitoring (e.g., ECGs) should be considered.

Oral attenuated androgens, such as danazol, are also used for prevention of HAE attacks in some countries but not all EU member states. While oral administration of androgens is convenient, unacceptable adverse effects (including androgenic hormonal effects [masculinisation], intracranial hypertension, and risk of hepatocellular adenoma/carcinoma and contraindications [including pregnancy]), as well as the fact that safety and efficacy have not been established in paediatric patients, limit their clinical use (Maurer and Magerl 2011; Cicardi et al. 2012). World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend the use of androgens only as second-line prophylaxis (recommendation 18, Maurer et al. 2022).

Therapies approved for prophylaxis in paediatric patients aged < 12 years are limited to Takhzyro, Berinert 2000/3000, and Cinryze (Table SI.2).

Table SI.2: Therapies Approved for Prophylaxis to Prevent HAE Attacks in ICH Regions (EU, US, and Japan) for Paediatric Patients Aged 2 to < 12 Years

Drug, Route of Administration	**European Union** (Date of Approval and Subject Age if Available)	**United States** (Date of Approval and Subject Age)	**Japan**
Takhzyro® (lanadelumab-flyo) SC	Approved (2023 for subjects aged ≥ 2 years)	Approved (2023 for subjects aged ≥ 2 years)	Not approved
Berinert® 2000/3000 (Brand name in the European Union) SC or Haegarda® (C1-INH [human]; brand name in the United States) SC	Approved in some EU member states (2021; evaluated in subjects aged ≥ 8 years)	Approved (2020 for subjects aged ≥ 6 years)	Not approved
Cinryze® (C1-INH [human]) IV	Approved (2017 for subjects aged ≥ 6 years; also for pre-procedure prevention of angioedema attacks in subjects aged ≥ 2 years)	Approved (2018 for subjects aged ≥ 6 years)	Not approved

Abbreviations: C1-INH = C1 esterase inhibitor; EU = European Union; HAE = hereditary angioedema; ICH = International Council for Harmonisation; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; US = United States.

Note: Age as stated in the approved prescribing information and label.

Oral androgens (e.g., danazol) have numerous side effects that limit dosing, efficacy, and tolerability; in addition, the safety and effectiveness of danazol in paediatric patients have not been established (Sanofi-Aventis 2011). The WAO/EAACI HAE guidelines do not recommend the use of long-term anabolic androgens for paediatric patients prior to Tanner Stage V (Maurer et al. 2022). Other oral agents used off-label in paediatric patients, such as tranexamic acid, lack efficacy data and are not recommended for prophylaxis per WAO/EAACI guidelines (Maurer et al. 2022). In 2012, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended that HAE be deleted as an indication from the tranexamic acid product information due to an unfavourable benefit-risk balance. However, in countries where targeted long-term prophylaxis (LTP) is not available, tranexamic acid may be helpful for paediatric HAE patients and is preferred to androgens due to its better safety profile (Maurer et al. 2022).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

HAE is a serious and potentially life-threatening genetically determined disease of dysregulation of the contact activation pathway (Kaplan and Joseph 2014). HAE is characterised clinically by recurrent episodes (attacks) of angioedema of the skin, pharynx, larynx, gastrointestinal (GI) tract, genitals, and extremities (Longhurst and Cicardi 2012).

The frequency of attacks in HAE patients not taking a prophylactic medication varies, from rarely in some to every few days in others, with 59% reporting at least 1 attack per month (Caballero et al. 2014). In the non-interventional survey of 242 patients discussed above, patients reported having a mean (range) of 12.5 (0 to 90) attacks during the previous 6-month period, with 31.8% having ≥ 13 attacks and 19.8% having 7 to 12 attacks. The majority (79.7%) of patients reported having an attack in the previous month (Mendivil et al. 2021).

Angioedema attacks may or may not be precipitated by a stimulus (such as stress, trauma, infection, or changes in hormonal levels with menses) and typically progress over several hours, with symptoms, if left untreated, subsiding gradually over the following 3 to 5 days (Zuraw and Christiansen 2011). Oropharyngeal and especially laryngeal swelling can be fatal, and the progression of symptoms is more rapid than in other locations due to the anatomy of the upper airway (Bork et al. 2012). Attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring. Abdominal attacks are especially painful and may result in unnecessary surgical procedures if HAE is not recognised as causal. Patients surveyed indicated attacks most frequently affected the trunk (75.6%) and extremities (43.0%), with laryngeal attacks reported by 6.6% of patients (Mendivil et al. 2021). The most commonly reported symptoms included: tiredness, abdominal pain, and abdominal swelling (> 50% each); swelling in the extremities, nausea, diarrhoea, dizziness, and pain outside the abdominal area (20.2% to 38% each). Life-threatening swelling of the throat or mouth were reported by 9.9% of patients and difficulty swallowing and difficulty breathing were reported by 7% each.

The presentation of disease in paediatric patients with HAE is similar to adults. Both adult and paediatric patients experience recurrent unpredictable acute attacks of painful SC or submucosal swelling of the face, larynx, tongue, GI tract, limbs, or genitalia, which, if untreated, may last up to 5 days and can be fatal (Frank 2006). The clinical disease presentation is similar; for example, Nanda et al. reported that in a paediatric cohort of 15 patients, abdominal, peripheral, and laryngeal attacks occurred at least once in 93%, 73%, and 27% of paediatric patients, respectively (Nanda et al. 2015). A study of 80 adults showed that abdominal, peripheral, and laryngeal attacks (included laryngeal, neck area, or oesophagus areas) occurred in 81.5%, 85.2%, and 28.4% of patients, respectively (Magerl et al. 2020), reflecting a similar profile of disease presentation in paediatric patients and adults.

HAE has a significant impact on functionality and QoL. In the patient survey, overall physical and mental health scores on the Short Form Health Survey (SF-12v2) were lower than those in the general population, indicating worse mental health in patients with HAE. A total of 38.0% and 17.4% of patients reported moderate to severe anxiety or depression as assessed by the Hospital Anxiety and Depression Scale (HADS) (Mendivil et al. 2021). Scores on the health-related QoL instrument EuroQoL 5-dimensional, 5-level questionnaire (EQ-5D-5L) in HAE patients in Sweden showed more severe impact on QoL with increased frequency of attacks, and absenteeism higher with increasing attack severity (Nordenfelt et al. 2014). In a survey of HADS scores in HAE patients in Spain, Germany, and Denmark, clinically meaningful anxiety and depression were seen in 38% and 14% of patients (Caballero et al. 2014), respectively, despite the widespread use of modern on-demand treatments for acute attacks (Caballero et al. 2014). In a US survey, HAE was associated with reduced productivity to a degree similar to severe asthma; missed opportunities in education and career advancement; decreased physical and mental health; and worse depression scores (Lumry et al. 2010).

Prior to introduction of modern treatments, the estimated risk of premature mortality from HAE was up to 30%. The risk of mortality from asphyxiation has substantially decreased due to improved diagnosis and treatment options but is still much higher in undiagnosed patients with HAE than in diagnosed patients (Minafra et al. 2022). However, deaths still occur in diagnosed patients with access to care at

centres of excellence, including in the EU (Bork et al. 2012). Although life-threatening laryngeal attacks represent a small proportion of attacks, approximately half of patients with HAE have had one or more laryngeal attacks, and the risk of asphyxiation due to laryngeal oedema is life-long (Bork et al. 2012). Asphyxiation ranks as the top fear in patients with HAE (Bygum 2009).

Important co-morbidities:

In the non-interventional survey of 242 patients discussed above (Mendivil et al. 2021), common reported comorbidities were anxiety (26.0%), GI disorders (17.8%), depression (16.9%), high cholesterol (13.6%), and hypertension (12.8%). Of the patients who reported having anxiety and depression, 33.3% and 43.9%, respectively, reported using medication to treat these conditions. A recent study in Sweden (Björkman et al. 2022) compared 239 patients with HAE to controls from the general population matched by age, gender, and county of residence and found the risk of cardiovascular disease was higher in patients with HAE (odds ratio [OR] 1.83 [95% confidence interval (CI) 1.32, 2.54]), including arterial thrombosis/embolus (OR 6.74 [95% CI 1.89, 24.06]), hypertension (OR 1.64 [95% CI 1.12, 2.39]), and venous thrombosis/embolus (OR 4.20 [95% CI 2.42, 7.23]). Patients with HAE also had an increased risk of autoimmune disease (OR 1.65 [95% CI 1.15, 2.35]) but did not have an increased risk of cancer (OR 0.89 [95% CI 0.57, 1.42]).

Part II: Module SII – Non-clinical part of the safety specification

The toxicological effects of berotralstat have been thoroughly evaluated in general toxicity studies of up to 26 weeks dosing duration in rats and up to 39 weeks dosing duration in non-human primates (NHPs).

These toxicity studies have identified the principal target organs in rats and NHPs, which are the liver and kidney. In addition, phospholipidosis (PLD) was observed in the liver via electron microscopy (EM) and suspected in the small intestine, lung, spleen, and lymphoid tissue. There were no direct toxicities associated with its presence. The respiratory system of rats is affected at higher doses, likely an indirect effect of irritant properties of berotralstat in the nasal cavity following gavage-related gastric reflux causing breathing-related difficulties. High doses of berotralstat in the 28-day studies were associated with findings of skeletal and cardiac (rat only) muscle degeneration which was not observed at the highest dose in the 26-week rat toxicity study. However, skeletal muscle necrosis/degeneration was noted in the 104-week rat carcinogenicity study although there were no clinical observations in any animal that correlated with this microscopic lesion.

Definitive embryo-foetal studies have been completed with berotralstat in rats and rabbits with no effect on fertility, pregnancy, foetal weights, malformations, embryolethality, or embryo-foetal growth or foetal dysmorphogenesis. Berotralstat has no identifiable genotoxic risks, as it was not mutagenic in bacteria, did not cause chromosomal aberrations in human lymphocytes, and was not clastogenic in the micronucleus assay. Overall, there are no concerns for reproductive toxicity or genotoxicity. In addition, berotralstat has no phototoxicity potential.

A comprehensive assessment of juvenile toxicity in juvenile rats has been completed with no BCX7353-related effects on survival, clinical findings, body weights/body weight gain, sexual maturation, femur/tibia length and width measurements, haematology parameters, or macroscopic findings at any dose level. Toxicological findings in the study were considered non-adverse and were limited to those previously observed in adult animals. Based on these results, there are no concerns for the administration of berotralstat to paediatric patients aged 2 to < 12 years.

Carcinogenicity studies found no definitive evidence for berotralstat-related increases in tumours in a 6-month transgenic mouse study or in a 2-year rat study. Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an area under the curve [AUC] basis) at the clinical 150 mg berotralstat dose. These findings are inconclusive, with an incidence slightly higher than in control groups.

The nonclinical development programme has thoroughly evaluated the pharmacology, pharmacokinetics (PK), drug disposition, and toxicity of berotralstat, and supported the approval of berotralstat for the prevention of angioedema attacks in adult and adolescent patients with HAE.

Table SII.1 summarises the safety concerns from nonclinical studies and the relevance to the proposed clinical use of berotralstat.

Table SII.1: Safety Concerns from Nonclinical Studies

Safety Concern	Relevance to Human Usage
Cardiovascular effects: During nonclinical development, berotralstat inhibited the hERG ion channel. Berotralstat caused a concentration-related inhibition of the potassium current carried by this channel; the IC_{50} was 0.29 µM. Although the hERG channel is inhibited, the APD in rabbit Purkinje fibers was not prolonged. Sodium and calcium channels were also inhibited and the lack of effect on the APD may be due to these counterbalancing effects. Although there was no evidence for any skeletal muscle or cardiac muscle injury in the 13-week studies in either rats or NHPs, or the 26-week study in rats and 39-week study in NHPs, in the 28-day study in rats, degeneration/necrosis and/or regeneration were noted in skeletal muscle and cardiac muscle and were considered adverse at 75 mg/kg/day. There was no evidence of foamy or vacuolated cells in the heart in either the rat or the NHPs. In addition, at high single doses of berotralstat, NHPs had decreases in BP and HR, with corresponding ECG changes consisting of slowing of the HR and lengthening of the RR, QT, and QTc intervals and QRS duration. However, ECG changes were not observed at doses up to 80 mg/kg/day for 39 weeks.	No clinically significant QTc prolongations or arrythmias were observed in the Phase 2/3 long-term studies. In the thorough QT/QTc Study 106, at the C_{max} of berotralstat at the recommended dose of 150 mg once daily, the mean QTc increased by 3.4 msec (90% upper CI bound of 6.8 msec), which is below the 10 msec threshold for regulatory concern. The effects of berotralstat on multiple cardiac ion channels may confer protection from TdP as suggested by the lack of J to T peak prolongation. At a supratherapeutic dose of 450 mg once daily, steady-state exposures were 4-fold higher than achieved at the recommended 150 mg dose, and QTc increased by a mean of 21.9 msec. Myocardial injury was assessed by CK-MB and troponins I and T, which were routinely monitored across the clinical development programme. Other than 1 subject in Study 204 who experienced an acute myocardial infarction due to a congenital myocardial bridge, no indication of cardiac injury was observed. Paediatric population: aged 2 to < 12 years: There were no TEAEs from the Torsade de pointes/QT prolongation SMQ or palpitation PT in Study 304. Also, no seizure events were reported.
Liver effects: In the 39-week chronic toxicology study in NHPs, there were increases in ALT and AST that were partially resolved during the study despite continued dosing. At the higher doses (≥ 30 mg/kg/day), mild to moderate increases in AST and ALT were noted in both sexes, partially resolved during dosing, and were fully resolved at the end of the recovery period. Increased liver weights corresponded to microscopic findings of centrilobular to panlobular hepatocellular hypertrophy, which was considered adverse at doses > 30 mg/kg/day given the severity of the	No subjects met the criteria for Hy's Law. In the integrated Phase 2/3 LTP studies the overall subject incidence of ALT > 3 × ULN was 4.7% (16 of 342 subjects); all 16 subjects had previously used androgens for HAE and 14 of the 16 subjects discontinued androgens within 7 to 9 days of starting berotralstat. ALT elevations were primarily laboratory abnormalities that occurred early on in treatment without clinical symptoms. All transaminase elevations resolved without treatment, and in some subjects while they continued dosing with berotralstat. This suggests an adaptive response. The association of transaminase elevation with acute androgen

Safety Concern	Relevance to Human Usage
findings and the associated ALT and AST increases. The liver microscopic findings resolved over the recovery phase.	cessation independent of berotralstat exposure has not previously been reported but has been observed in the berotralstat clinical programme. The subject incidence of baseline ALT > 1.5 × ULN was 3.8% (13 of 342) with 12/13 having prior androgen exposure. A single dose of berotralstat 150 mg was safe and generally well tolerated in subjects with hepatic impairment (mild, moderate, or severe; Study 108). No dose adjustment is required for patients with mild hepatic impairment. Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided. Paediatric population: aged 2 to < 12 years: No hepatotoxicity-related AEs were reported in Study 304. The paediatric development programme did not enrol subjects with hepatic impairment. A comprehensive review of laboratory results from Study 304 (subjects aged 2 to < 12 years) found no evidence to suggest that study drug resulted in clinically significant hepatic changes.

Safety Concern	Relevance to Human Usage
Renal effects: Mild to moderate tan discolouration of kidneys was seen in female NHPs at 80 mg/kg/day and male NHPs at 55 and 80 mg/kg/day when dosed for 39 weeks. These findings corresponded to renal tubular hyperplasia and/or mononuclear cell infiltration in affected animals. Kidney organ weights were increased in males at 55 and 80 mg/kg/day and females at 80 mg/kg/day and corresponded to microscopic findings of tubular epithelial hyperplasia. An array of kidney findings, including minimal to moderate tubular hyperplasia, minimal to mild mononuclear cell infiltrates, and/or minimal to mild tubular degeneration were seen in a generally dose-dependent pattern of increasing severity and/or incidence in males and females at 55 and 80 mg/kg/day.	Renal assessments of BUN, serum creatinine, CL_{CR}, and urinalysis were conducted routinely throughout the clinical development programme to monitor for renal safety. Based on the animal data, 2 additional measures of kidney health were monitored: NGAL, a novel marker for early tubular injury and UACR, a marker of glomerular injury. No signal was seen in Study 203. Continued assessment in the Phase 2/3 prophylactic HAE Studies 204 and 302 was performed. No evidence of early or chronic renal injury, either glomerular or tubular, was identified at any time in the clinical development programme. A single dose of berotralstat 200 mg was safe and generally well tolerated in subjects with severe renal impairment (Study 107). Renal excretion is not a significant route of elimination for berotralstat. Paediatric population: aged 2 to < 12 years: The paediatric development programme did not enrol subjects with renal impairment. A comprehensive review of renal chemistry results from Study 304 (subjects aged 2 to < 12 years) found no evidence to suggest that study drug resulted in clinically significant renal changes.
GI effects (berotralstat-related non-serious vomitus and diarrhoea): In NHPs, increased incidences of vomitus, soft faeces, and/or watery faeces were considered berotralstat-related clinical observations in animals given 55 or 80 mg/kg/day but were not considered adverse since none of the signs were observed every day and more severe signs did not develop during the dosing period. Thin appearance and inappetence were noted in animals at 80 mg/kg/day. These latter signs correlated with the lower body weights and body weight losses observed in the animals given 80 mg/kg/day.	Mild to moderate GI symptoms were initially noted in the FIH study. The events were primarily nausea, vomiting, abdominal pain, and diarrhoea. There was an increase in mild GI abdominal events in multiple-day dosing at the highest dose (500 mg [SN] QD × 7 days) and longer duration (350 mg [SN] QD × 14 days). The risk mainly represents one of tolerability as subjects have not had associated laboratory abnormalities or sequelae such as dehydration. Some subjects have discontinued study drug due to GI events, but all recovered. These reactions generally occurred early after initiation of treatment with berotralstat, became less frequent with time, and typically resolved without medication. These events were reported in the same manner as other TEAEs in the Phase 2 and 3 studies although there was additional analysis of GI events. Paediatric population: aged 2 to < 12 years:

Safety Concern	Relevance to Human Usage
	No increase in the severity of berotralstat GI AEs was noted in paediatric subjects compared with those seen in adults and adolescents.
Skeletal muscle effects: Although there was no evidence for any skeletal muscle or cardiac muscle injury in the 13-week studies in either rats or monkeys, or the 26-week study in rats and 39-week study in monkeys, in the 28-day study in rats, degeneration/necrosis and/or regeneration were noted in skeletal muscle and cardiac muscle and were considered adverse at 75 mg/kg/day. Although not designed for general toxicity findings, skeletal muscle degeneration/regeneration noted by histology only was present in the 104-week rat carcinogenicity study.	There has been no evidence of skeletal muscle effects from berotralstat. CPK levels were monitored throughout the clinical programme as a routine laboratory test and confirmed the lack of significant change with long-term dosing. During clinical development, there were no significant elevations in CPK that were not explained by exercise or injury. There was no evidence of any AEs of potential muscular injury or sequelae such as lethargy. Paediatric population: aged 2 to < 12 years: There was no evidence of skeletal muscle effects from berotralstat in the paediatric population. No significant elevations in CPK occurred and there was no evidence of any AEs of potential muscular injury.
Increases in urinary levels of the experimental biomarker for PLD, BMP: High doses induced effects that were consistent with a process known as PLD, which was subsequently confirmed in the liver via electron microscopic evaluation of the liver from rats in the 13-week toxicity studies. EM demonstrated myelinosomes within the cytoplasm of Kupffer cells. Dose-dependent increases in the urinary concentrations of the experimental biomarker for PLD, BMP, were observed in rats and NHPs. These effects observed by light and EM correlate with increased BMP in the urine in the rat and are consistent with PLD. PLD has been noted in nonclinical toxicity studies with several approved drugs, and the significance of PLD findings in humans is unknown (Chatman et al. 2009). PLD is considered an adaptive response to the presence of a drug, rather than a toxic manifestation, and PLD in animals is not predictive of similar findings clinically. PLD in humans becomes meaningful if there is associated organ toxicity.	As it was unknown if this process would occur in humans early in development, D_LCO was performed as a theoretical marker of foamy macrophage deposition in the lung. A 20% decrease was chosen as the threshold for analysis based on reported high intra-subject variability for subjects with high baseline D_LCO measurements (i.e., no baseline lung disease consistent with healthy volunteers and HAE subjects). Up to 35.5% of subjects in a study of patients without overt lung disease had a > 10% intra-subject change from baseline (Drummond et al. 2009), suggesting that up to 20% was a reasonable variation between measurements for any individual subject enrolled in this healthy subject study. In the studies utilising D_LCO, there was no dose- or duration-related increase in frequency or severity in vital signs or D_LCO. In addition, BMP, the experimental marker used in the toxicology studies, was measured in Study 203. There was no clinically meaningful CFB in plasma BMP levels in berotralstat-treated subjects vs. placebo or evidence of organ dysfunction in berotralstat-treated subjects. With the lack of clinical, D_LCO and BMP findings, there was no evidence of PLD occurring in humans with 28 days of berotralstat dosing. Based on the lack of toxicity in animals and the initial clinical

Safety Concern	Relevance to Human Usage
	data, PLD was to be assessed through routine safety measures to assess any organ injury. No further BMP or D_LCO testing was performed in subsequent studies, including the long-term safety study (Study 204) and the Phase 3 pivotal study (Study 302). Monitoring was by assessment of AEs and safety labs that could reveal organ involvement. Across the clinical development programme for berotralstat, there was no evidence of adverse effects due to PLD and no evidence of any end-organ changes. Paediatric population: aged 2 to <12 years: No PLD-related TEAEs were reported in Study 304.
Carcinogenicity: Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose. Undifferentiated sarcoma was present in 3 of 60 (5%) berotralstat-treated males at 20 mg/kg/day, compared to 0/60 control males. This increase was just statistically significant using the Poly-3 pair-wise test for rare tumours (p = 0.033). However, this tumour was not likely test article-related because there were no undifferentiated sarcomas in females at 8 or 20 mg/kg/day, and 1 of 60 control females (1.7%) were affected. Further, the plasma drug exposure to berotralstat is similar in male and female rats in this study and does not support a berotralstat effect in males or females. Undifferentiated sarcoma can include the differential diagnoses of liposarcoma, fibrosarcoma, leiomyosarcoma, malignant schwannoma, and rhabdomyosarcoma (Wojcinski et al. 2013). In the literature, the incidence of spontaneous sarcoma/ fibrosarcoma in male Wistar Han rats is up to 4% (Bomhard 1992). In the NTP database, the incidence of fibroma/fibrosarcoma, sarcoma, myoma, myosarcoma, or fibrous histioma is up to 4%. Thus, the incidence of sarcoma (5%) in the skin of male rats administered 20 mg/kg/day in the 2-year	It is unknown if this has any clinical relevance to humans. The longest duration of dosing is approximately 3 years and no reports of tumour thought to be related to berotralstat exposure have been reported. Paediatric population: aged 2 to < 12 years: No carcinogenicity-related TEAEs were reported in Study 304.

Safety Concern	Relevance to Human Usage
oncogenicity study is similar to spontaneous rates in published literature (4%), and therefore suggests the finding is not related to treatment with berotralstat. These nonclinical findings related to carcinogenicity are inconclusive, with an incidence slightly higher than in control groups.	

Abbreviations: AE = adverse event; ALT = alanine transaminase; APD = action potential duration; AST = aspartate transaminase; AUC = area under the curve; BMP = di-docosahexaenoyl (22:6)- Bis(mono)acylglycerol phosphate; BP = blood pressure; BUN = blood urea nitrogen; CFB = change from baseline; CI = confidence interval; CK-MB = creatinine kinase-MB; CL_{CR} = creatinine clearance; C_{max} = maximum observed concentration of the drug; CPK = creatine phosphokinase; D_LCO = pulmonary diffusion of carbon monoxide; ECG = electrocardiogram; EM = electron microscopy; EOP2 = end of Phase 2; FDA = Food and Drug Administration; FIH = first-in-human; GI = gastrointestinal; HAE = hereditary angioedema; hERG = human ether-à-go-go-related gene; HR = heart rate; IC_{50} = half-maximal inhibitory concentration; LTP = long-term prophylaxis; NGAL = neutrophil gelatinase-associated lipocalin; NHP = non-human primate; NTP = National Toxicology Program; PLD = phospholipidosis; PT = preferred term; QD = once daily; QRS = Q, R, and S waves complex; QTc = corrected QT interval; SMQ = standardised MedDRA query; SN = salt nomenclature; Study BCX7353-106 = Study 106; Study BCX7353-107 = Study 107; Study BCX7353-108 = Study 108; Study BCX7353-203 = Study 203; Study BCX7353-204 = Study 204; Study BCX7353-302 = Study 302; Study BCX7353-304 = Study 304; TdP = Torsade de Pointes; TEAE = treatment-emergent adverse event; UACR = urine microalbumin-to-creatinine ratio; ULN = upper limit of normal; US = United States.

Part II: Module SIII - Clinical trial exposure

The clinical development programme for berotralstat granules for routine prevention of recurrent attacks of HAE in subjects aged 2 to < 12 years consists of a single ongoing Phase 3, open-label, safety and PK study, Study BCX7353-304 (Study 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. Study 304 was designed to enrol subjects aged 2 to < 12 years. Consequently, median subject age in Study 304 was 8.0 years, ranging from 3 to 11 years.

A total of 1256 unique subjects had exposure to berotralstat across the clinical development programme. At the time this summary was prepared in 2023, there were 7 subjects from Study 304 (3 subjects received 108 mg granules and 4 subjects received 150 mg capsule) included in Table SIII.3. Given the differences in study designs and subject populations, information for all subjects from Study 304 has not been integrated with prior berotralstat clinical studies in adult and adolescent patients and is presented separately in support of the paediatric line extension for this RMP. Now that Study 304 is fully enrolled and an interim analysis is complete, the exposure summary for all 4 cohorts of Study 304 subjects (29 subjects) is presented in Table SIII.1 below.

As Study 304 is ongoing, an interim analysis is available (data cutoff date 11-Sep-2024, Table SIII.1). The integrated data set tables (Table SIII.2, Table SIII.3, Table SIII.4, and Table SIII.5) presented below were prepared in 2023.

These integrated tables were assessed for relevance over time and no new significant exposure data impacted the tables.

A summary of berotralstat exposure for all 4 cohorts (29 subjects) from Study 304 as of the data cutoff date 11-Sep-2024 is provided in Table SIII.1.

Table SIII.1: Study 304: Summary of paediatric exposure (subjects aged 2 to < 12 years) to berotralstat

Summary	Dose of Berotralstat[a]				
	Cohort 1 150 mg Capsules (N = 7)	Cohort 2 108 mg Granules (N = 9)	Cohort 3 96 mg Granules (N = 9)	Cohort 4 78 mg Granules (N = 4)	Total (N = 29)
Overall duration of exposure (weeks)[b]					
n	7	9	9	4	29
Mean	59.16	45.30	36.21	24.25	42.92
SD	12.213	20.145	14.023	0.703	18.336
Median	52.14	48.14	37.00	24.21	48.14
Min, max	47.9, 72.1	18.1, 73.0	12.1, 51.0	23.4, 25.1	12.1, 73.0
Overall duration of exposure categories (days)[c]					
≤ 84 days	0	0	0	0	0
85 – 168 days	0	2 (22.2%)	3 (33.3%)	1 (25.0%)	6 (20.7%)
169 – 252 days	0	1 (11.1%)	1 (11.1%)	3 (75.0%)	5 (17.2%)
253 – 336 days	1 (14.3%)	1 (11.1%)	1 (11.1%)	0	3 (10.3%)
337 – 504 days	3 (42.9%)	3 (33.3%)	4 (44.4%)	0	10 (34.5%)
505 – 672 days	3 (42.9%)	2 (22.2%)	0	0	5 (17.2%)
> 672 days	0	0	0	0	0
Overall cumulative exposure (mg)[d]					
n	7	9	9	4	29
Mean	51,521.1	32,729.3	23,752.0	12,207.0	31,648.6
SD	11,511.88	15,638.12	9130.57	702.00	17,183.89
Median	50,550.0	37,668.0	25,476.0	12,090.0	31,200.0
Min, max	36,510, 73,500	13,716, 55,080	8064, 34,080	11,622, 13,026	8064, 73,500
Day 1 – Week 12 (Part 1) cumulative exposure (mg)[d]					
n	7	9	9	4	29
Mean	11,723.1	8484.0	7893.3	6123.0	8756.9
SD	1294.75	801.15	229.09	809.35	2020.43
Median	12,450.0	8856.0	7968.0	6474.0	8100.0
Min, max	9300, 12,750	6588, 9072	7392, 8064	4914, 6630	4914, 12,750
Week 13 – Week 48 (Part 2) cumulative exposure (mg)[d]					
n	7	8	8	4	27
Mean	39,798.0	25,209.0	17,841.0	6084.0	23,974.9
SD	11,158.75	16,122.36	7601.95	709.19	15,589.40

Summary	Dose of Berotralstat[a]				
	Cohort 1 150 mg Capsules (N = 7)	Cohort 2 108 mg Granules (N = 9)	Cohort 3 96 mg Granules (N = 9)	Cohort 4 78 mg Granules (N = 4)	Total (N = 29)
Median	37,800.0	29,202.0	20,196.0	6240.0	24,192.0
Min, max	24,840, 60,900	4644, 46,224	7104, 26,400	5148, 6708	4644, 60,900

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation.
Note: As of the interim data cutoff date, 11-Sep-2024.
Note: Summary table is based on initial dose assignment. See Listing 16.2.5.2 (Study BCX7353-304) for subjects with a change in dosing. Exposure may be under-estimated because last visit prior to interim database lock is used for the calculation of exposure duration.
Note: Subjects were assigned to cohorts based on baseline weight and did not change cohorts in the event of a dose modification; therefore, a given cohort may have included subjects with differing dose levels at any given time.
[a] Cohort 1: ≥ 40 kg, Cohort 2: 32 to < 40 kg, Cohort 3: 24 to < 32 kg, and Cohort 4: 12 to < 24 kg at baseline.
[b] The duration of exposure in weeks was calculated as the duration of exposure in days divided by 7.
[c] The duration of exposure in days was calculated as last dose date - first dose date + 1.
[d] Cumulative exposure in milligrams was calculated as the number of doses multiplied by the dose amount of the period. Missing return information may have prevented this calculation for some subjects.
Source: Study BCX7353-304 CSR Table 14.1.5.1.1.

Subjects enrolled in Study 304 were almost evenly split by sex (48.3% female subjects and 51.7% male subjects), potentially reflective of the age of the subjects at study enrolment (i.e., subjects enrolled prior to puberty, when the onset of more severe symptoms are typically observed in females) (Cancian et al. 2023).

Study 304 is being conducted in countries in the EU (Austria, France, Germany, Italy, Poland, and Spain), the UK, Canada, and Israel.

HAE is a rare genetic disease that has no ethnic or geographic bias; however, early detection may vary based on the geographic region due to variation in disease awareness and accessibility of disease-specific laboratory assays. Phenotypic expression is similar across populations regardless of ethnicity or geographic region, as reflected in uniformity in international diagnostic and treatment guidelines that recommend similar approaches to diagnosis, treatment of acute attacks, and long-term prophylaxis for patients with HAE (Busse et al. 2021; Maurer et al. 2022).

Race and ethnicity information were only available for 75.9% and 86.2% of subjects in Study 304, respectively. Seven subjects were enrolled at sites in France, where the collection of race/ethnicity information is typically not permissible per country regulations.

All subjects who reported race and ethnicity were White and not Hispanic or Latino. Race and ethnicity information for subjects in Study 304 was similar to that observed in Study BCX7353-302 (Study 302) and Phase 3 studies of other prophylactic therapies (Longhurst et al. 2017; Banerji et al. 2018; Maurer et al. 2024) where the majority of subjects were White and not Hispanic or Latino.

The clinical development programme for berotralstat is comprised of 22 studies to date; 16 Phase 1 studies and 6 Phase 2 or 3 studies (including paediatric Study 304), 5 of which were for prophylaxis of HAE.

In all clinical studies, active study drug was administered as the berotralstat dihydrochloride salt. In describing the mg dose of investigational medical product administered, early studies used a

berotralstat salt dose nomenclature (denoted as SN) rather than a berotralstat free base equivalent nomenclature. For the integrated analyses, dose is described in free base equivalents. Throughout this RMP, after first mention, the clinical studies are referred to by abbreviated names in the text (as noted in this section), and the full study identifier is used in some tables.

A summary of duration of exposure by indication and dose in clinical studies is provided in Table SIII.2. Subsequent tables provide data in line with EU RMP requirements for duration of exposure by dose, age group and gender and ethnic origin are provided in subsequent tables below Table SIII.2, Table SIII.3, Table SIII.4, and Table SIII.5.

Table SIII.2: Duration of Exposure by Indication and Dose

Duration of exposure	Patients	Person time *
Cumulative for all indications		
< 1 month	56	1.48
1 to < 3 months	60	7.61
3 to < 6 months	41	12.78
≥ 6 months	416	862.84
Total	573	884.70
Indication: Prophylaxis[a]		
Duration of exposure	Patients	Person time*
< 1 month	44	1.42
1 to < 3 months	55	6.61
3 to < 6 months	40	12.32
≥ 6 months	421	881.44
Total	560	901.79
Acute attacks[a]		
< 1 month	58	0.30
1 to < 3 months	0	0
3 to < 6 months	0	0
≥ 6 months	0	0
Total	58	0.30
Treatment Group: 110 mg BCX7353[b]		
< 1 month	7	0.34
1 to < 3 months	18	2.48
3 to < 6 months	6	1.77
≥ 6 months	138	303.73
Total	169	308.32
Treatment Group: 150 mg BCX7353		
< 1 month	19	0.89
1 to < 3 months	25	3.80
3 to < 6 months	35	11.01
≥ 6 months	278	559.10
Total	357	574.80

[a] Subjects can be counted in both indications if they received active treatment in Study 202 and were also in Studies 203 or 204.
[b] Subjects who received 108 mg granules are included in the 110 mg group.
* Person time was calculated in person years.

Table SIII.3: Age Group and Gender by Indication and Dose

Age group	Patients		Person time *	
	M	F	M	F
Cumulative for all indications				
2-11 years	2	5	0.28	0.79
12-17 years	14	20	19.70	31.99
18-64 years	184	324	277.43	518.61
65-74 years	8	15	14.21	21.20
75-84 years	0	1	0	0.49
≥ 85 years	0	0	0	0
Total	208	365	311.63	573.07
Indication: Prophylaxis[a]				
2-11 years	2	5	0.28	0.79
12-17 years	14	20	19.70	32.91
18-64 years	182	313	281.45	529.39
65-74 years	8	15	15.13	21.66
75-84 years	0	1	0	0.49
≥ 85 years	0	0	0	0
Total	206	354	316.56	585.23
Acute Attacks[a]				
2-11 years	0	0	0	0
12-17 years	0	0	0	0
18-64 years	22	35	0.12	0.18
65-74 years	1	0	0.01	0
75-84 years	0	0	0	0
≥ 85 years	0	0	0	0
Total	23	35	0.12	0.18
Treatment Group: 110 mg BCX7353[b]				
2-11 years	0	3	0	0.31
12-17 years	3	5	5.76	9.13
18-64 years	49	100	88.21	187.61
65-74 years	4	5	10.40	6.89
75-84 years	0	0	0	0
≥ 85 years	0	0	0	0
Total	56	113	104.37	203.95
Treatment Group: 150 mg BCX7353				
2-11 years	2	2	0.28	0.47
12-17 years	11	15	13.94	22.86
18-64 years	116	197	188.59	330.06
65-74 years	3	10	3.81	14.31
75-84 years	0	1	0	0.49
≥ 85 years	0	0	0	0
Total	132	225	206.62	368.18

[a] Subjects can be counted in both indications if they received active treatment in Study 202 and were also in Studies 203 or 204.
[b] Subjects who received 108 mg granules are included in the 110 mg group.
* Person time was calculated in person years.

Table SIII.4: Duration of Exposure by Dose

Duration of exposure	Patients	Person time*
Cumulative for all indications		
< 100 mg BCX7353	9	0.02
110 mg BCX7353	169	308.32
125 mg BCX7353	6	0.46
150 mg BCX7353	357	574.80
> 150 mg BCX7353	32	1.09
Total	573	884.70
Indication: Prophylaxis[a]		
< 100 mg BCX7353	9	0.02
110 mg BCX7353	169	316.99
125 mg BCX7353	6	0.46
150 mg BCX7353	357	583.38
> 150 mg BCX7353	19	0.94
Total	560	901.79
Acute Attacks[a]		
< 100 mg BCX7353	0	0
110 mg BCX7353	0	0
125 mg BCX7353	0	0
150 mg BCX7353	0	0
> 150 mg BCX7353	58	0.30
Total	58	0.30

[a] Subjects can be counted in both indications if they received active treatment in Study 202 and were also in Studies 203 or 204.
* Person time was calculated in person years.

Table SIII.5: Ethnic Origin by Indication and Dose

Ethnic origin	Patients	Person time*
Cumulative for all indications		
Asian	40	76.95
Black	17	18.54
Caucasian	497	746.84
Other	15	37.94
American Indian or Alaska Native	2	1.80
Hawaiian or Other Pacific Islander	1	2.59
Not Reported	0	0
Unknown	1	0.04
Total	573	884.70
Indication: Prophylaxis[a]		
Asian	40	78.79
Black	17	19.00
Caucasian	484	761.17

Ethnic origin	Patients	Person time*
Other	15	38.40
American Indian or Alaska Native	2	1.80
Hawaiian or Other Pacific Islander	1	2.59
Not Reported	0	0
Unknown	1	0.04
Total	560	901.79
Acute Attacks[a]		
Asian	0	0
Black	0	0
Caucasian	58	0.30
Other	0	0
American Indian or Alaska Native	0	0
Hawaiian or Other Pacific Islander	0	0
Not Reported		0
Unknown	0	0
Total	58	0.30
Treatment Group: 110 mg BCX7353[b]		
Asian	21	34.29
Black	2	1.17
Caucasian	139	261.16
Other	5	9.08
American Indian or Alaska Native	0	0
Hawaiian or Other Pacific Islander	1	2.59
Not Reported	0	0
Unknown	1	0.04
Total	169	308.32
Treatment Group: 150 mg BCX7353		
Asian	19	42.66
Black	14	17.37
Caucasian	313	484.18
Other	9	28.79
American Indian or Alaska Native	2	1.80
Hawaiian or Other Pacific Islander	0	0
Not Reported	0	0

Ethnic origin	Patients	Person time*
Unknown	0	0
Total	357	574.80

[a] Subjects can be counted in both indications if they received active treatment in Study 202 and were also in Studies 203 or 204.
[b] Subjects who received 108 mg granules are included in the 110 mg group.
* Person time was calculated in person years.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria discussed below were primarily applicable to pivotal studies for adult and adolescent subjects with HAE. Those also applicable to the paediatric population aged 2 to < 12 years are indicated with a *.

***Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increases the risk to the subject by participating in the study.**

Reason for exclusion: Avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

Dementia, altered mental status, or any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study.

Reason for exclusion: Ethical reasons regarding informed consent.

Is it considered to be included as missing information? No

Rationale: The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

Anticipated use of short-term prophylaxis of angioedema attacks for a pre-planned procedure during the screening or study periods.

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information? No

Rationale: This requirement was added to avoid efficacy-confounding factors, and not for safety reasons. There is no adverse interaction between short-term prophylaxis (C1-INH IV infusion) and berotralstat.

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

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information? No

Rationale: The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

***Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a corrected QT interval using Fridericia's method (QTcF) > 470 msec for female subjects ≥ 12 years old, a QTcF > 450 msec for male subjects ≥ 12 years old, PR interval > 220 msec (both sexes ≥ 12 years old), >450 msec for paediatric subjects aged < 12 years, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.**

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

Known family history of sudden cardiac death. Family history of sudden death from HAE is not exclusionary.

History of or current implanted defibrillator or pacemaker.

Reason for exclusion: During in vitro evaluation of berotralstat, safety pharmacology studies indicated multiple cardiac ion channel effects, including human ether-à-go-go-related gene (hERG) K^+ channel and the Na^+ and Ca^{2+} channels. Studies in NHPs showed quantitatively small drug-related prolongation of the QT interval.

Is it considered to be included as missing information? No

Rationale: Overall, the potential effects of berotralstat on cardiac safety have been thoroughly studied, and there is a low concern for proarrythmic events from berotralstat at the labelled dose. The thorough QT Study BCX7353-106 (Study 106) showed that at the therapeutic dose of berotralstat 150 mg QD, the estimated mean baseline-adjusted, placebo-corrected (ΔΔ) QTcF (ΔΔQTcF) at the geometric mean (GM) maximum observed concentration of the drug (C_{max}; 158 ng/mL) was 3.4 msec and the 2-sided 90% upper bound (UB) was 6.8 msec. The effect of berotralstat on QTcF at the recommended dose is below the regulatory threshold of concern (> 10 msec), with the potential exception of moderate to severe hepatic failure. In the berotralstat clinical programme, there have been no instances of clinically concerning QTcF prolongation, or any persistent changes from baseline QTcF. Additionally, a thorough review of all adverse events (AEs) indicates that there are no events of arrhythmia or symptoms that could represent an arrhythmia attributable to QT prolongation.

No clinically meaningful QT effects are expected at the therapeutic dose. However, QT prolongation is included as an important potential risk in patients who have elevated exposure to berotralstat or may have coexisting risk of QT prolongation. The risk in patients with moderate to severe hepatic failure is based on exposure-response modelling and not on actual reported clinical data. A review of post-marketing data for this risk does not alter the risk-benefit profile of berotralstat, and the category of the risk should remain as an important potential risk based on safety information available at the time of this assessment.

***Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the investigator, is clinically significant and relevant for this study. A calculated creatinine clearance (CL_{CR}) of ≤ 30 mL/min or AST or ALT value ≥ 3 × the upper limit of the normal (ULN) reference range value obtained during screening is exclusionary.**

Reason for exclusion: This broad exclusion criterion was for patient safety as well to avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information? No

Rationale: No dose adjustment is required for patients with mild or moderate renal impairment, (see Section SIV.3) as renal excretion is not an important route of drug elimination. In patients aged 12 years or older, it is preferable to avoid the use of berotralstat in patients with severe renal impairment. In children aged 2 to < 12 years, use of berotralstat in patients with severe renal impairment should be avoided. Hepatic impairment does not lead to exposures requiring dose adjustment. Transaminase elevation does not correlate to hepatic impairment.

The decision to treat patients with clinically significant laboratory findings with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

Suspected C1-INH resistance in the opinion of the investigator or sponsor.

Reason for exclusion: Subjects with C1-INH resistance were at risk of not responding to other kallikrein treatments such as berotralstat used for HAE. This could confound the assessment of efficacy. In addition, all subjects had to be medically appropriate for on-demand treatment, such as C1-INH therapy, as the sole medicinal management for their HAE during the study.

Is it considered to be included as missing information? No

Rationale: This requirement was added to avoid efficacy-confounding factors. The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

History of alcohol or drug abuse within the previous year prior to the screening visit, or current evidence of substance dependence or abuse (self-reported alcohol intake > 3 drinks/day).

Reason for exclusion: Avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: This was a general safety precaution. The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

Positive serology for human immunodeficiency virus or current infection with hepatitis B virus or hepatitis C virus.

Reason for exclusion: Avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

***Pregnant, planning to become pregnant during the study, or nursing.**

Reason for exclusion: Although the animal data indicate there is no risk to developing embryos/foetuses, there are no or limited amount of data from the use of berotralstat in pregnant

females. Animal studies are insufficient with respect to reproductive toxicity. Pregnant and breastfeeding women are routinely excluded from clinical studies.

Is it considered to be included as missing information? Yes

Rationale: Limited number of patients in this category exposed to berotralstat. Safety profile in pregnancy and breastfeeding is included as missing information.

Positive drugs of abuse screen (unless drug is used as medical treatment with a prescription).

Reason for exclusion: Avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: The decision to treat with berotralstat will be taken by the healthcare provider after consideration of the patient's medical history/present condition and the prescribing information.

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

Reason for exclusion: Patients with a history of severe hypersensitivity may be at greater risk of hypersensitivity to berotralstat.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity is included as an important potential risk.

Use of androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to the Screening visit or initiation during the study.

Reason for exclusion: To avoid confounding factors for efficacy assessments and to a lesser extent safety. In addition, it was unknown whether berotralstat would affect androgen metabolism through cytochrome P450 (CYP) 3A4 inhibition.

Is it considered to be included as missing information? No

Rationale: This requirement was added to avoid efficacy-confounding factors, and not primarily for safety reasons. Since then, a drug-drug interaction (DDI) study has demonstrated that berotralstat does not lead to increased androgen exposure but rather decreased exposure likely due to decreased androgen absorption.

Use of C1-INH for prophylaxis of HAE attacks within the 14 days prior to the Screening visit or initiation during the study. Use of a C1-INH therapy for treatment of attacks is not excluded at any time, nor is C1-INH for preprocedure prophylaxis for an unplanned/unforeseen procedure.

Reason for exclusion: To avoid confounding factors affecting efficacy assessments in Study 302. In Study BCX7353-204 (Study 204), concomitant use of C1-INH therapy for prophylaxis of attacks was not prohibited. There were no adverse interactions reported.

Is it considered to be included as missing information? No

Rationale: This requirement was added to avoid efficacy-confounding factors, and not for safety reasons.

***Use of concomitant medications that are metabolised by CYP2D6, CYP2C9, CYP2C19, and CYP3A4 and have a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.**

Reason for exclusion: In vitro studies showed that berotralstat had potential for drug interactions due to inhibition of CYP enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A).

Is it considered to be included as missing information? No

Rationale: Subsequent studies confirmed berotralstat is a moderate inhibitor of CYP2D6 and CYP3A4, but only a weak inhibitor of CYP2C9 and not an inhibitor of CYP2C19 at the therapeutic dose.

DDI with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4 is included as an important potential risk.

Note: Concomitant medications with narrow therapeutic index that are metabolised by CYP2D6 or CYP3A4 were prohibited in the paediatric pivotal Study 304.

Use of a medication that is clinically known to prolong the QT interval and is metabolised by CYP2D6, CYP2C9, CYP2C19, and/or CYP3A4 7 days prior to the baseline visit or planned initiation during the study.

Reason for exclusion: In vitro studies showed that berotralstat had potential for drug interactions due to inhibition of CYP enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A) and there was concern for increased exposure of QT interval prolonging drugs metabolised by these enzymes.

Is it considered to be included as missing information? No

Rationale: Subsequent studies confirmed berotralstat is a moderate inhibitor of CYP2D6 and CYP3A4, but only a weak inhibitor of CYP2C9 and not an inhibitor of CYP2C19 at the therapeutic dose.

DDI with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4 that are QT prolongers are included as important potential risks and use in patients with pre-existing prolonged QT or family history of sudden death is included as missing information.

***Use of a medication that is transported by P-glycoprotein (P-gp) and has a narrow therapeutic range, within 7 days of the baseline visit or planned initiation during the study.**

Reason for exclusion: Study BCX7353-105 (Study 105), a Phase 1 DDI study, found berotralstat 350 mg to be a weak inhibitor of P-gp increasing exposure to digoxin, with an approximate 50% increase in exposure when co-administered with berotralstat.

Is it considered to be included as missing information? No

Rationale: Berotralstat is a weak inhibitor of the P-gp substrate digoxin. For concomitant medicines that are P-gp substrates, particularly those with a narrow therapeutic index (e.g., digoxin) or whose prescribing information recommends therapeutic monitoring (e.g., dabigatran), dose adjustments of these medicines may be required.

***Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study.**

Reason for exclusion: Angiotensin-converting-enzyme inhibitors are generally contraindicated in subjects with HAE, as they may precipitate angioedema events. This effect could confound the assessment of efficacy as well as be a safety risk for subjects.

Is it considered to be included as missing information? No

Rationale: This requirement was added to avoid efficacy-confounding factors, as well as a general safety precaution.

Initiation of an oestrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study.

Reason for exclusion: Oestrogen is a known trigger for HAE attacks. New initiation of oestrogen may result in an unstable baseline attack rate which could confound the assessment of efficacy. Long-term stable use of oestrogens was not prohibited.

Is it considered to be included as missing information? No

Rationale: This requirement was added to avoid efficacy-confounding factors, and not for safety reasons. Co-administration of oestrogen-containing hormonal contraception, if initiated more than 56 days prior to screening, was allowed.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions, such as uncommon or rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure longer than those experienced by subjects on trial. Because the disease under study is a rare disease, the safety database size is appropriate. In addition, continued berotralstat exposure is occurring in the ongoing clinical trials, providing valuable information about both events with longer latency and cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant females</td><td>Pregnant or breastfeeding women were excluded from clinical trials. Up to the data lock point for this RMP, 18 cases have been documented in the BioCryst global safety database from clinical sources. The following PTs and pregnancy outcomes were reported:
<table>
<tr><th>PT</th><th>Count of Event PT Name</th></tr>
<tr><td>Pregnancy</td><td>6</td></tr>
<tr><td>Maternal exposure during pregnancy</td><td>6</td></tr>
<tr><td>Paternal exposure during pregnancy</td><td>5</td></tr>
<tr><td>Abortion spontaneous</td><td>4</td></tr>
<tr><td>Normal newborn</td><td>2</td></tr>
<tr><td>Ruptured ectopic pregnancy</td><td>1</td></tr>
<tr><td>Foetal exposure during pregnancy</td><td>1</td></tr>
<tr><td>Abortion induced</td><td>1</td></tr>
<tr><td>Meconium aspiration syndrome</td><td>1</td></tr>
<tr><td>Grand Total</td><td>27</td></tr>
</table>
All events were assessed as not related or not assessable due to lack of clinically relevant information.</td></tr>
<tr><td>Breastfeeding women</td><td>Breastfeeding women were excluded from the clinical development programme. There were no reports of use in breastfeeding women from clinical studies.</td></tr>
<tr><td>Patients with relevant comorbidities:
Patients with hepatic impairment
Patients with renal impairment
Patients with cardiovascular impairment
Immunocompromised patients
Patients with a disease severity</td><td>Patients with hepatic impairment: The PK of a single 150 mg oral dose of berotralstat were studied in patients with mild, moderate, and severe hepatic function (Child-Pugh Class A, B, or C). The PK of berotralstat were unchanged in patients with mild hepatic impairment compared to patients with normal hepatic function. In patients with moderate or severe hepatic impairment, C_{max} was increased by 50%, while AUC was increased by 38%. The changes in berotralstat exposure were not clinically relevant and no dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). However, dose-response modelling has indicated that at steady state, subjects with moderate to severe hepatic impairment would have a geometric mean C_{max} of 240 mg which has an UB for ΔΔQTcF of 10.9 msec. This is just above the regulatory threshold of concern of 10 msec. Subjects with this degree of hepatic failure were not enrolled in the clinical trials and this potential effect is based only on</td></tr>
</table>

different from inclusion criteria in clinical trials	modelling. The paediatric development programme did not enrol subjects with hepatic impairment. **Patients with renal impairment:** The PK of a single 200 mg oral dose of berotralstat were studied in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). When compared to a concurrent cohort with normal renal function (eGFR > 90 mL/min/1.73 m^2), no clinically relevant differences were observed; C_{max} was increased by 39%, while no difference was observed in AUC. No dose adjustment is required for patients with mild, moderate, or severe renal impairment. The pharmacokinetics of berotralstat in patients with kidney failure requiring haemodialysis has not been studied. The paediatric development programme did not enrol subjects with renal impairment. **Patients with cardiovascular impairment:** Subjects with congenital QT prolongation, a family history of sudden death or arrythmia, or active uncontrolled cardiac disease were excluded from clinical trials. Of note, patients with a history of cardiovascular disease were not excluded from clinical trials, and many subjects had both a history of coronary artery disease or comorbidities such as hypertension, diabetes mellitus, and hypercholesterolaemia. The use of berotralstat in patients with risk factors for increased drug exposure such as hepatic failure or independent risk factors for QT prolongation such as family history, electrolyte disturbance, and congenital QT prolongation was not studied. **Immunocompromised patients:** With the exception of patients with the human immunodeficiency virus, the clinical development programme did not generally exclude immunocompromised patients otherwise meeting the inclusion/exclusion criteria (see Section SIV.1). **Patients with a disease severity different from inclusion criteria in clinical trials:** All patients with HAE meeting the exclusion/inclusion criteria were eligible; there was no selection on the basis of disease severity. In Study BCX7353-302 (Study 302), patients had to have had a certain number of attacks during the run-in period in order to be eligible (in order to facilitate the assessment of efficacy); this was not a requirement for Study BCX7353-204 (Study 204). Current guidelines indicate that the use of prophylactic therapy for HAE is an individual choice and should be made by the physician and patient based on all factors, not just disease severity.
Population with relevant different ethnic origin	In Study 302 and Study 204, 94.4% (Study 302 Part 2), 95.1% (Study 302 Part 3), and 87.3% (Study 204) of patients were White, respectively. Population PK[a] analyses showed that race did not meaningfully influence the PK of berotralstat after correlating for body weight. In Study BCX7353-304, all subjects who reported race were White.

Subpopulations carrying relevant genetic polymorphisms	The available HLA genotyping data indicate that occurrence of drug-induced rash after administration of berotralstat, which clinically manifested in almost all cases as benign self-limited maculo-papular rash, was not associated with known HLA risk alleles for either drug-induced rash or autoimmune diseases. In addition, the allele frequencies in subjects with drug-induced rash did not indicate increased frequency of any particular HLA alleles in affected subjects.
Other	<not included in the clinical development programme>

Abbreviations: AUC = area under the concentration vs. time curve; C_{max} = maximum observed concentration of the drug; eGFR = estimated glomerular filtration rate; HAE = hereditary angioedema; HLA = human leucocyte antigen; PK = pharmacokinetic; PT = preferred term; QTCF = QT interval using Fridericia's method; UB = upper bound.

[a] Population PK analyses include data from 12 studies (Studies BCX7353-101, -102, -103, -105, -106, -107, -108, -112, -113, -203, -204, and -302) in 753 subjects.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

To complete a patient-years calculation for post-marketing exposure, the following points should be considered:

- Defined daily dose (DDD) for the product as per World Health Organization (WHO) ATC/DDD index
- Calculation from the sales data provided the number of international units (IU) sold (e.g., mg of medicinal product)

Patient-years = Total IU product sold (e.g., mg)/ DDD * 365.25

SV.1.2 Exposure

Post-marketing exposure data is not yet available for patients aged 2 to < 12 years as berotralstat is not yet approved for this age group.

Exposure in patient-years (adults and adolescent patients for the capsule formulation) was estimated to be 4,577 cumulatively, based on sales data for the post-marketing period to a data cutoff of 02-Dec-2024, and an assumption that the DDD is 150 mg with calculation based on the WHO-recommended DDD of 0.15 g (150 mg).

Estimation of post-marketing exposure is based on number of berotralstat units (individual capsules) sold in a given territory. The exact numbers of patients administered product is unknown. This method could result in slight overestimation of the actual patient exposure since not all drug distributed will necessarily have been taken by the patient.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Berotralstat would be expected to have a low drug abuse potential given its mechanism of action. There have been no reports of berotralstat dependence from any clinical trial and no neuropsychiatric adverse reactions have been reported.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

This section is "locked", the RMP was already approved.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Safety has been acceptable with a positive risk-benefit balance. No significant risks have been identified because most adverse reactions have been mild to moderate with complete recovery. The most common types of side effects noted have been GI events of diarrhoea, nausea, vomiting, and abdominal pain. Events of delayed-type, self-limited maculo-papular rash hypersensitivity reactions have occurred but have not resulted in sequelae or discontinuation in most patients. Lastly, transient and asymptomatic transaminase elevations, without evidence of hepatitis, and that were strongly associated with recent androgen discontinuation have emerged as potential safety signal.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

> abdominal pain (including abdominal discomfort, abdominal pain upper, and abdominal tenderness), diarrhoea (including frequent bowel movement), vomiting, gastroesophageal reflux, and flatulence

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Potential Risk 1: Hepatotoxicity

Risk-benefit impact: The liver was considered a target organ in toxicology studies due to reversible, non-adverse transaminase elevations seen in NHPs dosed for 39 weeks, along with hepatocellular hypertrophy. In rats, there were no enzyme elevations but there was extrahepatic and liver bile duct hyperplasia and PLD. In humans, ALT elevations and to a lesser degree, AST elevations > 3 × ULN have been seen in clinical trials of subjects with HAE, but no clinical signs of jaundice, synthetic liver dysfunction, or liver injury, and no subject met the criteria for Hy's Law. No subjects had evidence of hepatitis or any synthetic dysfunction. In most of the subjects, transaminase levels were documented to have returned to normal or Grade 1 and were reported by the investigators as resolved. Only 1 subject's transaminase elevation was reported as not recovered / not resolved; this subject withdrew consent prior to any follow-up. In addition, 2 subjects were followed only until transaminases improved to Grade 2; however, the corresponding AEs were reported as resolved by the investigators in both cases.

All of the cases of transaminase elevations > 3 × ULN were confounded by prior androgen use, particularly recent androgen discontinuation, and in some cases pre-existing hepatic injury and comorbidities such as colitis, steatosis of the liver, and GI infections. The temporal pattern of enzyme elevations and resolution with continued drug exposure are compatible with an adaptive response to berotralstat. The lack of symptoms, normal hepatic function, and resolution without sequelae make severe drug-induced liver toxicity (DILI) unlikely in HAE patients, even those who have previously used androgens. As such, the impact on the risk-benefit balance is considered minimal for this disease that may be severe and life-threatening.

Important Potential Risk 2: Hypersensitivity

Risk-benefit impact: Delayed-type hypersensitivity rash was identified as an event of special interest (EOSI) during initial Phase 1 studies in healthy subjects. The cases of rash observed with berotralstat to date have been benign maculo-papular exanthems with no mucosal involvement, no organ involvement, no fever, and no clinically significant laboratory abnormalities. The rashes resolved in all subjects. Most subjects continued dosing with berotralstat without interruption and the rashes did not reoccur with continued dosing, or in cases where dosing was interrupted, when berotralstat was restarted. As such, the impact on the risk-benefit balance is considered minimal for this disease that may be severe and life-threatening.

Important Potential Risk 3: QT prolongation

Risk-benefit impact: Studies in NHPs showed quantitatively small drug-related prolongation of the QT interval. In humans, no clinically significant QTc prolongations or arrythmias were observed in the Phase 2/3 long-term studies. In the thorough QT/corrected QT (QTc) Study 106, at the steady state C_{max} of berotralstat at the recommended dose of 150 mg once daily, the mean QTc increased by 3.4 msec (90% UB of 6.8 msec), which is below the 10 msec threshold for regulatory concern. At a dose of 450 mg once daily, steady-state exposures were 4-fold higher than achieved at the recommended 150 mg dose, and QTc increased by a mean of 21.9 msec.

QT prolongation has not been reported in prophylactic berotralstat clinical trials; however, increased exposure could lead to QT prolongation. Based on exposure-response modelling, at the highest anticipated clinically relevant exposure in a worst-case scenario of GM C_{max} of 240 ng/mL, in the setting of hepatic impairment (moderate and severe hepatic failure, Pugh-Child class B and C), the estimated ΔΔQTcF was 7.0 msec (2-sided 90% UB 10.9 msec). These values exceed the International

Council for Harmonisation (ICH) E14 threshold for potential clinical significance. It should be noted that in Study BCX7353-108, conducted in subjects who had varying degrees of hepatic failure including moderate and severe, no clinically significant ECG changes were observed, no subject had a change from baseline in QTcF > 30 msec, and no subject had a QTcF > 500 msec. The study was single dose so the risk with multiple-dose administration cannot be confirmed and has not been studied. No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh Class A). Berotralstat should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

Additionally, low weight could increase berotralstat exposures. Adolescents and adults weighing < 40 kg were excluded from the development programme. As weight is the primary covariate affecting PK in the population PK model, modelling indicates that at lower weights, berotralstat exposure is higher than at higher weights. Modelling indicates that at lower weights, around 35 kg, patients are simulated to have C_{max} exposure of approximately 222 ng/mL, the concentration at which the 2-sided 90% UB for ΔΔQTcF is 10 msec. There are no clinical data in subjects weighing < 40 kg, and it is appropriate to restrict use of berotralstat in these subjects. No dose adjustment is required for patients weighing at least 40 kg.

This risk could be exacerbated in patients with independent risk factors for prolonged QT, whether intrinsic or extrinsic. Extrinsic factors include electrolyte disturbances and concomitant use of other drugs known to either prolong the QTc or increase berotralstat drug levels (eg, cyclosporine). Intrinsic factors include known pre-existing QTc prolongation either acquired or familial and advanced age. Subjects with congenital QT prolongation, a family history of sudden death or arrhythmia, or active uncontrolled cardiac disease were excluded from clinical trials. There will be very few patients with pre-existing QT prolongation or family history of sudden cardiac death in this rare disease indication. Of note, patients with a history of cardiovascular disease were not excluded from clinical trials, and many subjects had both a history of coronary artery disease or comorbidities such as hypertension, diabetes mellitus, and hypercholesterolaemia. It should be noted that the risk of Torsade de Pointes (TdP), even with prolonged QT, is very low. Given the low risk of TdP and the precautions specified in the SmPC, the risk-benefit impact is considered minimal.

Important Potential Risk 4: Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4

Risk-benefit impact: Berotralstat at a dose of 150 mg once daily is a moderate inhibitor of CYP2D6 and CYP3A4 and may increase exposure to concomitant medications that are predominantly metabolised by CYP2D6 or CYP3A4. Although no such DDIs were observed during the clinical development programme, appropriate monitoring of therapeutic drug levels is recommended for concomitant medications with a narrow therapeutic index that are predominantly metabolised by CYP2D6 and CYP3A4. This potential DDI is addressed as an important potential risk.

Given the monitorability of many narrow therapeutic index drugs and the guidance provided in the SmPC, the risk-benefit impact is considered low.

Important Potential Risk 5: Phospholipidosis

Risk-benefit impact: Toxicity studies of berotralstat in rats and NHPs demonstrated microscopic findings consistent with PLD. These studies also found increased urinary levels of di-docosahexaenoyl (22:6)-bis(mono)acylglycerol phosphate (BMP), an investigational biomarker for PLD. The clinical relevance of these findings is unknown. In human studies with berotralstat, there was no dose- or duration-related increase in frequency or severity in vital signs or diffusion of carbon dioxide (D_LCO), a theoretical biomarker of foamy macrophage deposition in the lung. In addition, in Study 203 there was no clinically meaningful change from baseline in plasma BMP levels in berotralstat-treated subjects vs.

placebo or evidence of organ dysfunction in berotralstat-treated subjects. Across the berotralstat clinical development programme, there was no evidence of adverse effects due to PLD. Nevertheless, PLD is addressed as an important potential risk.

The lack of any clinical evidence of PLD occurring in humans as well as the inconclusive evidence that PLD is detrimental, the risk-benefit impact is considered minimal.

Important Potential Risk 6: Carcinogenicity

Risk-benefit impact: Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose. These findings are inconclusive, with an incidence slightly higher than in control groups. The clinical relevance of these findings is unknown. Across the berotralstat clinical development programme, there was no evidence of carcinogenicity. Nevertheless, carcinogenicity is addressed as an important potential risk.

Given the lack of any clinical evidence of carcinogenicity occurring in humans, the risk-benefit impact is considered minimal.

Missing information 1: Safety profile in pregnancy and breastfeeding

Risk-benefit impact: Pregnant or breastfeeding women were excluded from clinical trials. Although there were 4 subject pregnancies (2 at the time of the data cutoff and 2 subsequently), all 4 women discontinued as soon as the pregnancy was recognised. The data are too limited to make any determination of safety in this population. The SmPC indicates that berotralstat use in pregnancy is not recommended and use during breastfeeding should take into account individual risk-benefit.

Missing information 2: Long-term safety in paediatric patients.

Risk-benefit impact: Although a small number of paediatric patients aged 2 to 17 were included in clinical trials, there are no long-term clinical trial data on the use of berotralstat in paediatric patients. The safety and efficacy of berotralstat in paediatric patients were similar to adults and support a positive benefit-risk balance. The safety of long-term use of berotralstat in paediatric patients has been included as missing information and will be assessed as part of ongoing Study 304 (paediatric patients aged 2 to < 12 years), ongoing continued access Study 312 (paediatric patients aged ≥ 2 years), and a non-interventional post-authorisation safety study (NI-PASS) (adolescents aged 12 to < 18 years).

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There was no new information reviewed that altered the current important potential risks. No previously listed potential risks were confirmed and therefore remain under evaluation.

The safety profile in the paediatric population aged 2 to < 12 years is consistent with what has been observed in prior studies of berotralstat in the adult and adolescent population.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: None

Important Potential Risk: Hepatotoxicity

Potential mechanisms:

The mechanism of the transaminase elevations is unknown. Metabolism of berotralstat yields no major metabolites. Excretion is primarily via the bile. It is pertinent to review androgen liver injury since the transaminase elevations were seen exclusively in those with prior androgen exposure. Liver injury is a well-recognised complication of androgen use. Cholestatic jaundice and elevated levels of alkaline phosphatase as well as elevation of liver transaminases are the frequently described liver abnormalities seen with androgens (Sánchez-Osorio et al. 2008).

As no clinical signs of jaundice, synthetic liver dysfunction, or liver injury were reported and no subject met the criteria for Hy's law, the events reported currently just represent transaminase elevation, and hepatotoxicity is considered an important potential risk rather than an important identified risk. The impact on the risk-benefit balance is expected to be low. Subjects were generally asymptomatic or had confounding symptoms of general abdominal pain that were also consistent with berotralstat-reported adverse reactions (i.e., not liver tenderness), and the ALT elevations were primarily laboratory abnormalities without clinical symptoms. All improved or recovered, some while continuing on berotralstat.

Evidence source(s) and strength of evidence:

The liver was considered a target organ in toxicology studies due to reversible, non-adverse transaminase elevations seen in monkeys (non-human primates) dosed for 39 weeks, along with hepatocellular hypertrophy. In rats, there were no enzyme elevations but there was extrahepatic and liver bile duct hyperplasia and PLD. In humans, ALT elevations and to a lesser degree, AST elevations > 3 × ULN have been seen in clinical studies of subjects with HAE, but no clinical signs of jaundice, synthetic liver dysfunction, or liver injury, and no subject met the criteria for Hy's Law. The association is not clear because transaminase elevations were not seen in the absence of prior androgen exposure and was strongly associated with very recent androgen exposure.

Characterisation of the risk:

In order to assess this potential risk, preferred terms (PTs) from the following individual Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) were analysed on the integrated long-term berotralstat study populations: cholestasis and jaundice of hepatic origin (SMQ), Narrow Terms; hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions (SMQ), Narrow Terms; hepatitis, non-infectious (SMQ), Narrow Terms; and liver-related investigations, signs and symptoms (SMQ), Narrow Terms.

As a note, the PT of liver function test (LFT) increased is not a narrow term in any of these SMQs but was a reported PT in the long-term berotralstat studies.

Subjects reporting AEs associated with hepatotoxicity (any dose of berotralstat):

Phase 1 single-dose berotralstat trials in healthy subjects:

Berotralstat (N = 241): 1 (0.4%) subject. PT: transaminases increased, non-serious 1 (0.4%).
Placebo (N = 18): none

Phase 1 multiple-dose berotralstat trials in healthy subjects:

Berotralstat (N = 78): none
Placebo (N = 22): none

Phase 2/3 long-term trials in subjects with Type 1 or 2 HAE:

Berotralstat 110 or 150 mg (N = 342): 25 (7.3%) subjects. PTs: ALT increased, 15 (4.4%); AST increased, 11 (3.2%); gamma-glutamyl transferase (GGT) increased, 5 (1.5%); LFT abnormal, 3 (0.9%); hepatic enzyme increased, 2 (0.6%); hepatic steatosis, 2 (0.6%); blood bilirubin increased, 1 (0.3%); transaminases increased, 1 (0.3%).

Placebo (N = 39): 1 (2.6%) subject. PT: GGT increased, 1 (2.6%).

It is important to note that in the randomised, double-blind, placebo-controlled pivotal Study 302, there was only 1 subject with ALT > 3 × ULN. The subject had a history of past androgen use. The above reported AEs were reported almost exclusively in Study 204, a long-term safety study that was open label (without a control arm) and which allowed androgen use up to 1 week prior to initiating berotralstat. Use of androgens within 28 days of screening, which could last 56 days, was not allowed in Study 302.

Study 204 has now completed. Overall, 13.7% of subjects experienced a Grade 3 or 4 TEAE. One of the most common Grade 3 or 4 TEAEs was ALT increased (1.8%). Of the 11 subjects (2.8%) who had events related to abnormal liver enzyme tests (i.e., ALT increased, AST increased, hepatic enzyme increased, LFT abnormal), 9 discontinued due to elevations in ALT and/or AST. All but one of these laboratory abnormalities were associated with prior androgen use; the other was thought to be due to cholelithiasis (and possibly confounded by the administration of azathioprine). Elevations of ALT were strongly associated with very recent discontinuation of androgens, and less strongly associated with overall duration of previous androgen treatment. No subject had a concurrent elevation in bilirubin > 1.5 × ULN and ALT or AST > 3 × ULN. Therefore, no subject met the criteria for Hy's law during the study.

In most of the subjects, transaminase levels were documented to have returned to normal or Grade 1 and were reported by the investigators as resolved. Only 1 subject's transaminase elevation was reported as not recovered / not resolved; this subject withdrew consent prior to any follow-up. In addition, 2 subjects were followed only until transaminases improved to Grade 2; however, the corresponding AEs were reported as resolved by the investigators in both cases.

The cases of transaminase elevations > 3 × ULN were confounded by prior androgen use, particularly recent androgen discontinuation, and in some cases pre-existing hepatic injury and comorbidities such as colitis, steatosis of the liver, and GI infections. The temporal pattern of enzyme elevations and resolution with continued drug exposure are compatible with an adaptive response to berotralstat. The lack of symptoms, normal hepatic function, and resolution without sequelae make severe DILI unlikely in HAE patients, even those who have previously used androgens. As such, the impact on the risk-benefit balance is considered minimal for this disease that may be severe and life-threatening.

Since Marketing Authorisation Application (MAA) approval in Apr-2021, no new serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) have been reported in the clinical development programme for berotralstat for the important potential risk of hepatotoxicity.

Paediatric population: aged 2 to < 12 years:

No hepatotoxicity-related AEs were reported in Study 304.

The paediatric development programme did not enrol subjects with hepatic impairment. A comprehensive review of laboratory results from Study 304 (subjects aged 2 to < 12 years) found no evidence to suggest that study drug resulted in clinically significant hepatic changes.

Post-marketing reporting data

An analysis of potential hepatotoxicity events reported during the post-marketing period using the Drug-related hepatic disorders - comprehensive search SMQ (MedDRA v.27.1) was performed.

A search of all post-marketing data (all spontaneous, solicited, and literature reports, including listed and unlisted events) up to the data lock point of 02-Dec-2024 found that 54 cases with 69 PTs concerning hepatotoxicity have been reported. The majority of cases were assessed as non-serious with only 4 cases assessed as serious (PTs: hepatic cirrhosis [2], hepatic failure, hepatic enzyme increased). Of the 4 serious cases, 3 were solicited and 1 was spontaneous. One report of hepatic cirrhosis was assessed as not related due to the patient's medical history of chronic liver cirrhosis, and the remaining 3 cases were not assessable due to lack of meaningful clinical data.

A review of post-marketing data for this risk does not alter the risk-benefit profile of berotralstat and the category of the risk should remain as an important potential risk based on safety information available at the time of this assessment.

The EU SmPC for berotralstat (Section 4.8) lists ALT and AST increased with a frequency of common. The following text is also included in Section 4.8 of the berotralstat SmPC: LFT elevations, which generally improved with or without discontinuation of berotralstat, were observed in some patients, primarily in those who discontinued androgen therapy within 14 days of initiating Orladeyo treatment. Abrupt discontinuation of androgens immediately prior to initiating Orladeyo should be avoided. Data from this review do not change the overall assessment of this risk.

Hepatotoxicity will continue to be categorised as an important potential risk until further long-term safety data are available. Liver function will continue to be monitored by laboratory assessment in clinical studies. The nature and severity of the reported hepatotoxicity events reflect the known safety profile of berotralstat with no increase in severity. Section 4.8 of the Core Company Data Sheet (CCDS) specifically documents LFT increased (e.g., ALT increased; AST increased).

Across the clinical programme, increases in transaminases were observed in adolescents and adults that were asymptomatic and transient. As no clinical signs of jaundice, synthetic liver dysfunction, or liver injury were reported and no subject met the criteria for Hy's law, hepatotoxicity is considered an important potential risk rather than an important identified risk.

Elevated transaminases have been reported during clinical development. The liver was a target organ of toxicity in the nonclinical studies. There have been subjects with transient elevated transaminases but no evidence for any liver function impairment or biliary stasis. Prior androgen use, particularly recent abrupt androgen discontinuation, is the strongest risk factor for transaminase elevation. Liver enzyme elevations occurred almost exclusively in subjects with prior androgen use.

At the approved 150 mg dose, the association is strongest with recent androgen discontinuation, specifically discontinuation < 2 weeks before initiating berotralstat. In the absence of past androgen use, no ALT elevations > 3 × ULN have occurred in subjects with HAE.

Risk factors and risk groups:

An association between prior androgen use and asymptomatic elevations in ALT was identified. More important than lifetime exposure was recent abrupt discontinuation of androgens. Prior androgen use is high in patients with HAE. In the long-term safety studies, 63.2% of subjects had prior androgen use.

Preventability:

Liver function will continue to be monitored by laboratory assessment in clinical studies and all protocols will have clear discontinuation criteria in the case of liver transaminase elevations based on the Food and Drug Administration (FDA) Guidance *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (DHHS 2009). Re-challenge with berotralstat after a transient transaminase elevation will be allowed in future protocols and amendments.

The SmPC provides details on the association of transaminase elevation with recent abrupt androgen discontinuation. The SmPC indicates that abrupt discontinuation of androgens immediately prior to initiating berotralstat should be avoided.

As berotralstat is commercialised, special attention will be paid to post-marketing reports of transaminase elevations and any other reports collected under the drug-related hepatic disorders SMQ to further elucidate this risk.

In addition, a non-interventional post-authorisation safety study (NI-PASS) is collecting safety data on real-life berotralstat use in accordance with the current labelling.

Impact on the risk-benefit balance of the product:

HAE is a life-threatening and disabling condition: laryngeal attacks can be fatal, while attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring and have a significant impact on functionality, mood disorders, and QoL, with significant morbidity (see Part II: Module SI). Berotralstat provides clinically relevant treatment benefits through reduction in the rate of attacks in HAE patients. As no clinical signs of jaundice, synthetic liver dysfunction, or liver injury were reported during the clinical development programme and no subject met the criteria for Hy's Law, the impact on the risk-benefit balance is expected to be low. Past androgen use is high in this population but unlikely to be associated with elevated transaminases if the last use was > 30 days in the past.

Public health impact:

HAE is a rare condition with low prevalence. The transaminase elevations were primarily asymptomatic laboratory abnormalities that all resolved without sequelae, in some cases with continued dosing. As clinically significant liver injury was not observed during the clinical development programme, the magnitude of impact of the potential risk to public health is considered to be low.

Important Potential Risk: Hypersensitivity (Hypersensitivity SMQ)

Potential mechanisms:

A non-major histocompatibility complex (MHC)-mediated CD4 cell sensitisation.

Evidence source(s) and strength of evidence:

During nonclinical development, no hypersensitivity or skin rashes were noted in any animal species dosed. Delayed-type hypersensitivity rash was identified as an EOSI during initial Phase 1 studies in healthy subjects, but few events have been reported in patients with HAE, and these were mild to moderate, self-limited, and not dose-dependent. The rashes resolved in all subjects. Most subjects continued dosing with berotralstat without interruption, and the rashes did not reoccur with continued dosing, or in cases where dosing was interrupted, when berotralstat was restarted.

Characterisation of the risk:

Subjects reporting AEs associated with hypersensitivity SMQ (any dose of berotralstat):

Phase 1 single-dose berotralstat trials in healthy subjects:

Berotralstat (N = 241): 5 (2.1%) subjects. PTs: dermatitis contact, 2 (0.8%); dermatitis, eczema, rash, urticaria, 1 (0.4%) subject each.

Placebo (N = 18): none

None of the above events were serious.

Phase 1 multiple-dose berotralstat trials in healthy subjects:

Berotralstat (N = 78): 6 (7.7%) subjects. PTs: rash maculo-papular, 2 (2.6%); rash, rash macular, dermatitis contact, Type IV hypersensitivity reaction, rhinitis allergic, 1 (1.3%) subject each.

Placebo (N = 22): 2 (9.1%) subjects. PT: dermatitis contact, 2 (9.1%).

None of the above events were serious.

Phase 2/3 long-term trials in subjects with Type 1 or 2 HAE (adolescent and adult population):

Berotralstat 110 or 150 mg (N = 342): 39 (11.4%) subjects. PTs: HAE, 12 (3.5%); rash, 10 (2.9%); urticaria, 7 (2.0%); dermatitis contact, 3 (0.9%); rhinitis allergic, 2 (0.6%); angioedema, dermatitis, dermatitis acneiform, dermatitis psoriasiform, drug eruption, eczema, rash erythematous, rash generalised, rash pruritic, eye allergy, eyelid oedema, 1 (0.3%) subject each.

Placebo (N = 39): none

Twelve subjects (3.5%) had SAEs of HAE, the disease under study (due to hospitalisation), none of which were considered drug related. All other hypersensitivity events were non-serious.

When all events reported in this SMQ were medically reviewed, only 3 events in the 342 subjects (0.88%) treated in the long-term studies had rashes compatible with a delayed-type hypersensitivity reaction. In addition, another maculo-papular rash was reported in Study BCX7353-301 in a subject receiving 150 mg (4 in 355 subjects or 1.1%). Although reported by the investigator as unlikely related, sponsor medical review assessed the case as possibly a drug rash. All the other reported rashes were urticarial, fleeting, or inconsistent with a drug rash despite being reported as such.

Since MAA approval in Apr-2021, only one SAE under the Hypersensitivity SMQ (PT: asthma) has been reported in the berotralstat clinical development programme. A causality assessment of not related by investigator and company assessment was provided.

Paediatric population: aged 2 to <12 years:

In Study 304 (as of the data cutoff of 11-Sep-2024, 4 subjects (13.8%) experienced 5 TEAEs (including rash, rash maculo-papular, urticaria, allergic eosinophilia, and hypersensitivity) in the

Hypersensitivity SMQ. Three cases containing hypersensitivity MedDRA narrow terms were reviewed since they may represent clinically relevant cases for the hypersensitivity risk containing the following PTs: rash maculo-papular (1), allergic eosinophilia (1), and hypersensitivity (1). All were assessed as not related to study drug.

Post-marketing reporting data

In order to investigate a possible causal association between berotralstat treatment and hypersensitivity, a search of the global safety database using the Hypersensitivity SMQ (MedDRA version 27.1) was carried out.

Up to the data lock point 02-Dec-2024, 247 cases under the hypersensitivity SMQ with 291 PTs concerning hypersensitivity have been reported, 213 solicited and 34 spontaneous reports. Of the 247 cases reported, 27 cases were assessed as serious: 19 solicited cases and 8 spontaneous. Of these 27 serious cases, 6 were assessed as related (PTs of anaphylactoid reaction [2], hypersensitivity [2], and 1 report each of urticaria, pruritus, and swollen tongue), however, confounding factors such as concomitant medications, medical history of anaphylaxis or other allergies, and underlying disease of HAE, were present. Sixteen were assessed as not related, and 5 were assessed as not assessable due to lack of clinically meaningful information on the reported PT.

A review of post-marketing data for this risk does not alter the risk-benefit profile of berotralstat and the category of the risk should remain as an important potential risk based on safety information available at the time of this assessment.

Risk factors and risk groups:

Patients with hypersensitivity to the active substance or any of the excipients in berotralstat are at increased risk. There is no association with human leucocyte antigen (HLA) type or other comorbidity.

Preventability:

Orladeyo is contraindicated in patients with hypersensitivity to the active substance or to any of its excipients, which is described in the SmPC Section 4.3. Rash is described as an ADR in the SmPC (Section 4.8) and is not considered a contraindication.

Impact on the risk-benefit balance of the product:

HAE is a life-threatening and disabling condition: laryngeal attacks can be fatal, while attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring, and have a significant impact on functionality, mood disorders, and QoL, with significant morbidity (see Part II: Module SI). Berotralstat provides clinically relevant treatment benefits through reduction in the rate of attacks in HAE patients. As no serious or severe drug hypersensitivity reactions were seen in human studies, the impact on the risk-benefit balance is thought to be low.

Public health impact:

HAE is a rare condition with low prevalence. The rash was benign and recovered in all cases without sequelae, often while dosing continued. In subjects who interrupted dosing, the rash did not reoccur with re-exposure to berotralstat. As serious hypersensitivity was not observed during the clinical development programme, the magnitude of impact of the potential risk to public health is considered to be low.

Important Potential Risk: QT prolongation

Potential mechanisms:

Safety pharmacology studies indicated effects on multiple cardiac ion channels (hERG, hCav1.2, and hNav1.5). The effect of berotralstat on QTcF at the recommended dose is below the regulatory threshold of concern, which is more than 10 msec. A supratherapeutic dose of berotralstat appears to selectively prolong the T peak to T end (Tp-Te; late prolongation) sub-interval and not prolong the heartrate-corrected J-Tpc (early prolongation) sub-interval. Minimal prolongation of the PR interval and QRS duration was also observed, and together with little influence on J-Tpc and prolongation of QTcF is supportive of mixed-ion channel block, not pure hERG block. The small effect on ΔΔQTcF at therapeutic concentrations and this constellation of findings support the conclusion that berotralstat would not likely be associated with arrhythmia.

Evidence source(s) and strength of evidence:

Studies in NHPs showed quantitatively small drug-related prolongation of the QT interval.

A thorough QT study was conducted and showed that at steady state, the C_{max} of berotralstat at the recommended dose of 150 mg once daily resulted in a mean QTc increase of 3.4 msec (90% upper CI bound of 6.8 msec), which is below the 10 msec threshold for regulatory concern. Exposures 4-fold higher than achieved at the recommended dose increased the QTc by 21.9 msec (mean). Based on exposure-response modelling, at the highest anticipated clinically relevant exposure in a worst-case scenario of GM C_{max} of 240 ng/mL, in the setting of hepatic impairment (moderate and severe hepatic failure, Pugh-Child class B and C), the estimated ΔΔQTcF was 7.0 msec (2-sided 90% UB 10.9 msec). These values exceed the ICH E14 threshold for potential clinical significance. It should be noted that in Study BCX7353-108, conducted in subjects who had varying degrees of hepatic failure including moderate and severe, no clinically significant ECG changes were observed, no subject had a change from baseline in QTcF > 30 msec, and no subject had a QTcF > 500 msec. The study was single dose so the risk cannot be confirmed. Subjects with moderate to severe hepatic failure were not enrolled in the LTP clinical studies and this potential effect is based only on modelling.

Additionally, low weight could increase berotralstat exposures. Adolescents and adults weighing < 40 kg were excluded from the development programme. As weight is the primary covariate affecting PK in the population PK model, modelling indicates that at lower body weights, berotralstat exposure is higher than at higher body weights. Exposures in patients aged > 12 years and weighing 40 kg taking the recommended 150 mg capsule do not exceed concentrations at which there is a concern for prolonged QT. Modelling indicates that at lower weights, around 35 kg, patients aged > 12 years and receiving 150 mg capsules are simulated to have C_{max} of approximately 222 ng/mL, the concentration at which the 2-sided 90% UB for ΔΔQTcF is 10 msec. No dose adjustment is required for patients weighing at least 40 kg. For paediatric patients aged 2 to <12 years, based on Monte Carlo simulations using the population PK model, the proposed doses of 132 mg granules administered to those weighing at least 40 kg, 108 mg granules to those weighing 32 to < 40 kg, 96 mg granules to those weighing 24 to < 32 kg, and 78 mg granules to those weighing < 24 kg will result in predicted median steady-state C_{max} of 158, 156, 165, and 180 ng/mL, respectively, which are all below 222 ng/mL.

An additional analysis of the QT sub-intervals revealed that multiple supratherapeutic daily doses of berotralstat prolonged the QTc interval but had little effect on the J to T peak sub-interval, which suggests that the QT prolongation reported with berotralstat can be categorised as "benign" and unlikely to be associated with proarrhythmic risk, similar to marketed drugs ranolazine or verapamil.

No subjects in the 3 LTP studies (204, 301, and 302) experienced clinically significant QT prolongation for the adolescent and adult population. No subjects in Study 304 (aged 2 to <12 years) experienced clinically significant QT prolongation.

Characterisation of the risk:

Subjects reporting AEs contained in the Torsade de Pointes/QT prolongation SMQ (any dose of berotralstat):

Phase 1 single-dose berotralstat trials in healthy subjects:

Berotralstat (N = 241): 2 (0.8%). PT: syncope, 2 (0.8%).

Placebo (N = 18): none

None of the above events were serious.

Phase 1 multiple-dose berotralstat trials in healthy subjects:

Berotralstat (N = 78): 1 (1.3%). PT: syncope, 1 (1.3%).

Placebo (N = 22): none

None of the above events were serious.

Phase 2/3 long-term trials in subjects with Type 1 or 2 HAE in the adolescent and adult population:

Berotralstat 110 or 150 mg (N = 342): 2 (0.6%). PT: syncope, 2 (0.6%).

Placebo (N = 39): none

None of the above events were serious.

In summary, TdP was not observed in the above pools. The only PT reported from the SMQ Torsade de Pointes/QT prolongation was syncope. All reports of syncope were non-serious and considered not related to study drug due to etiologies other than arrythmia.

Table SVII.1 Summary of QTcF Assessments with Potentially Clinically Significant QTcF Values by Treatment Group Phase 2/3 Prophylactic Long-term Trials in Subjects (Adolescent and Adult Population) with Type 1 or 2 HAE (Safety Population)

Summary	110 mg (N=158)	150 mg (N=184)	Total (N=342)	Placebo (N=39)
Any QTcF assessment	975	1195	2170	259
Any potentially clinically significant QTcF measurement	36 (3.7%)	78 (6.5%)	114 (5.3%)	13 (5.0%)
> 450 to ≤ 480 msec	18 (1.8%)	40 (3.3%)	58 (2.7%)	12 (4.6%)
> 480 to ≤ 500 msec	0	2 (0.2%)	2 (0.1%)	0
> 500	0	0	0	0
CFB > 30 to ≤ 60 msec	20 (2.1%)	47 (3.9%)	67 (3.1%)	7 (2.7%)
CFB > 60 msec	0	0	0	0

Abbreviations: CFB = QTcF interval change from baseline; HAE = hereditary angioedema; QTcF = QT interval corrected using Fridericia's method.

There have been no clinically concerning QTcF prolongations, nor any persistent changes from baseline QTcF in the berotralstat clinical programme at therapeutic doses. Additionally, a thorough review of all

AEs indicates that there are no events of arrhythmia or symptoms that could represent an arrhythmia attributable to QT prolongation.

The small effect on ΔΔQTcF at therapeutic concentrations and this constellation of findings support the conclusion that berotralstat would not likely be associated with arrhythmia.

Paediatric population: aged 2 to < 12 years:

Table SVII.2 Summary of QTcF Assessments with Potentially Clinically Significant QTcF Values in Study 304 Subjects (Paediatric Population) with Type 1 or 2 HAE (Safety Population)

	Dose of Berotralstat[a]				
Parameter (units) Time Point Interval	**Cohort 1 150 mg capsules (N = 7)**	**Cohort 2 108 mg granules (N = 9)**	**Cohort 3 96 mg granules (N = 9)**	**Cohort 4 78 mg granules (N = 4)**	**Total (N = 29)**
QTcF interval					
Worst QTcF post-baseline					
≤ 450 msec	7/ 7 (100%)	9/ 9 (100%)	9/ 9 (100%)	4/ 4 (100%)	29/29 (100%)
> 450 msec and ≤ 470 msec	0	0	0	0	0
> 470 msec and ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
Increase from baseline to worst QTcF post-baseline					
< 30 msec	5/ 7 (71.4%)	7/ 9 (77.8%)	6/ 9 (66.7%)	4/ 4 (100%)	22/29 (75.9%)
≥ 30 to ≤ 60 msec	2/ 7 (28.6%)	2/ 9 (22.2%)	3/ 9 (33.3%)	0	7/29 (24.1%)
> 60 msec	0	0	0	0	0

Abbreviations: ECG = electrocardiogram; ICH = International Council for Harmonisation; QTcF = QT interval corrected using Fridericia's method.
Note: Note: Categories for QTcF interval and QTcF interval increases were based on ICH E14 guidelines. ECG parameters were captured in triplicate at pre-dose on Day 1 and all other ECGs were single assessments. Baseline was defined as the average of the non-missing pre-dose values obtained prior to administration of the first dose of berotralstat on Day 1. If these values are missing, then the last non-missing value obtained prior to administration of the first dose of berotralstat was utilised for the baseline value. Denominators are based on the number of subjects with a non-missing value at a given visit.
[a] Cohort 1: ≥ 40 kg, Cohort 2: 32 to < 40 kg, Cohort 3: 24 to < 32 kg, and Cohort 4: 12 to < 24 kg at baseline.
Source: Study BCX7353-304 Table 14.3.5.1.3

There have been no clinically concerning QTcF prolongations, nor any persistent changes from baseline QTcF in the berotralstat paediatric clinical programme (Study 304) at therapeutic doses.

There were no TEAEs from the Torsade de pointes/QT prolongation SMQ or palpitation PT in Study 304. Also, no seizure events were reported.

Post-marketing reporting data

Up to the data lock point, 20 cases with 20 PTs in the TdP SMQ have been reported. Fifteen cases were serious. Thirteen of them were unlisted and 4 events were considered related.

A review of post-marketing data for this risk does not alter the risk-benefit profile of berotralstat and the category of the risk should remain as an important potential risk based on safety information available at the time of this assessment.

Risk factors and risk groups:

- Patients with moderate or severe (Child-Pugh Class B and C) liver failure
- Patients with weight < 40 kg

Patients with independent risk factors for QT prolongation

Extrinsic:

- Electrolyte disturbances
- Concomitant use of other drugs known to either prolong the QTc or increase berotralstat drug levels (e.g., cyclosporine)

Intrinsic:

- Congenital QT prolongation
- Acquired QT prolongation
- Advanced age

Preventability:

Berotralstat use should be avoided in patients with risk of increased berotralstat exposure such as moderate or severe hepatic failure. This is clearly described in the SmPC Section 4.4. Although based on modelling, the UB 95% confidence interval for the QT prolongation in moderate hepatic failure is estimated to be > 10 msec and therefore the risk-benefit is altered.

Based on the recommendation for dose adjustment due to weight, but not age, for paediatric patients aged 2 to < 12 years, and the recommendation of 108 mg granules QD for such patients weighing < 40 kg, a dose of 108 mg granules QD may also be considered for patients aged > 12 years and weighing < 40 kg.

In patients with independent risk factors for QT prolongation, there are no data on use of berotralstat. The SmPC (section 4.4) describes conditions in which QT may be prolonged and provides the guidance that monitoring considered appropriate for the underlying risk be performed. In some cases, this may be assessment and correction of electrolytes or monitoring of concomitant medication drug levels, and in some cases may be ECG monitoring. Examples of monitoring include assessing changes from baseline in QTcF and absolute QTcF after berotralstat steady state is reached. Appropriate monitoring is recommended for concomitant medications with a narrow therapeutic index that are known QT prolongers that are predominantly metabolised by CYP2D6 or CYP3A4 or are P-gp substrates. The use of berotralstat in patients with congenital or acquired prolonged QT intervals should be made after careful considerations of the risk-benefit in each individual subject.

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance with appropriate use is considered to be low. This is evidenced by the lack of clinically concerning QTcF prolongations, or any persistent changes from baseline QTcF at therapeutic doses in the berotralstat clinical programme. Additionally, a thorough review of all AEs indicated that there are no events of arrythmia or symptoms that could represent an arrythmia attributable to QT prolongation. In addition, the sub-interval analysis suggests that the QT

prolongation seen at supratherapeutic doses of berotralstat is not likely to cause TdP. Most importantly, the risk of TdP, which is the clinical outcome of a prolonged QT that results in harm, is uncommon even when QT prolongation is present. This risk is considered significant enough with moderate or severe hepatic failure and low weight, which can increase berotralstat concentrations, to provide precautionary wording in the SmPC. With concurrent conditions that may prolong the QT, it is not anticipated that berotralstat would further increase the QT unless the exposure to berotralstat were increased.

Public health impact:

HAE is a rare condition with low prevalence. Subjects with HAE and moderate or severe hepatic failure would be even rarer. The risk has not been confirmed in these subjects and the potential risk is based on exposure-response modelling data. The hepatic impairment study dosed a single dose and no subjects with Child-Pugh Class B or C have been chronically dosed with berotralstat. Relevant QT prolongation is not anticipated with the marketed dose of 150 mg berotralstat in patients but cannot be excluded in patients with liver failure or weight < 40 kg, which is why use is to be avoided in these populations. TdP was not seen during the clinical development programme. Although the concern is valid when exposures are supratherapeutic, it should be noted that TdP is uncommon, even when QT is prolonged. Therefore, the magnitude of impact to public health with routine use is considered to be low.

Important Potential Risk: DDI with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4

Potential mechanisms:

In Study BCX7353-115 (Study 115), a DDI study at the therapeutic dose of berotralstat 150 mg QD, berotralstat increased the AUC of dextromethorphan by 3-fold and midazolam by 2.2-fold, suggesting that berotralstat is a moderate inhibitor of CYP2D6 and CYP3A4.

Evidence source(s) and strength of evidence:

DDI studies with various doses of berotralstat.

Characterisation of the risk:

Berotralstat at a dose of 150 mg once daily is a moderate inhibitor of CYP2D6 and CYP3A4 and may increase exposure to concomitant medications that are predominantly metabolised by CYP2D6 or CYP3A4.

Clinically relevant interaction of berotralstat with drugs metabolised by CYP2D6 or CYP3A4 was not observed during the LTP studies, although it should be noted that use of such drugs was an exclusion criterion if they had a narrow therapeutic range.

Although no such DDIs were observed during the clinical development programme for the adolescent and adult population, appropriate monitoring of therapeutic drug concentrations is recommended for concomitant medications with a narrow therapeutic index that are predominantly metabolised by CYP2D6 and CYP3A4.

Paediatric population: aged 2 to < 12 years:

No DDI-related TEAEs were reported in Study 304.

Post-marketing reporting data

To date, 19 reports of DDI have been received from post-marketing sources, all containing the PT drug interaction. All of them were non-serious, 17 not assessable due to lack of details, and 2 were related. This potential DDI is addressed as an important potential risk.

A review of post-marketing data for this risk does not alter the risk-benefit profile of berotralstat and the category of the risk should remain as an important potential risk based on safety information available at the time of this assessment.

Risk factors and risk groups:

Patients taking berotralstat concomitantly with drugs metabolised by CYP2D6 or CYP3A4.

Given the monitorability of many narrow therapeutic index drugs and the guidance provided in the SmPC, the risk-benefit impact is considered low.

Preventability:

Berotralstat may increase concentrations of concomitant medicines that are substrates of CYP2D6 or CYP3A4. For concomitant medicines that are predominantly metabolised by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine, fentanyl), particularly those with a narrow therapeutic index, dose adjustments of these medicines may be required.

Impact on the risk-benefit balance of the product:

The potential health risk is low due to the ability to monitor most narrow therapeutic index drugs, either through serum drug levels or clinical signs. Subjects who require narrow therapeutic index drugs should undergo monitoring as appropriate.

Public health impact:

HAE is a rare condition with low prevalence. As such, the magnitude of impact to public health of potential DDIs is considered to be low.

Important Potential Risk: Phospholipidosis

Potential mechanisms:

Based on the nonclinical findings, potential target organs of PLD included the liver, lungs, small intestine, and spleen.

In NHPs, pigmented and foamy macrophages were present in all regions of the small intestine, in mesenteric lymph nodes, and in liver Kupffer cells at doses ≥ 30 mg/kg/day in females, and at doses ≥ 55 mg/kg/day in males. Dose-dependent increases in the urinary concentrations of the experimental biomarker for PLD, BMP, were observed in both rats and NHPs. Electron microscopy evaluation of liver from rats in the 13-week toxicity studies demonstrated myelinosomes within the cytoplasm of Kupffer cells. These effects are consistent with PLD, a phenomenon noted in nonclinical toxicity studies with several approved drugs.

In the first-in-human Study BCX7353-101 (Study 101; multiple dosing only) and Study 203, D_LCO assessments were implemented as a theoretical biomarker of foamy macrophage deposition in the lung. A 20% decrease was chosen as the threshold for analysis based on reported high intra-subject variability for subjects with high baseline D_LCO measurements (i.e., no baseline lung disease). In a study of patients without overt lung disease, up to 35.5% of subjects had a > 10% intra-subject

change from baseline, suggesting that up to 20% was a reasonable variation between measurements for any individual subject enrolled in this healthy subject study.

In these human studies with berotralstat, there was no dose or duration-related increase in frequency or severity in vital signs or D_LCO. In addition, in Study 203 there was no clinically meaningful change from baseline in plasma BMP levels in berotralstat-treated subjects vs. placebo or evidence of organ dysfunction in berotralstat-treated subjects. With the lack of clinical, D_LCO, and BMP findings, there was no evidence of PLD occurring in humans with 28 days of berotralstat dosing. In subsequent studies, monitoring of potential PLD was by assessment of vital signs, AEs, and safety labs that could reveal organ involvement.

Evidence source(s) and strength of evidence:

Toxicity studies of berotralstat in rats and NHPs demonstrated the presence of foamy and/or vacuolated macrophages in several tissues and organs of both rats and NHPs, including liver, lung, small intestine, spleen, and lymph nodes.

Characterisation of the risk:

Toxicity studies of berotralstat in rats and monkeys also found increased urinary levels of BMP, an investigational biomarker for PLD. The clinical relevance of these findings is unknown.

In human studies across the berotralstat clinical development programme for the adolescent and adult population, there was no evidence of adverse effects due to PLD. Specifically, there were no significant changes in vital signs following prolonged treatment with berotralstat and no pattern of AEs or laboratory abnormalities in berotralstat-treated subjects consistent with PLD-associated effects in the target organs. PLD is considered an adaptive response to the presence of a drug, rather than a toxic manifestation, and PLD in animals is not predictive of similar findings clinically.

Paediatric population: aged 2 to < 12 years:

No PLD-related TEAEs were reported in Study 304.

Post-marketing reporting data

To date, no reports of PLD have been received from post-marketing sources. Nevertheless, PLD is addressed as an important potential risk.

Risk factors and risk groups:

Unknown

Given the lack of any clinical evidence of PLD occurring in humans as well as the inconclusive evidence that PLD is detrimental, the risk-benefit impact is considered minimal.

Preventability:

Unknown

Impact on the risk-benefit balance of the product:

HAE is a life-threatening and disabling condition: laryngeal attacks can be fatal, while attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring and have a significant impact on functionality, mood disorders, and QoL, with significant morbidity (see Part II: Module SI). Berotralstat provides clinically relevant treatment benefits through reduction in the rate of attacks in HAE patients. PLD has been noted in nonclinical toxicity studies with several approved drugs, and the significance of PLD findings in humans is unknown (Chatman et al. 2009). PLD is considered

an adaptive response to the presence of a drug, rather than a toxic manifestation. As no clinical signs of PLD were reported during the clinical development programme, the impact on the risk-benefit balance is expected to be minimal.

Public health impact:

HAE is a rare condition with low prevalence. Across the clinical development programme for berotralstat, there was no evidence of adverse effects due to PLD. As PLD was not observed during the clinical development programme, the magnitude of impact of the potential risk to public health is considered to be minimal.

Important Potential Risk: Carcinogenicity

Potential mechanisms:

Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose.

Undifferentiated sarcoma was present in 3 of 60 (5%) berotralstat-treated males at 20 mg/kg/day, compared to 0/60 control males. This increase was just statistically significant using the Poly-3 pair-wise test for rare tumours ($p = 0.033$). However, this tumour was not likely test article-related because there were no undifferentiated sarcomas in females at 8 or 20 mg/kg/day, and 1 of 60 control females (1.7%) were affected. Further, the plasma drug exposure to berotralstat is similar in male and female rats in this study and does not support a berotralstat effect in males or females.

Undifferentiated sarcoma can include the differential diagnoses of liposarcoma, fibrosarcoma, leiomyosarcoma, malignant schwannoma, and rhabdomyosarcoma (Wojcinksi 2013). In the literature, the incidence of spontaneous sarcoma/fibrosarcoma in male Wistar Han rats is up to 4% (Bomhard 1992). In the National Toxicology Program database (https://ntp.niehs.nih.gov/), the incidence of fibroma/fibrosarcoma, sarcoma, myoma, myosarcoma, or fibrous histioma is up to 4%. Thus, the incidence of sarcoma (5%) in the skin of male rats administered 20 mg/kg/day in the 2-year oncogenicity study is similar to spontaneous rates in published literature (4%), and therefore suggests the finding is not related to treatment with berotralstat.

These nonclinical findings related to carcinogenicity are inconclusive, with an incidence slightly higher than in control groups. The clinical relevance of these findings is unknown.

There have been no findings of carcinogenicity in the berotralstat clinical development programme.

Evidence source(s) and strength of evidence:

Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose.

These findings are inconclusive, with an incidence slightly higher than in control groups. The clinical relevance of these findings is unknown. Across the berotralstat clinical development programme, there was no evidence of carcinogenicity. Nevertheless, carcinogenicity is addressed as an important potential risk.

Characterisation of the risk:

Undifferentiated sarcoma was present in 3 of 60 (5%) berotralstat-treated males at 20 mg/kg/day, compared to 0/60 control males. This increase was just statistically significant using the Poly-3

pair-wise test for rare tumours (p = 0.033). However, this tumour was not likely test article-related because there were no undifferentiated sarcomas in females at 8 or 20 mg/kg/day, and 1 of 60 control females (1.7%) were affected. Further, the plasma drug exposure to berotralstat is similar in male and female rats in this study and does not support a berotralstat effect in males or females.

Undifferentiated sarcoma can include the differential diagnoses of liposarcoma, fibrosarcoma, leiomyosarcoma, malignant schwannoma, and rhabdomyosarcoma. In the literature, the incidence of spontaneous sarcoma/fibrosarcoma in male Wistar Han rats is up to 4% (Bomhard 1992). In the National Toxicology Program database, the incidence of fibroma/fibrosarcoma, sarcoma, myoma, myosarcoma, or fibrous histioma is up to 4%. Thus, the incidence of sarcoma (5%) in the skin of male rats administered 20 mg/kg/day in the 2-year oncogenicity study is similar to spontaneous rates in published literature (4%), and therefore suggests the finding is not related to treatment with berotralstat.

Across the clinical development programme for berotralstat in the adolescent and adult population, there was no evidence of carcinogenicity.

Paediatric population: aged 2 to < 12 years:

No carcinogenicity-related TEAEs were reported in Study 304.

Post-marketing reporting data

Up to the data lock point of this report, 27 post-marketing cases have been assessed under the Malignancies SMQ. Four cases were non-serious and 23 were serious. Of these 27 cases, 26 were received from post-marketing sources (21 solicited and 5 spontaneous) and 1 from a Phase 4 study. A fatal outcome was reported in 3 cases. Most of them had confounding factors reported such as the known etiopathogenesis of the cancer, long latency period of reported cancer events, previous medical history, family history, or concomitant medication use. In summary, based on the lack of a plausible biologic mechanism and short latency period, it is considered unlikely that there is a causal association between berotralstat use and carcinogenicity risk.

Given the lack of any clinical evidence of carcinogenicity occurring in humans, the risk-benefit impact is considered minimal.

Risk factors and risk groups:

None

Preventability:

Unknown

Impact on the risk-benefit balance of the product:

HAE is a life-threatening and disabling condition: laryngeal attacks can be fatal, while attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring and have a significant impact on functionality, mood disorders, and QoL, with significant morbidity (see Part II: Module SI). Berotralstat provides clinically relevant treatment benefits through reduction in the rate of attacks in HAE patients. As no clinical signs of carcinogenicity were reported during the clinical development programme, the impact on the risk-benefit balance is expected to be minimal.

Public health impact:

HAE is a rare condition with low prevalence. Across the clinical development programme for berotralstat, there was no evidence of carcinogenicity. As carcinogenicity was not observed during the

clinical development programme, the magnitude of impact of the potential risk to public health is considered to be minimal. Cancer is the second most important cause of morbidity and mortality in Europe (WHO Regional Office for Europe 2021) and causes 20% of all deaths. Both modifiable (lifestyle, tobacco, alcohol, etc.) and nonmodifiable (spontaneous mutations, genetic risk factors, gender) factors are significant contributors to cancer. It is not anticipated that additional risk from berotralstat can be detected given the rare prevalence of HAE and the very common incidence and prevalence of cancer.

SVII.3.2. Presentation of the missing information

Missing information 1: Safety profile in pregnancy and breastfeeding

Evidence source: Definitive embryo-foetal studies have been completed in rats and rabbits. In the rat study, the number of corpora lutea, implantation sites, live and dead foetuses, resorptions, sex ratio, and pre-and post-implantation losses were unaffected by berotralstat administration up to doses of 75 mg/kg/day. At this dose, there was also no effect of berotralstat on foetal weights and no berotralstat-related malformations. In rabbits, there was no evidence of embryo lethality, no effect on embryo-foetal growth, and no foetal dysmorphogenesis at doses up to 100 mg/kg/day. These studies did demonstrate placental transfer of berotralstat in pregnant rats and rabbits, although the C_{max} in foetal plasma was 4% to 7% and 7% to 11% of the maternal plasma C_{max} in rats and rabbits, respectively.

There are no or limited data from the use of berotralstat in pregnant females. Animal studies are insufficient with respect to reproductive toxicity. Berotralstat is not recommended during pregnancy. Therefore, pregnant females will continue to be excluded from participation in berotralstat clinical studies. Additionally, any female subject who becomes pregnant during a study will be immediately removed from study drug and followed through the end of the pregnancy.

Population in need of further characterisation: Use in pregnancy and breastfeeding

Anticipated risk/ Consequences of the missing information:

Until the data lock point, there have been 54 cases involving subject or patient pregnancies or breastfeeding, with 68 events being reported from post-marketing sources. Out of 68 events, 13 PTs of exposure during pregnancy, 34 PTs of maternal exposure during pregnancy, 2 PTs of maternal exposure before pregnancy, 3 PTs of maternal exposure during breastfeeding, 1 PT of ectopic pregnancy, and 4 PTs of pregnancy were reported. In addition, 11 events of pregnancy outcomes were reported: 2 with PT of normal newborn, 2 with PT of abortion induced, 3 with PT of abortion spontaneous, 1 with PT of premature delivery, 1 with PT of term baby, 1 PT of term birth, and 1 with PT of premature baby. There are insufficient data in pregnant females available to inform drug-related risks with berotralstat use in pregnancy.

Between 10% to 15% of known pregnancies end in miscarriage. About 80% of miscarriages happen in the first trimester (Pedersen et al. 2013). Most pregnancy losses are due to factors the woman cannot control. Early in pregnancy, genetic issues are a major cause of miscarriage. Foetuses are most vulnerable early in development, so other factors can have the most damaging effects at this time. This is why most miscarriages occur early in pregnancy. Even if a woman has this type of pregnancy loss, she is generally able to go on to have a healthy pregnancy. The event of ruptured ectopic pregnancy was reported in a 30-year-old subject who was taking norethindrone as contraception. The investigator assessed the event as unlikely related to berotralstat. If a woman becomes pregnant while using norethindrone as contraception, the likelihood that the pregnancy is ectopic is higher than in females not using this type of contraception.

Based upon review of all safety information to date, it is the sponsor's determination that these individual case safety reports do not change the risk-benefit profile of berotralstat and therefore do not warrant revision of the current protocols, informed consent forms, Investigator's Brochure, labels, or CCDS.

Missing information 2: Long-term safety in paediatric patients.

Evidence Source: In the pre- and postnatal development study in rats, the presence of berotralstat in the plasma from pups at all dose levels on lactation day 14 confirmed that there was lactational exposure.

In the offspring (F1) animals retained on study after postnatal Day 28, no effect was observed on body weights (growth or gestation), sexual maturation, clinical findings, behaviour (motor activity, learning, and memory), reproductive performance/fertility indices, gestation Day 13 uterine implantation data, or macroscopic findings.

The prevention indication Studies 302 and 204 included children from 12 to < 18 years of age, Study 304 includes children from 2 to < 12 years of age, and Study 312 includes children 2 years of age and older.

Although a small number of paediatric patients aged 2 to 17 were included in clinical studies, there are no long-term clinical study data on the use of berotralstat in paediatric patients ≥2 years of age. The safety and efficacy of berotralstat in paediatric patients were similar to adults and support a positive benefit-risk balance.

Paediatric Patients Aged 2 to < 12 Years

Results of interim analysis from Study 304 indicate that berotralstat was safe and generally well tolerated in the paediatric population aged < 12 years with no safety signals observed in 29 subjects. Two TEAEs (PT: nausea and headache) related to study drug were reported, neither of which led to discontinuation or interruption of study drug.

No clinically significant Grade 3 or 4 laboratory abnormalities, TESAEs related to study drug, or deaths were reported. The safety profile is consistent with what has been observed in prior studies of berotralstat in the adult and adolescent population. No TEAEs related to study drug were reported in the Hypersensitivity, Anaphylactic reaction, or Severe cutaneous adverse reaction SMQs. No clinically relevant elevations in LFTs were observed, and no subject had a post-baseline elevation in AST, ALT, or total bilirubin > 1.5 × ULN. No clinically significant or persistent QTc prolongation was observed. No QTcF > 450 msec was observed, and no subjects had a QTcF change from baseline > 60 msec. No PTs contained in the Torsade de pointes/QT prolongation SMQ and no events of palpitation or seizure were reported.

No new safety concerns were observed in the paediatric population.

Population in need of further characterisation: Paediatric patients

Anticipated risk/consequences of the missing information:

Up to the data lock point of this report, 161 post-marketing cases concerning 323 PTs have been assessed in the paediatric population. Of the 323 PTs reported, 23 were assessed as serious and 300 as non-serious. Of the 323 PTs, 121 were assessed as related, 85 were not assessable, and 115 were assessed as not related to berotralstat therapy. Of the 121 events assessed as related, the following system organ classes were most frequently reported: Gastrointestinal disorders (94 events), Nervous system disorders (12 events), and Skin and subcutaneous tissue disorders (8 events). No new safety

concerns have been identified in the paediatric (Study 304) subjects aged 2 to < 12 years, or from Study 312 with subjects aged 2 years and older.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity Hypersensitivity QT prolongation Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4 Phospholipidosis Carcinogenicity
Missing information	Safety profile in pregnancy and breastfeeding Long-term safety in paediatric patients

Abbreviations: CYP = cytochrome P450.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for any reported AE found in the TdP SMQ (broad PT terms): the follow-up form will specifically request information on independent risk factors for QT prolongation, both intrinsic and extrinsic.

Specific adverse reaction follow-up questionnaires for pregnancy: reported pregnancies will be collected with specialised forms. Attempts will be made to follow all pregnancies to outcome.

Specific adverse reaction follow-up questionnaires for paediatric patients (2 to < 12 years of age): reported adverse reactions and special situations will be collected with a specialised form.

III.2 Additional pharmacovigilance activities

Non-interventional post-authorisation safety study (NI-PASS) summary

Study short name and title: Study 401: Non-interventional post-authorisation study to evaluate the safety, tolerability, and effectiveness of berotralstat for patients with HAE in a real-world setting (APeX-N)

Rationale and study objectives: On 25-Feb-2021, the EMA CHMP adopted a positive opinion, recommending marketing authorisation for berotralstat for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older (EMA 2021). This was approved by the European Commission on 30-Apr-2021. On 12-May-2021, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisation for oral, once daily berotralstat for the routine prevention of recurrent HAE attacks in HAE patients aged 12 years and older. A category 3 NI-PASS was recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to further evaluate the long-term safety of berotralstat in paediatric patients as an additional pharmacovigilance activity.

As soon as berotralstat becomes commercially available in the respective country and these patients decide to start berotralstat or continue berotralstat treatment from the existing early access programmes, these patients will be invited to participate in this NI-PASS, which aims to monitor long-term safety and tolerability as well as effectiveness of berotralstat in a real-world setting.

The primary objective of this NI-PASS is to observe the safety and tolerability of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients during long-term administration in a real-world setting. The secondary objectives are to assess growth and development in adolescent patients 12 to 17 years of age, to evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting, and to assess QoL during long-term administration of berotralstat in a real-world setting.

Study design: This study is designed as a prospective, multicentre NI-PASS.

Study population: Patients will be adults and adolescents 12 years of age and older who have a confirmed diagnosis of HAE, can provide informed consent (assent for adolescent patients with legal

caregiver consent), and who are initiating treatment with berotralstat in accordance with current EMA- or MHRA-approved labelling. Patients who have a contraindication to treatment with berotralstat according to the current product labelling or who are currently participating in an interventional clinical trial will be excluded.

Milestones:

Estimated study duration: 60 months
Estimated enrolment period: 36 months
Estimated observation period: up to 60 months or ≥ 24 months after the last patient enrols
Date first patient enrolled: Jul-2022

Date last patient in: 04-Dec-2024
Estimated end of data collection: 01-Nov-2027
Estimated final study report: 26-Feb-2028

Registration in EU PAS Register: EUPAS43575. Registered on 10-Aug-2021.

Protocol Submission to PRAC: 02-Dec-2021

Interim progress Reports: Submitted as appendix to Periodic Benefit Risk Evaluation Report (PBRER): 3rd progress report submitted with PBRER #6 (data lock point 02-Dec-2024).

Study 304

Study short name and title: Study 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

Rationale and study objectives: The EMA (EMA, 2006), FDA (FDA, 2022), and ICH (FDA, 2018) provide guidelines for development of therapeutics in the paediatric population. Use of berotralstat in the prophylaxis of HAE meets the criteria specified in the FDA guidance for a PK and safety approach to extrapolation for development of drugs in the paediatric 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 programme. 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.

The primary objective is to describe the PK parameters of berotralstat administered orally to paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg. Secondary objectives are to 1) assess the safety and tolerability of berotralstat administered orally to paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg and 2) to summarise the effectiveness of berotralstat in paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

Study design: This is a sequential, three-part, open-label study.

Study population: Subjects with a clinical diagnosis of HAE who are 2 to < 12 years of age at enrolment, who have a confirmed diagnosis of HAE, with a parent/caregiver willing and able to provide written, informed consent (with assent from the child where appropriate), who stop prior long-term prophylaxis before start of treatment (if applicable), and who have a documented history of ≥ 2 HAE attacks in the 6 months prior to the enrolment visit. Subjects who have a concurrent diagnosis of any other type of recurrent angioedema are excluded.

Milestones:

Final report submission: within 6 months of study completion

Study 312

Study short name and title: Study 312: An Open-Label Study to Provide Berotralstat Access to Subjects with Type 1 and 2 HAE Who Were Previously Enrolled in Berotralstat Studies

Rationale and study objectives: Studies 302 and 204 met their objectives to generate sufficient efficacy, effectiveness, and safety data to support marketing applications of berotralstat and are now closed. Study 304 was designed to collect safety and pharmacokinetics data and provide access for up to 144 weeks. Berotralstat is not available in all countries where the clinical studies were or are being conducted. Study 312 allows enrolment of subjects from Studies 302, 204, and 304 to provide continued access to berotralstat for those who are benefiting from treatment and do not have another means of access to berotralstat and to collect additional long-term data on safety and growth in paediatric subjects.

The primary objective of the study is to monitor the long-term safety of berotralstat. The secondary objectives of the study are as follows: to provide continued access to berotralstat to subjects who have participated in Studies 302 and 204, are expected to continue benefitting from treatment with berotralstat, and do not have other means of access to berotralstat; and to provide continued access to berotralstat to patients who have participated in Study 304 and are expected to continue to benefit from treatment with berotralstat.

Study design: Single-arm, open-label, multicentre study for subjects who were enrolled in berotralstat Studies 302, 204, or 304.

Milestones:

Final report submission: within 6 months of study completion.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional PV activities				
Study 401: NI-PASS to evaluate safety, tolerability, and effectiveness of berotralstat for patients with Hereditary Angioedema in a real-world setting (APeX-N) Ongoing	Primary objective: To monitor safety and tolerability of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients during long-term administration in a real-world setting Secondary objectives: To assess growth and development in	<u>Important Potential Risks</u> • Hepatotoxicity • Hypersensitivity • QT Prolongation • Phospholipidosis • Carcinogenicity <u>Missing Information</u>	-Progress report submitted in line with PBRER schedule (as per EURD list) -Final study report	Progress reports are submitted as an appendix to the PBRER as agreed with PRAC. To date, 3 progress reports have been submitted.

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	adolescent patients 12 to 17 years of age, to evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting, and to assess QoL during long-term administration of berotralstat in a real-world setting	• Long-term safety in paediatric patients		Final report anticipated approximately 5.5 years after last patient enrols
Study 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 Ongoing	Primary objective: To describe the PK parameters of berotralstat administered orally to paediatric 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 paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg, and to summarise the effectiveness of berotralstat in paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.	<u>Important Potential Risks</u> • Hepatotoxicity • Hypersensitivity • QT Prolongation • Phospholipidosis • Carcinogenicity <u>Missing Information</u> • Long-term safety in paediatric patients	Final study report	Final report submission within 6 months of study completion.
Study 312: An Open-Label Study to Provide Berotralstat Access to Subjects with Type 1 and 2 HAE Who Were Previously Enrolled	Primary objective: To monitor the long-term safety of berotralstat. Secondary objectives: To provide continued access to berotralstat to subjects who have participated in Studies	<u>Missing Information</u> • Long-term safety in paediatric patients	Final study report	Final report submission within 6 months of study completion.

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
in Berotralstat Studies Ongoing	302 and 204, are expected to continue benefitting from treatment with berotralstat, and do not have other means of access to berotralstat. To provide continued access to berotralstat to patients who have participated in Study 304 and are expected to continue to benefit from treatment with berotralstat.			

Abbreviations: CSR = clinical study report; EURD = European Union reference dates; HAE = hereditary angioedema; NI-PASS = non-interventional post-authorisation safety study; PBRER = Periodic Benefit Risk Evaluation Report; PRAC = Pharmacovigilance Risk Assessment Committee; PV = pharmacovigilance; QD = once daily; QoL = quality of life.

Part IV: Plans for post-authorisation efficacy studies

There are no planned or ongoing imposed post-authorisation efficacy studies which are a condition of marketing authorisation or which are specific obligations in the context of conditional marketing authorisation or marketing authorisation under exceptional circumstances.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities[a]
Hepatotoxicity	Routine risk communication: Capsules SmPC Section 4.8 Granules SmPC Section 4.8 Capsules PL Sections 2, 4 Granules PL Sections 2, 4

Safety concern	Routine risk minimisation activities[a]
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription
Hypersensitivity	Routine risk communication: Capsules SmPC Sections 4.3, 4.8 Granules SmPC Sections 4.3, 4.8 Capsules PL Sections 2, 4 Granules PL Sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription
QT prolongation	Routine risk communication: Capsules SmPC Sections 4.4, 5.1, 5.2 Granules SmPC Sections 4.4, 5.1, 5.2 Capsules PL Sections 2, 3 Granules PL Sections 2, 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided In patients aged 12 years or older, it is preferable to avoid the use of berotralstat in patients with severe renal impairment. In children aged 2 years to < 12 years, use of berotralstat in patients with severe renal impairment should be avoided. Appropriate monitoring for patients with independent risk factors for QT prolongation should be considered. Other routine risk minimisation measures beyond the SmPC:

Safety concern	Routine risk minimisation activities[a]
	Legal status: medical prescription
Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4	Routine risk communication: Capsules SmPC Sections 4.5, 5.2 Granules SmPC Sections 4.5, 5.2 Capsules PL Section 2 Granules PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Appropriate monitoring is recommended for concomitant use of medicines with a narrow therapeutic index that are predominantly metabolised by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine, fentanyl) particularly those with a narrow therapeutic index, dose adjustments of these medicines may be required Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription
Phospholipidosis	Routine risk communication: Capsules SmPC Section 5.3 Granules SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription
Carcinogenicity	Routine risk communication: Capsules SmPC Section 5.3 Granules SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription

Safety concern	Routine risk minimisation activities[a]
Safety profile in pregnancy and breastfeeding	Routine risk communication: Capsules SmPC Sections 4.6, 5.3 Granules SmPC Sections 4.6, 5.3 Capsules PL Section 2 Granules PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Berotralstat use during pregnancy is not recommended and use during breastfeeding should be based on individual risk-benefit Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription
Long-term safety in paediatric patients	Routine risk communication: Capsules SmPC Section 4.8 Granules SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription

Abbreviations: CYP = cytochrome P450; PL = package leaflet; SmPC = summary of product characteristics.
[a] Orladeyo capsules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Orladeyo granules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to less than 12 years.

V.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures[a]	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures: Capsules SmPC Section 4.8 Granules SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures[a]	Pharmacovigilance activities
	Capsules PL Sections 2, 4 Granules PL Sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304
Hypersensitivity	Routine risk minimisation measures: Capsules SmPC Sections 4.3, 4.8 Granules SmPC Sections 4.3, 4.8 Capsules PL Sections 2, 4 Granules PL Sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304
QT prolongation	Routine risk minimisation measures: Capsules SmPC Sections 4.4, 5.1, 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted questionnaire for all reported AEs with

Safety concern	Risk minimisation measures[a]	Pharmacovigilance activities
	Granules SmPC Sections 4.4, 5.1, 5.2 Capsules PL Sections 2, 3 Granules PL Sections 2, 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided In patients aged 12 years or older, it is preferable to avoid use of berotralstat in patients with severe renal impairment. In children aged 2 years to < 12 years, use of berotralstat in patients with severe renal impairment should be avoided. Appropriate monitoring for patients with independent risk factors for QT prolongation will be considered Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	PTs contained in the broad terms of the TdP SMQ Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304
Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4	Routine risk minimisation measures: Capsules SmPC Sections 4.5, 5.2 Granules SmPC Sections 4.5, 5.2 Capsules PL Section 2 Granules PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures[a]	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: For concomitant medicines that are predominantly metabolised by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine, fentanyl), particularly those with a narrow therapeutic index, dose adjustments of these medicines may be required. (SmPC Section 4.5) Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	
Phospholipidosis	Routine risk minimisation measures: Capsules SmPC Section 5.3 Granules SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304
Carcinogenicity	Routine risk minimisation measures: Capsules SmPC Section 5.3 Granules SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304

Safety concern	Risk minimisation measures[a]	Pharmacovigilance activities
	None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	
Safety profile in pregnancy and breastfeeding	Routine risk minimisation measures: Capsules SmPC Sections 4.6, 5.3 Granules SmPC Sections 4.6, 5.3 Capsules PL Section 2 Granules PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use during pregnancy is not recommended and use during breastfeeding should take into consideration the individual risk-benefit Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: For all reported pregnancies, use of a specialised pregnancy form to ensure all pertinent details obtained. Attempts will be made to follow any reported pregnancy to outcome. Additional pharmacovigilance activities: None
Long-term safety in paediatric patients	Routine risk communication: Capsules SmPC Section 4.8 Granules SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the SmPC:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for paediatric patients (2 to < 12 years of age) Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304, Study BCX7353-312

Safety concern	Risk minimisation measures[a]	Pharmacovigilance activities
	Legal status: medical prescription	

Abbreviations: AE = adverse event, CYP = cytochrome P450; NI PASS = non interventional post authorisation safety study; SmPC = summary of product characteristics, SMQ = Standardised MedDRA Queries; TdP = Torsade de Pointes.

[a] Orladeyo capsules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Orladeyo granules are indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to less than 12 years.

Part VI:

Summary of risk management plan for Orladeyo (berotralstat)

This is a summary of the risk management plan (RMP) for Orladeyo. The RMP details important risks of Orladeyo, how these risks can be minimised, and how more information will be obtained about Orladeyo's risks and uncertainties (missing information).

Orladeyo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Orladeyo should be used.

This summary of the RMP for Orladeyo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Orladeyo's RMP.

I. The medicine and what it is used for

Orladeyo is authorised for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and children aged 2 years and older (see SmPCs for the full indications). It contains berotralstat as the active substance and it is given by mouth once a day (orally) in capsule form in patients aged 12 years and older and orally in granules in patients aged 2 to less than 12 years.

Further information about the evaluation of Orladeyo's benefits can be found in Orladeyo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage Orladeyo | European Medicines Agency (EMA).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Orladeyo, together with measures to minimise such risks and the proposed studies for learning more about Orladeyo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Orladeyo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Orladeyo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Orladeyo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Hepatotoxicity Hypersensitivity QT prolongation Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4 Phospholipidosis Carcinogenicity
Missing information	Safety profile in pregnancy and breastfeeding Long-term safety in paediatric patients

II.B Summary of important risks

Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	The liver was considered a target organ in toxicology studies due to reversible, non-adverse transaminase elevations seen in monkeys (non-human primates) dosed for 39 weeks, along with hepatocellular hypertrophy. In rats, there were no enzyme elevations but there was extrahepatic and liver bile duct hyperplasia and phospholipidosis (PLD). In humans, alanine transaminase (ALT) elevations and to a lesser degree, aspartate transaminase (AST) elevations > 3 × upper limit of normal (ULN) have been seen in clinical studies of subjects with HAE, but no clinical signs of jaundice, synthetic liver dysfunction, or liver injury, and no subject met the criteria for Hy's Law. The association is not clear because transaminase elevations were not seen in the absence of prior androgen exposure, particularly very recent exposure.

Risk factors and risk groups	An association between prior androgen use and asymptomatic elevations in ALT was identified. More important than lifetime exposure was recent abrupt discontinuation of androgens. Prior androgen use is high in patients with HAE. In the long-term safety studies, 63.2% of subjects had prior androgen use.
Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Section 4.8 Granules SmPC Section 4.8 Capsules PL Sections 2, 4 Granules PL Sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided. Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	NI-PASS 401, Study BCX7353-304

Important potential risk: Hypersensitivity	
Evidence for linking the risk to the medicine	During nonclinical development, no hypersensitivity or skin rashes were noted in any animal species dosed. Delayed-type hypersensitivity rash was identified as an event of special interest (EOSI) during initial Phase 1 studies in healthy subjects, but few events have been reported in patients with HAE, and these were mild to moderate, self-limited, and not dose-dependent. The rashes resolved in all subjects. Most subjects continued dosing with berotralstat without interruption, and the rashes did not reoccur with continued dosing, or in cases where dosing was interrupted, when berotralstat was restarted.
Risk factors and risk groups	Patients with hypersensitivity to the active substance or any of the excipients in berotralstat are at increased risk. There is no association with human leukocyte antigen (HLA) type or other comorbidity.

Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Sections 4.3, 4.8 Granules SmPC Sections 4.3, 4.8 Capsules PL Sections 2, 4 Granules PL Sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	NI-PASS 401, Study BCX7353-304

Important potential risk: QT prolongation	
Evidence for linking the risk to the medicine	Studies in non-human primates showed quantitatively small drug-related prolongation of the QT interval. A thorough QT study was conducted and showed that at steady state, the maximum observed plasma concentration (C_{max}) of berotralstat at the recommended dose of 150 mg once daily resulted in a mean corrected QT (QTc) increase of 3.4 msec (90% CI upper bound [UB] of 6.8 msec), which is below the 10 msec threshold for regulatory concern. Exposures 4-fold higher than achieved at the recommended dose increased the QTc by 21.9 msec (mean). Based on exposure-response modelling, at the highest anticipated clinically relevant exposure in a worst-case scenario of GM C_{max} of 240 ng/mL, in the setting of hepatic impairment (moderate and severe hepatic failure, Pugh-Child class B and C), the estimated ΔΔQTcF was 7.0 msec (2-sided 90% UB 10.9 msec). These values exceed the ICH E14 threshold for potential clinical significance. It should be noted that in Study BCX7353-108, conducted in subjects who had varying degrees of hepatic failure including moderate and severe, no clinically significant ECG changes were observed, no subject had a change from baseline in QTcF > 30 msec, and no subject had a QTcF > 500 msec. The study was single dose so the risk cannot be confirmed. Subjects with moderate to severe hepatic failure were not

	enrolled in the long-term prophylaxis (LTP) clinical studies and this potential effect is based only on modelling. Additionally, low weight could increase berotralstat exposures. Adolescents and adults weighing < 40 kg were excluded from the development programme. As weight is the primary covariate affecting PK in the population PK model, modelling indicates that at lower weights, berotralstat exposure is higher than at higher weights. Exposures in patients aged > 12 years weighing 40 kg taking the approved 150 mg dose do not exceed concentrations at which there is a concern for prolonged QT. Modelling indicates that at lower weights, around 35 kg, patients are simulated to have C_{max} exposure of approximately 222 ng/mL, the concentration at which the 2-sided 90% UB for ΔΔQTcF is 10 msec. No dose adjustment is required for patients weighing at least 40 kg. An additional analysis of the QT sub-intervals revealed that multiple supratherapeutic daily doses of berotralstat prolonged the QTc interval but had little effect on the J to T peak sub-interval, which suggests that the QT prolongation reported with berotralstat can be categorised as "benign" and unlikely to be associated with proarrhythmic risk, similar to marketed drugs ranolazine or verapamil. No subjects in the 3 LTP studies (204, 301, and 302) experienced clinically significant QT prolongation.
Risk factors and risk groups	Patients with moderate or severe (Child-Pugh Class B and C) liver failure Patients with independent risk factors for QT prolongation Extrinsic: Electrolyte disturbances Concomitant use of other drugs known to either prolong the QTc or increase berotralstat drug levels (e.g., cyclosporine) Intrinsic: Congenital QT prolongation Acquired QT prolongation Advanced age

Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Sections 4.4, 5.1, 5.2 Granules SmPC Sections 4.4, 5.1, 5.2 Capsules PL Sections 2, 3 Granules PL Sections 2, 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided In patients aged 12 years or older, it is preferable to avoid use of berotralstat in patients with severe renal impairment. In children aged 2 years to < 12 years, use of berotralstat in patients with severe renal impairment should be avoided. Appropriate monitoring for patients with independent risk factors for QT prolongation will be considered Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted questionnaire for all reported AEs with PTs contained in the broad terms of the TdP SMQ Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304

Important potential risk: Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4	
Evidence for linking the risk to the medicine	Drug-drug interaction studies with various doses of berotralstat.
Risk factors and risk groups	Patients taking berotralstat concomitantly with narrow therapeutic index drugs metabolised by CYP2D6 or CYP3A4. Given the monitorability of many narrow therapeutic index drugs and the guidance provided in the SmPC, the risk-benefit impact is considered low.

Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Sections 4.5, 5.2 Granules SmPC Sections 4.5, 5.2 Capsules PL Section 2 Granules PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: For concomitant medicines that are predominantly metabolised by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine, fentanyl), particularly those with a narrow therapeutic index, dose adjustments of these medicines may be required. Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none

Important potential risk: Phospholipidosis	
Evidence for linking the risk to the medicine	Toxicity studies of berotralstat in rats and non-human primates demonstrated the presence of foamy and/or vacuolated macrophages in several tissues and organs of both rats and non-human primates, including liver, lung, small intestine, spleen, and lymph nodes.
Risk factors and risk groups	Unknown The lack of any clinical evidence of PLD occurring in humans as well as the inconclusive evidence that PLD is detrimental, the risk-benefit impact is considered minimal.
Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Section 5.3 Granules SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription

	Additional risk minimisation measures: none
Additional pharmacovigilance activities	NI-PASS 401, Study BCX7353-304

Important potential risk: Carcinogenicity	
Evidence for linking the risk to the medicine	Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose. These findings are inconclusive, with an incidence slightly higher than in control groups. The clinical relevance of these findings is unknown. Across the berotralstat clinical development programme and post-marketing, there was no evidence of carcinogenicity. Nevertheless, carcinogenicity is addressed as an important potential risk.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Section 5.3 Granules SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	NI-PASS 401, Study BCX7353-304

Important missing risk: safety profile in pregnancy and breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: Capsules SmPC Sections 4.6, 5.3 Granules SmPC Sections 4.6, 5.3 Capsules PL Section 2 Granules PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use during pregnancy is not recommended and use during breastfeeding should take into consideration the individual risk-benefit Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none

Important missing information: long-term safety in paediatric patients	
Risk minimisation measures	Routine risk communication: Capsules SmPC Section 4.8 Granules SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: NI-PASS 401, Study BCX7353-304, Study BCX7353-312 Specific adverse reaction follow-up questionnaires for paediatrics (aged 2 to< 12 years of age): reported adverse reactions and special situations will be collected with a specialised form.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Study 401: NI-PASS to evaluate safety, tolerability, and effectiveness of berotralstat for patients with HAE in a real-world setting (APeX-N)

Ongoing
Purpose of the study: On 25-Feb-2021, the EMA CHMP adopted a positive opinion, recommending marketing authorisation for berotralstat for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older. This was approved by the European Commission on 30-Apr-2021. On 12-May-2021, the UK's MHRA granted marketing authorisation for oral, once-daily berotralstat for the routine prevention of recurrent HAE attacks in HAE patients aged 12 years and older. A category 3 NI-PASS was recommended by PRAC to further evaluate the long-term safety of berotralstat in paediatric patients as an additional pharmacovigilance activity.

As soon as berotralstat becomes commercially available in the respective country and these patients decide to start berotralstat or continue berotralstat treatment from the existing early access programmes, these patients will be invited to participate in this NI-PASS which aims to monitor long-term safety and tolerability as well as effectiveness of berotralstat in a real-world setting.

The primary objective of this NI-PASS is to observe the safety and tolerability of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients during long-term administration in a real-world setting.

The secondary objectives are to assess growth and development in adolescent patients 12 to 17 years of age, to evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting, and to assess QoL during long-term administration of berotralstat in a real-world setting.

Study 304: 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

Ongoing

Purpose of the study: The EMA (EMA, 2006), FDA (FDA, 2022), and ICH (FDA, 2018) provide guidelines for development of therapeutics in the paediatric population. Use of berotralstat in the prophylaxis of HAE meets the criteria specified in the FDA guidance for a PK and safety approach to extrapolation for development of drugs in the paediatric 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 programme. 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.

The primary objective is to describe the PK parameters of berotralstat administered orally to paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg. Secondary objectives are to 1) assess the safety and tolerability of berotralstat administered orally to paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg and 2) to summarise the effectiveness of berotralstat in paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg.

Study 312: An open-label study to provide berotralstat access to subjects with type I and II hereditary angioedema who were previously enrolled in berotralstat studies

Ongoing

Purpose of the study: Studies 302 and 204 met their objectives to generate sufficient efficacy, effectiveness, and safety data to support marketing applications of berotralstat and are now closed. Study 304 was designed to collect safety and pharmacokinetics data and provide access for up to 144 weeks.

Berotralstat is not available in all countries where the clinical studies were or are being conducted. Study 312 allows enrolment of participants from Studies 302, 204, and 304 to provide continued access to berotralstat for those who are benefiting from treatment and do not have another means of access to berotralstat and to collect additional long-term data on safety and growth in paediatric subjects.

The primary objective of the study is to monitor the long-term safety of berotralstat. The secondary objectives of the study are as follows: to provide continued access to berotralstat to subjects who have participated in Studies 302 and 204, are expected to continue benefitting from treatment with berotralstat, and do not have other means of access to berotralstat; and to provide continued access to berotralstat to patients who have participated in Study 304 and are expected to continue to benefit from treatment with berotralstat.

Part VII: Annexes

Annex 1 - EudraVigilance Interface

Not applicable

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	**Summary of objectives**	**Safety concerns addressed**	**Protocol link** **milestones**
Study 401: NI-PASS to evaluate safety, tolerability, and effectiveness of berotralstat for patients with HAE in a real-world setting (APeX-N) Ongoing (Category 3)	Primary objective: To monitor safety and tolerability of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients during long-term administration in a real-world setting Secondary objectives: To assess growth and development in adolescent patients 12 to 17 years of age, to evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting, and to assess QoL during long-term administration of berotralstat in a real-world setting	Long-term safety in patients receiving Orladeyo® as marketed product Long-term impact of berotralstat administration on growth and development of adolescent patients	Study 401 protocol Enrolment complete; a total of 165 subjects (including 8 adolescent patients) have been enrolled. Final report anticipated approximately 5.5 years after last patient enrols
Study 304: A Phase 3 Study to Evaluate the Safety and	Primary objective: • To describe the PK parameters of	Long-term safety in paediatric patients	Study 304 protocol – for information only

Study	Summary of objectives	Safety concerns addressed	Protocol link milestones
Pharmacokinetics of Berotralstat Prophylaxis in Children with Hereditary Angioedema Who Are 2 to < 12 Years of Age Ongoing (Category 3)	berotralstat administered orally to paediatric 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 paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg, and to summarise the effectiveness of berotralstat in paediatric subjects with HAE aged 2 to < 12 years old and weighing ≥ 12 kg		Final report submission within 6 months of study completion.
Study 312: An Open-Label Study to Provide Berotralstat Access to Subjects with Type 1 and 2 HAE Who Were Previously Enrolled in Berotralstat Studies Ongoing	Primary objective: To monitor the long-term safety of berotralstat. Secondary objectives: To provide continued access to berotralstat to subjects who have participated in Studies 302 and 204, are expected to	Long-term safety in paediatric patients	Study 312 protocol – for information only Final report submission within 6 months of study completion.

Study	Summary of objectives	Safety concerns addressed	Protocol link milestones
	continue benefitting from treatment with berotralstat, and do not have other means of access to berotralstat. To provide continued access to berotralstat to patients who have participated in Study 304 and are expected to continue to benefit from treatment with berotralstat.		

Abbreviations: HAE = hereditary angioedema; NI-PASS = non-interventional post-authorisation safety study; PK = pharmacokinetics; QoL = quality of life.

Table 2 Annex II: Completed Studies

Study	Summary of objectives	Safety concerns addressed	Date of final study report submission link to report
Study 204: An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type 1 and 2 hereditary angioedema	Primary objective: • To evaluate the long-term safety and tolerability of daily dosing of oral berotralstat (BCX7353) in subjects with hereditary angioedema (HAE) Secondary objectives: • To assess the effectiveness (i.e., HAE attack frequency, severity, and disease activity over time) of berotralstat during	Long-term safety and tolerability of daily dosing of oral berotralstat (BCX7353) in subjects with HAE	Final CSR submitted on 26-Oct-2022.

	long-term administration • To evaluate QoL during long-term administration of berotralstat • To evaluate subjects' satisfaction with medication during long-term administration of berotralstat		
Study 302: A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of 2 dose levels of berotralstat as an oral treatment for the prevention of attacks in subjects with hereditary angioedema	Part 1 objectives: Primary: • To determine the efficacy of prophylactic berotralstat (BCX7353) 110 and 150 mg administered QD for 24 weeks compared to placebo in subjects with HAE Secondary: • To assess the safety and tolerability of berotralstat 110 and 150 mg administered QD for 24 weeks • To assess the effects of berotralstat on HAE disease activity and HAE attack characteristics • To evaluate the effects of berotralstat on QoL • To characterise the PD effects of berotralstat Part 2 Objectives: Primary: • To evaluate the long-term safety and tolerability of berotralstat 110 and 150 mg administered QD over a 24- to 48-week administration	To evaluate the long-term safety and tolerability of berotralstat administered QD	Final CSR submitted on 07-Oct-2022.

	period in subjects with HAE Secondary: • To assess the effectiveness (i.e., HAE attack frequency over time) of berotralstat over a 24- to 48-week administration period • To evaluate QoL and HAE disease activity of berotralstat over a 24- to 48-week administration period • To evaluate subject satisfaction with berotralstat over a 24- to 48-week administration period Part 3 Objectives: Primary: • To evaluate the long-term safety and tolerability of berotralstat administered QD over a 48- to up to 144-week administration period in subjects with HAE Secondary: • To assess the effectiveness (i.e., HAE attack frequency over time) of berotralstat over a 48- to up to 144-week administration period • To evaluate QoL and HAE disease activity of berotralstat over a 48- to up to 144-week administration period • To evaluate subject satisfaction with berotralstat over a 48- to up to 144-week administration period		

Abbreviations: CSR = clinical study report; HAE = hereditary angioedema; PD = pharmacodynamics; QD = once daily; QoL = quality of life.

Annex 3 - Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

Approved protocols: PASS 401 Protocol

Procedure number: EMEA/H/C/005138/MEA/002

Final protocols not reviewed or not approved: Study BCX7353-304 Protocol and Study BCX7353-312 Protocol – submitted for information only.

Annex 4 - Specific adverse drug reaction follow-up forms

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Follow-up forms

Pregnancy and Breastfeeding Follow-Up Form V 2.0

Orladeyo Arrhythmia Follow-Up Questionnaire

Orladeyo Paediatric Follow-up Questionnaire

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 - Other supporting data (including referenced material)

Agostoni, A. and M. Cicardi (1992). "Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients." Medicine (Baltimore) 71(4): 206-215.

Banerji, A., M. Riedl, J. Bernstein, M. Cicardi, H. Longhurst, B. Zuraw, P. Busse, J. Anderson, M. Magerl, I. Martinez-Saguer, M. Davis-Lorton, A. Zanichelli, H. Li, T. Craig, J. Jacobs, D. Johnston, R. Shapiro, W. Yang, W. Lumry, M. Manning, L. Schwartz, M. Shennak, D. Soteres, R. Zaragoza-Urdaz, S. Gierer, A. Smith, R. Tachdjian, H. Wedner, J. Hebert, S. Rehman, P. Staubach, J. Schranz, J. Baptista, W. Nothaft and M. Maurer (2018). "Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: A randomized clinical trial." JAMA 320(20):2108–2121.

Bomhard, E. (1992). "Frequency of spontaneous tumors in Wistar rats in 30-months studies." Exp Toxicol Pathol 44(7): 381-392.

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

Busse, P. J., S. C. Christiansen, M. A. Riedl, A. Banerji, J. A. Bernstein, A. J. Castaldo, T. Craig, M. Davis-Lorton, M. M. Frank, H. H. Li, W. R. Lumry and B. L. Zuraw (2021). "US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema." J Allergy Clin Immunol Pract 9(1):132-150.e3.

Bygum, A. (2009). "Hereditary angio-oedema in Denmark: a nationwide survey." Br J Dermatol 161(5): 1153-1158.

Caballero, T., E. Aygoren-Pursun, A. Bygum, K. Beusterien, E. Hautamaki, Z. Sisic, S. Wait and H. B. Boysen (2014). "The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe." Allergy Asthma Proc 35(1): 47-53.

Cancian, M., P. Triggianese, S. Modica, F. Arcoleo, D. Bignardi, L. Brussino, C. Colangelo, E. Di Agosta, D. Firinu, M. D. Guarino, F. Giardino, M. Giliberti, V. Montinaro and R. Senter (2023). "The impact of puberty on the onset, frequency, location, and severity of attacks in hereditary angioedema due to C1-inhibitor deficiency: A survey from the Italian Network for Hereditary and Acquired Angioedema (ITACA)." Front Pediatr 11:1141073.

Chatman, L. A., D. Morton, T. O. Johnson and S. D. Anway (2009). "A strategy for risk management of drug-induced phospholipidosis." Toxicol Pathol 37(7): 997-1005.

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

DHHS (2009). " Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation". https://www.fda.gov/media/116737/download.

Drummond, M. B., P. F. Schwartz, W. T. Duggan, J. G. Teeter, R. J. Riese, R. C. Ahrens, R. O. Crapo, R. D. England, N. R. MacIntyre, R. L. Jensen and R. A. Wise (2008). "Intersession variability in single-breath diffusing capacity in diabetics without overt lung disease." Am J Respir Crit Care Med 178(3): 225-232.

EMA (2021). "Assessment Report Orladeyo". https://www.ema.europa.eu/en/documents/assessment-report/orladeyo-epar-public-assessment-report_en.pdf.

EMA. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population 2006.

Eurostat. Population on 1 January by age group and sex (2025). https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJANGROUP

FDA. General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products 2022.

FDA. E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population 2018.

Frank, M. M (2006). "Hereditary angioedema: The clinical syndrome and its management in the United States." Immunol Allergy Clin North Am 26(4):653–668.

Kaplan, A. P. and K. Joseph (2014). "Pathogenic mechanisms of bradykinin mediated diseases: dysregulation of an innate inflammatory pathway." Adv Immunol 121: 41-89.

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

Longhurst, H., M. Cicardi, T. Craig, K. Bork, C. Grattan, J. Baker, H. Li, A. Reshef, J. Bonner, J. Bernstein, J. Anderson, W. Lumry, H. Farkas, C. Katelaris, G. Sussman, J. Jacobs, M. Riedl, M. Manning, J. Hebert, P. Keith, S. Kivity, S. Neri, D. Levy, M. Baeza, R. Nathan, L. Schwartz, T. Caballero, W. Yang, I. Crisan, M. Hernandez, I. Hussain, M. Tarzi, B. Ritchie, P. Králíčková, M. Guilarte, S. Rehman, A. Banerji, R. Gower, D. Bensen-Kennedy, J. Edelman, H. Feuersenger, J. Lawo, T. Machnig, D. Pawaskar, I. Pragst and B. Zuraw (2017). "Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor." N Engl J Med 376(12):1131–1140.

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

Magerl, M., H. Gothe, S. Krupka, A. Lachmann and C. Ohlmeier (2020). "A Germany-wide survey study on the patient journey of patients with hereditary angioedema." Orphanet J Rare Dis 15(1):221.

Martello, J. L., M. R. Woytowish and H. Chambers (2012). "Ecallantide for treatment of acute attacks of hereditary angioedema." Am J Health Syst Pharm 69(8): 651-657.

Maurer, M. and M. Magerl (2011). "Long-term prophylaxis of hereditary angioedema with androgen derivates: a critical appraisal and potential alternatives." J Dtsch Dermatol Ges 9(2): 99-107.

Maurer, M., M. Magerl, S. Betschel, W. Aberer, I. J. Ansotegui, E. Aygören-Pürsün, A. Banerji, N. Bara, I. Boccon-Gibod, K. Bork, L. Bouillet, H. B. Boysen, N. Brodszki, P. J. Busse, A. Bygum, T. Caballero, M. Cancian, A. Castaldo, D. M. Cohn, D. Csuka, H. Farkas, M. Gompels, R. Gower, A. S. Grumach, G. Guidos-Fogelbach, M. Hide, H. Kang, A. P. Kaplan, C. Katelaris, S. Kiani-Alikhan, W. Lei, R. Lockey, H. Longhurst, W. R. Lumry, A. MacGinnitie, A. Malbran, I.M. Saguer, J. J. Matta, A. Nast, D. Nguyen, S. A. Nieto-Martinez, R. Pawankar, J. Peter, G. Porebski, N. Prior, A. Reshef, M. Riedl, B. Ritchie, F. R. Sheikh, W. B. Smith, P. J. Spaeth, M. Stobiecki, E. Toubi, L. A. Varga, K. Weller, A. Zanichelli, Y. Zhi, B. Zuraw and T. Craig (2022). "The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update." World Allergy Organ J 15(3):100627.

Maurer, M., W. R. Lumry, H. H. Li, E. Aygören-Pürsün, P. J. Busse, J. Jacobs, C. Nurse, M. A. Ahmed, M. Watt, M. Yu, S. Investigators, W. H. Yang, E Aygören-Pürsün, I. Martinez-Saguer, M. Maurer, H. Farkas, M. Perosa, J. Bernstein, P. Busse, J. S. Jacobs, H. H. Li, W. R. Lumry, S. M. Rehman, R. Tachdjian, H. J. Wedner and M. E. Weinstein (2024). "Lanadelumab in patients 2 to less than 12 years

old with hereditary angioedema: Results from the Phase 3 SPRING study." J Allergy Clin Immunol Pract 12(1):201-211.e6.

Mendivil, J., R. Murphy, M. de la Cruz, E. Janssen, B. Boysen, G. Jain, E. Aygören-Pürsün, I. Hirji and G. Devercelli (2021). "Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey." Orphanet J Rare Dis 16(1): 94.

Minafra, F. G., L. A. O. Cunha, R. G. de Souza Mariano, G. A. Goebel, L. S. de Lima and J. A. Pinto (2022). "Investigation of Mortality of Hereditary Angioedema in a Reference Center in Brazil." J Allergy Clin Immunol Pract 10(7): 1805–1812.

Nanda, M. K., S. Elenburg, J. A. Bernstein and A. H. Assa'ad (2015). "Clinical features of pediatric hereditary angioedema." J Allergy Clin Immunol Pract 3(3):392–395.

Nordenfelt, P., S. Dawson, C. F. Wahlgren, A. Lindfors, L. Mallbris and J. Bjorkander (2014). "Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden." Allergy Asthma Proc 35(2): 185-190.

Nordenfelt, P., M. Nilsson, J. Bjorkander, L. Mallbris, A. Lindfors and C. F. Wahlgren (2016). "Hereditary Angioedema in Swedish Adults: Report From the National Cohort." Acta Derm Venereol 96(4): 540-545.

Pedersen, N. G., L. Sperling, K. R. Wojdemann, S. Larsen Oleson and A. Tabor (2013). "First trimester growth restriction and uterine artery blood flow in the second trimester as predictors of adverse pregnancy outcome." Eur J Obstet Gynecol Reprod Biol 168(1):20–25.

Prenzel F., S. Abraham, C. Hirche, G. Müller, S. Kaiser, L. Serdani-Neuhaus, R. Zingel and I. Martinez-Saguer (2023). "Epidemiology and treatment of children with hereditary angioedema in Germany: A retrospective database study." Clin Transl Allergy 13(11):e12313.

Psarros, F., N. Koutsostathis, E. Farmaki, M. G. Speletas and A. E. Germenis (2014). "Hereditary angioedema in Greece: the first results of the greek hereditary angioedema registry." Int Arch Allergy Immunol 164(4): 326-332.

Sanofi-Aventis (2011). "Danocrine US Prescribing Information." https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017557s033s039s040s041s042lb l.pdf

Sanchez-Osorio, M., A. Duarte-Rojo, B. Martinez-Benitez, A. Torre and M. Uribe (2008). "Anabolic-androgenic steroids and liver injury." Liver Int 28(2): 278-282.

Stray-Pedersen, A., T. G. Abrahamsen and S. S. Froland (2000). "Primary immunodeficiency diseases in Norway." J Clin Immunol 20(6): 477-485.

Sundler Björkman, L., B. Persson, D. Aronsson, L. Skattum, P. Nordenfelt and A. Egesten (2022). "Comorbidities in hereditary angioedema-A population-based cohort study." Clin Transl Allergy 12(3): e12135.

WHO Regional Office for Europe. (2021). "Cancer Data and Statistics." Retrieved 15 February, 2021, from https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics.

Wojcinski, Z. W., L. Andrews-Jones, D. I. Aibo and R. Dunstan (2013). Chapter 19: Skin. In: Sahota, P. S., J. A. Popp, J. F. Hardisty and C. Gopinath, eds. *Toxicologic Pathology Nonclinical Safety Assessment*, 1st ed. Boca Raton, FL: CRC Press. pp 831-894.

Zanichelli, A., F. Arcoleo, M. P. Barca, P. Borrelli, M. Bova, M. Cancian, M. Cicardi, E. Cillari, C. De Carolis, T. De Pasquale, I. Del Corso, P. C. Di Rocco, M. D. Guarino, I. Massaro, P. Minale, V. Montinaro, S. Neri, R. Perricone, S. Pucci, P. Quattrocchi, O. Rossi, M. Triggiani, G. Zanierato and A. Zoli (2015). "A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy." Orphanet J Rare Dis 10: 11.

Zuraw, B. L., A. Banerji, J. A. Bernstein, P. J. Busse, S. C. Christiansen, M. Davis-Lorton, M. M. Frank, H. H. Li, W. R. Lumry, M. Riedl and Hereditary Association Medical Advisory Board (2013). "US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency." J Allergy Clin Immunol Pract 1(5): 458-467.

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

Zuraw, B.L. (2010). "The pathophysiology of hereditary angioedema." World Allergy Organ J. 3(9 Suppl): S25-S28.

Annex 8 - Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
2.0	EMEA/H/C/005138/IB/0014 20/10/2023	-Module SIII - Clinical trial exposure data updated -Module SV.1 - post-authorisation exposure experience added -Safety concerns All safety concerns were updated with post-marketing data. -Pharmacovigilance Plan Study 204 and 302: • Removed as study has been completed and obligation has been fulfilled -Annexes • Annex 3: Protocols for ongoing studies in the pharmacovigilance plan added • Annex 8: Summary of changes to RMP over time updated
3.0	EMA/X/0000268892 N/A	-Part I - Information on the proposed indication, dosage, and pharmaceutical form relating to the use of the granules formulation in the paediatric population (aged 2 to < 12 years) was added. - Part II/Module SI - Updated indications for capsule and granules formulation were added. Information on the prevalence, the main existing treatment options, WAO/EAACI guidelines, and the natural history of the indicated conditions in the untreated population, including mortality and morbidity relating to the paediatric population, was added. -Part II/Module SII - Results for the assessment of BCX7353 toxicity in juvenile rats were added. Safety data from Study 304 for the paediatric population were added to Table SII.1: Safety Concerns from Nonclinical Studies. -Part II/Module SIII - An introduction to Study 304, designed to enrol subjects 2 to < 12 years old, was added. It was clarified that in the previous version of the RMP, the first 7 subjects enrolled into Study 304 were included in the integrated data tables (Table SIII.2, Table SIII.3, Table SIII.4 and Table SIII.5) which were prepared in 2023. Rather than integrate the subsequently enrolled 304 population into these tables, it was explained that the Study 304 exposure data are being presented separately and not being integrated with data from other clinical studies in the current version of the document due

		to differences in study design and subject population. Therefore, the exposure summary from the interim analysis for all 4 cohorts of Study 304 subjects (29 subjects) is presented as a separate table. The previously presented tables were not amended as the clinical trial exposures for adults and adolescents were not significantly changed. The initial exposure information on those 7 paediatric subjects also remain in those tables but are now presented in their entirety as of the cutoff date in Table SIII.1. Information on race, sex, ethnicity, and exposure data for Study BCX7353-304 was added. Information was also added on the countries where Study 304 is being conducted. Updated information on number of studies conducted in adults and adolescent patients aged 12 years and older in the berotralstat clinical development programme. Updated information on exposure of subjects across the berotralstat clinical development programme. -Part II/Module SIV.1 - Added clarification on exclusion criteria that were relevant for adult and adolescents and paediatric population aged 2 to < 12 years. Added age specification of "≥ 12 years" to the language describing clinically significant abnormal ECG criteria at screening. Criteria of corrected QT interval using QTcF > 450 msec for paediatric subjects aged < 12 years was added. Updated the criteria for use of berotralstat in patients with varying degrees of renal impairment to align with the SmPC. Added a note to clarify that concomitant medications with narrow therapeutic index that are metabolised by CYP2D6 and CYP3A4 were prohibited in Study 304. -Part II/Module SIV.3 - Updated Table SIV.1 with the following: Exposure data from pregnant or breastfeeding women, a note stating patients with hepatic and renal impairment were not enrolled in the paediatric development programme, percentage of patients that were White in Study 302 Parts 2 and 3. Added a Study 304 limitation in respect to populations typically underrepresented in the clinical trial development programme that all enrolled subjects who reported race in the paediatric development programme were White. -Part II/Module SV.1.2 - Clarification was added that post-marketing exposure data are not available for patients aged 2 to < 12 years as berotralstat is not yet

		approved for this age group. Updated cumulative exposure in patient-years for adults and adolescent patients based on sales data. -Part II/Module SVII.2 - Added language explaining that the safety profile in paediatric patients 2 to < 12 years is consistent with observations from prior studies of berotralstat in the adult and adolescent population. -Part II/Module SVII.3.1 - Updated post-marketing reporting data and any TEAEs reported in the paediatric development programme for important potential risks hepatotoxicity, hypersensitivity, QT prolongation, drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4, phospholipidosis, and carcinogenicity. Information on recommended doses using Monte Carlo simulations for paediatric patients aged 2 to < 12 years was added. Table SVII.2 and text providing a summary of QTcF assessments with potentially clinically significant QTcF values in Study 304 subjects with Type 1 or 2 HAE was added. A dosing recommendation of 108 mg granules QD for paediatric patients aged > 12 years and weighing < 40 kg was added. -Part II/Module SVII.3.2 - Updated post-marketing reporting data for missing information: safety profile in pregnancy and breastfeeding, long-term safety in paediatric patients. Added a summary of safety conclusions from Study 304. -Part III.2 - Updated dates for Study 401 milestones. -Part III.3 - Updated the information on number of progress reports that have been submitted. -Part V.1 - Following updates made to Table Part V.1: Added/updated PL and SmPC section numbers for each of the safety concerns. -Part V.2 - Following updates made to Table Part V.2: Added/updated PL and SmPC section numbers for each of the safety concerns. -Part VI.I - Updated the proposed indication for the capsule and granules formulation. -Part VI.II - Added/updated PL and SmPC section numbers for each of the important potential risks. -Annex 2 - Updated milestones for Study 401 in Table 1. -Annex 7 - Updated references.

		Updated throughout in response to EU Day 120 questions 62 and 63: • Updated terminology from lactation to breastfeeding • Updated information on indication RMP Part VI 2C and Annex 2 have been updated in response to EU Day 120 question 61: • Paediatric follow-up questionnaire was proposed as an additional pharmacovigilance activity. Updated proposed dosage from 78 mg to 72 mg. Updated throughout in response to EU Day 180 questions 16 and 17: Study 304 as a Category 3 study in paediatric patients 2 to < 12 years of age Updated throughout in response to EU Day 195 assessment: Study 312 as a Category 3 study in paediatric patients 2 to < 18 years of age
4.0	EMA/X/0000268892 26/06/2026	Updated Opinion date

Signature Page for VV-PVG-000089 v7.0

Approval Task	Galina Marr Safety 22-Jun-2026 18:05:37 GMT+0000

Approval Task	Luke Lawlor Safety 22-Jun-2026 18:14:19 GMT+0000

Signature Page for VV-PVG-000089 v7.0

BIOCRYST

PHARMACEUTICALS, INC.

Protocol No. BCX7353-312

An open-label study to provide berotralstat access to subjects with type I and II hereditary angioedema who were previously enrolled in berotralstat studies

Version 4.0: 15 January 2025

EU Clinical Trial No. 2024-511285-37

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

SIGNATURE PAGE

Protocol No: BCX7353-312

Protocol Title: An open-label study to provide berotralstat access to subjects with type I and II hereditary angioedema who were previously enrolled in berotralstat studies

Date: Version 4.0: 15 January 2025

Sponsor's Approval

The protocol has been approved by BioCryst Pharmaceuticals, Inc.

Responsible Medical Officer:

Please see last page for electronic signature.

_____

Donald S. Fong, MD, MPH Date
Chief Medical Officer
BioCryst Pharmaceuticals, Inc.

Sponsor's Authorized Signatory:

Please see last page for electronic signature.

_____

Phil Collis, PhD Date
Senior Vice President Global Development
BioCryst Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure/Summary of Product Characteristics for berotralstat. I have read the Study BCX7353-312 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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

INFORMATION IN CASE OF EMERGENCY

Table 1: Emergency Information

Protocol Number:	BCX7353-312
Study Title:	An open-label study to provide berotralstat access to subjects with type I and II hereditary angioedema who were previously enrolled in berotralstat studies
EU Clinical Trial No.	2024-511285-37
Investigational Product:	Berotralstat (BCX7353)
Indication Studied:	Hereditary angioedema
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA
Sponsor Medical Monitor:	Phone (24 hours): +1 919-853-7905 Email Address: mm@biocryst.com
Clinical Study Manager:	Hillary Simpson Sr. Clinical Study Manager BioCryst Pharmaceuticals Office: + 1 919-745-0534 Email Address: hsimpson@biocryst.com
Principal Investigator:	Dr. Vesna Grivcheva-Panovska, MD PhD Head of the Unit of Allergy and Clinical Immunology Head of the Diagnostic PHI University Clinic of Dermatology Mother Teresa 17 1000 Skopje Republic of North Macedonia ++389 70 564 313 vesna_grivcheva_panovska@yahoo.com
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), International Council for Harmonisation Guidelines, and all locally applicable regulations. Essential study documents are currently archived in accordance with applicable regulations.
Final Protocol Date:	Version 4.0 15 January 2025

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: BCX7353-312	**Phase:** 3B	**Country:** Multinational
Title of Study: An open-label study to provide berotralstat access to subjects with type I and II hereditary angioedema who were previously enrolled in berotralstat studies		
Study center(s): Multicenter. May include sites in Canada, Europe, Asia-Pacific, Israel, and South Africa		
Principal Investigator: Vesna Grivcheva-Panovska, MD PhD		
Studied period (years): Date first subject enrolled: July 2021 Estimated duration is based on participant's clinical study history: • Participants from Studies BCX7353-302 and BCX7353-204: up to 10 years or until another mechanism is available to provide berotralstat (eg, market access) • Participants from BCX7353-304: until participant is 16 years of age and has access to berotralstat via another mechanism; or up to 5 years		**Phase of development:** 3B

Objectives:

Primary: To monitor the long-term safety of berotralstat.

Secondary:

- To provide continued access to berotralstat to patients who have participated in Studies BCX7353-302 (Study 302) and BCX7353-204 (Study 204), are expected to continue benefiting from treatment with berotralstat, and do not have other means of access to berotralstat.
- To provide continued access to berotralstat to patients who have participated in BCX7353-304 (Study 304) and are expected to continue to benefit from treatment with berotralstat.

Study Design: This is a single-arm, open-label, multicenter study for participants who were enrolled in berotralstat Studies 302, 204, or 304. For participants in Studies 204 or 302, the study will be conducted in countries where berotralstat is not available either commercially or via another mechanism. The study is also planned to be conducted in countries where pediatric participants have been enrolled in Study 304 (eg, Austria, Canada, France, Germany, Israel, Italy, Poland, Spain, United Kingdom).

Rationale:

Studies 302 and 204 have met their objectives to generate sufficient efficacy, effectiveness, and safety data to support marketing applications of berotralstat and are now closed. Study 304 was designed to collect safety and pharmacokinetics data and provide access for up to 144 weeks.

Berotralstat is not available in all countries where the clinical studies were or are being conducted. The current study allows enrollment of participants from Studies 302, 204, and 304 to provide continued access to berotralstat for those who are benefiting from treatment and do not have another means of access to berotralstat and to collect additional long-term data on safety and growth in pediatric participants.

Methodology:

Eligible participants will be enrolled into Study BCX7353-312 (Study 312) from Studies 302, 204, and 304. Participants ≥ 12 years of age and ≥ 40 kg will receive berotralstat 150 mg administered orally once daily (QD) and participants less than 12 years of age will receive a berotralstat dose QD based on participant weight.

Participants from Studies 302 and 204 will return to the clinic every 24 weeks for drug dispensation and safety monitoring for up to 480 weeks (approximately 10 years) or until another mechanism is available to provide drug to the subject (eg, market access), or until the sponsor discontinues all global commercialization and development of berotralstat for the prevention of angioedema attacks, whichever comes first.

Participants from Study 304 will return to the clinic every 24 weeks for drug dispensation and safety monitoring until 16 years of age and have access to berotralstat via another mechanism, or up to 5 years, or until the sponsor discontinues all global commercialization and development of berotralstat for the prevention of angioedema attacks, whichever comes first.

Safety and tolerability will be evaluated through assessment of serious adverse events (SAEs) and treatment-related, treatment-emergent adverse events (TEAEs). The following assessments will be performed at Baseline and all post-Baseline study visits: clinical chemistry, targeted physical examinations, concomitant medications, treatment-related TEAEs, and SAEs regardless of causality. The study assessments obtained at the final on-treatment visit in Study 302, 204, or 304 may serve as the Baseline visit assessments in the current study for participants continuing into Study 312.

Berotralstat will be discontinued for participants who are deriving no clinical benefit, are intolerant of berotralstat, or who experience an unacceptable laboratory abnormality or TEAE.

Sample Size Justification:

Not applicable.

Number of patients (planned):

Up to 139 participants are planned.

Diagnosis and main criteria for inclusion:

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

- Males and non-pregnant, non-lactating females who are currently enrolled as a subject or were previously enrolled and did not discontinue due to an adverse event or due to noncompliance in BioCryst-sponsored Study 302, 204, or 304.
- Participant or parent/legally designated representative (for participants < 18 years of age) able to provide written informed consent. For participants < 18 years of age, based on the child's age and local regulatory requirements, participant assent will be collected as appropriate.
- Would benefit from continued berotralstat treatment in the opinion of the investigator.
- Female participants of childbearing potential must agree to use acceptable effective contraception as defined in Section 7.1.
- In the opinion of the investigator, the participant is expected to adequately comply with all required study procedures.

Exclusion criteria:

- Any condition or situation, including medical history or changes in medical history, which, in the opinion of the investigator or sponsor, would interfere with the subject's safety or ability to participate in the study.
- Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or participation in the study.
- Hypersensitivity to the active substance or any of the excipients in Section 9.1.
- Use of other medications for long-term prophylaxis of hereditary angioedema attacks at the Baseline visit or anytime during the study. These include: C1 esterase inhibitors (C1-INH), tranexamic acid, androgens, or lanadelumab.
- Use of any other investigational medicinal product at the Baseline visit or any time during the study.
- Pregnancy or breastfeeding.
- Participants with an immediate family relationship to either sponsor employees, the investigator, or employees of the study site who are named on the delegation log.
- Participants who are held in an institution by a governmental or judicial order.

Investigational product, dosage and mode of administration:

For participants ≥ 12 years of age:

- Berotralstat (BCX7353) 150 mg orally administered QD

For participants < 12 years of age:

- Berotralstat (BCX7353) granules or capsules, orally administered QD based on participant weight

Age (years)	Dose[a]	Weight Band
≥ 12	150 mg capsule	≥ 40 kg[b]
2 to < 12	132 mg granules or 150 mg capsule[c]	≥ 40 kg
	108 mg granules	32 to < 40 kg
	96 mg granules	24 to < 32 kg
	78 mg granules	12 to < 24 kg

[a] Dose may be adjusted to align with regulatory authority-approved commercial doses for patients < 12 years of age.
[b] Participants ≥ 12 years of age and weighing < 40 kg should remain on previous dose until weight is ≥ 40 kg.
[c] Participants enrolling from Study 304 and receiving a dose of 150 mg will remain at that dose. All other participants who are < 12 years of age and weigh ≥ 40 kg will receive 132 mg.

Please refer to Treatment Assignments (Section 6.4) and Dose Adjustment Criteria (Section 6.5) for additional details.

Duration of treatment:

For Study 302 and 204 participants: up to 10 years or until another mechanism is available to provide berotralstat (eg, market access).

For Study 304 participants: until 16 years of age and have access to berotralstat via another mechanism; or up to 5 years, whichever comes first.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy:

No evaluations of efficacy will be performed.

Safety:

Safety will be evaluated by treatment-related TEAEs and all SAEs.

Statistical methods:

Data will be listed and summarized using descriptive statistics.

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BMI	body mass index
C1-INH	C1 esterase inhibitor
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
GCP	Good Clinical Practice
GI	gastrointestinal
HAE	hereditary angioedema
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
P-gp	p-glycoprotein efflux pump
PK	pharmacokinetic(s)
QD	once daily

Abbreviation or Specialist Term	Explanation
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SoC	standard of care
SOC	system organ class
Study 204	BCX7353-204
Study 302	BCX7353-302
Study 304	BCX7353-304
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization
WOCBP	woman of childbearing potential

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 among patients, from rarely in some patients to every few days in others. Angioedema attacks may or may not be precipitated by a stimulus (such as stress, trauma, or estrogen) and are typically rapid in onset, with symptoms subsiding gradually over the following 3 to 5 days (Zuraw and Christiansen 2011). Oropharyngeal swelling can be life-threatening (Bork et al. 2012), while attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring, and have a significant impact on functionality and quality of life (Lumry et al. 2010). Although mortality risk from asphyxiation is much higher in undiagnosed patients with HAE, deaths still occur in patients who have been diagnosed with HAE and have access to healthcare at centers of excellence (Bork et al. 2012).

Berotralstat (BCX7353) is a potent, synthetic, small-molecule inhibitor of plasma kallikrein. In contrast to parenterally administered options commercially available for treatment of HAE attacks, inhibition of kallikrein with an orally bioavailable small molecule such as berotralstat offers the advantage of oral administration. Inhibition of plasma kallikrein with berotralstat is expected to have significant benefits for patients with HAE by reducing the duration and/or severity of attacks. Berotralstat has been approved by the United States (US) Food and Drug Administration, European Medicines Agency (EMA), United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency, and other regulatory agencies for the prevention of attacks of HAE in adults and pediatric patients aged 12 years and older, and by the Ministry of Health, Labor and Welfare in Japan for suppression of the onset of acute hereditary angioedema attacks for adults and children aged 12 years or older. Regulatory filings to include patients 2 to < 12 years of age are anticipated, starting in 2025.

This study will be conducted in accordance with the requirements of Good Clinical Practice (GCP), the clinical study protocol, and applicable regulatory requirements.

4.2. Nonclinical Findings for Berotralstat

The principal results of nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies of berotralstat can be found in the berotralstat Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC) (approved for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older).

4.3. Clinical Findings for Berotralstat

4.3.1. Summary of Clinical Studies

Multiple clinical studies have been completed for berotralstat in support of indication of prophylaxis to prevent attacks of HAE. 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. Ongoing study BCX7353-304 (Study 304) is summarized in Section 4.3.1.1.

4.3.1.1. Study 304

The disease pathophysiology and diagnostic criteria are similar in adults and pediatric patients with HAE. In accordance with International Council for Harmonisation (ICH) guidance E11A Pediatric Extrapolation (ICH 2024), Study 304 was designed to support a PK and safety approach to pediatric extrapolation, given that there is evidence that adult and pediatric patients share a similar disease course and response to treatment to allow for exposure matching to establish efficacy. Therefore, Study 304 provides PK and safety data to match effective and safe exposures in the adult (reference) population and supportive clinical effectiveness data.

Study 304 is an ongoing Phase 3 open-label study designed to evaluate the PK, safety, and effectiveness of berotralstat for prophylaxis in pediatric participants 2 to < 12 years of age with HAE. The study includes 4 weight-based cohorts, with weight determined at baseline (Day 1). Study 304 consists of a 12-week standard of care (SoC) period followed by an open-label berotralstat treatment period lasting up to 144 weeks. An interim data cut (11 September 2024) to support global filings was completed once at least 15 patients completed 1 year of berotralstat treatment. Top-line results are summarized below.

A total of 29 participants, ages ranged 3 to 11 years and weight ranged from 14.90 to 69.70 kg at baseline, were enrolled across 9 countries and 11 sites. Participants were assigned to 4 different cohorts of decreasing starting doses of berotralstat based on their weight on Day 1. Of the 29 enrolled participants, 7 participants were assigned to Cohort 1 (150 mg capsules; ≥ 40 kg), 9 participants were assigned to Cohort 2 (108 mg oral granules; 32 to < 40 kg), 9 participants were assigned to Cohort 3 (96 mg oral granules; 24 to < 32 kg), and 4 participants were assigned to Cohort 4 (78 mg oral granules; 12 to < 24 kg).

At the time of the interim data cutoff, median participant exposure to berotralstat was 48.1 weeks (range: 12.1 to 73.0 weeks). All 29 participants had completed at least 12 weeks of berotralstat treatment, and 17 participants had completed dosing through Week 48. A total of 25 participants (86.2%) were still ongoing in the study. Of the 4 participants (13.8%) who had discontinued the study, 3 participants (10.3%) discontinued due to perceived lack of efficacy (2 participants after 48 weeks of treatment) and 1 participant (3.4%) discontinued due to withdrawal by participant on Day 195 following lack of compliance with prescribed dosing.

Overall, 25 participants (86.2%) have experienced TEAEs. TEAEs were generally similar across cohorts and most commonly included events in the infections and infestations system organ class (SOC) (18 participants [62.1%]). Nasopharyngitis (8 participants [27.6%]) and upper respiratory tract infection (7 participants [24.1%]) were the most frequently reported TEAEs. Six participants (20.7%) reported 11 TEAEs in the GI disorders SOC. Vomiting was the most frequently reported event in the SOC and was experienced by 3 participants (10.3%). Two participants (6.9%) each reported TEAEs of abdominal pain (3 events) and nausea (2 events). With the exception of 1 TEAE of nausea, no TEAEs in the GI disorders SOC were assessed as related to study drug.

No participant experienced a TEAE that led to interruption or discontinuation of study intervention or study, and no deaths were reported. Except for 2 treatment-emergent serious adverse events (SAEs) experienced by 1 participant considered unrelated to berotralstat (verbatim terms: skateboarding accident and fractured elbow, both Grade 3), all TEAEs were

Grade 1 (mild) or Grade 2 (moderate) in severity. Two participants (6.9%) experienced drug-related TEAEs, one event each of Grade 1 nausea and Grade 2 headache.

There was no evidence of increased risk of rash, with or without systemic symptoms. Two participants reported rashes (preferred terms [PTs]: rash and maculopapular rash) during the study, both assessed as unrelated to study intervention. Because more severe hypersensitivity reactions are a potential risk of berotralstat, all hypersensitivity/anaphylactic reactions events were evaluated. Eight participants experienced 11 TEAEs; however, all were Grade 1 or 2 and were not related to study intervention. Hypersensitivity events were primarily localized and limited to skin symptoms. No cases of anaphylaxis were identified in the program.

As of the interim data cutoff date, no participant experienced treatment-emergent laboratory changes related to study intervention. No clinically meaningful changes in liver function tests and no impact on vital signs or height and weight based on the World Health Organization (WHO) Child Growth Standards were observed. In addition, no cardiac TEAEs were reported, and no participant experienced clinically meaningful QT observations.

Effectiveness was measured by HAE attack rate with the 12-week SoC period serving as baseline compared to Part 1 (Day 1 through Week 12) and Parts 1 and 2 (Day 1 up to Week 48). During the 12-week SoC period, the median attack rate (based on all 29 evaluable participants) was 0.96 attacks/month (range 0.00 to 5.03 attacks/month). During Part 1, the median attack rate was 0.33 attacks/month (range 0.00 to 2.33 attacks/month). The median attack rate was 0.41 attacks/month (range 0.00 to 1.95 attacks/month) during Parts 1 and 2. Participants reported a median 63.5% and 63.9% reduction in attack rates relative to baseline in Parts 1 and in Parts 1 and 2, respectively.

When looking at attack rates on a monthly basis, the median attack rate decreased from 0.96 attacks/month (range 0.00 to 5.03 attacks/month) at baseline to 0 attacks/month starting at Month 1 on treatment. Median attack rates remained at 0 attacks/month for each month through Parts 1 and 2 of the study.

Berotralstat has been safe and well tolerated in Study 304 with no new safety signals and a safety profile consistent with that identified in patients ≥ 12 years of age. Participants reported a median 63.5% reduction in attack rate through Week 12 relative to baseline.

No new safety or tolerability signals beyond those previously described in patients 12 years of age and older were identified in Study 304 (age 2 to < 12 years).

4.3.2. Safety and Tolerability of Berotralstat in Participants ≥ 12 Years of Age

Berotralstat was well tolerated in Phase 1, 2, and 3 studies conducted in participants 12 years of age and older. Predominantly mild GI symptoms, including diarrhea, abdominal pain, and nausea, have been noted, particularly at higher doses in both healthy and HAE participants, when berotralstat is ingested. A few participants have stopped berotralstat due to GI intolerability at 150 mg dose but none of these participants had any demonstrable laboratory abnormalities. In addition, mild to moderate delayed hypersensitivity drug rash has been reported in < 1% of participants exposed to multiple dose administration of berotralstat, but no subject has had a severe or serious skin reaction. Adverse reactions of increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) have been commonly observed (incidence ≥ 1/100 to < 1/10) with berotralstat, primarily in those who discontinued androgen

therapy within 14 days of initiating berotralstat. Abrupt discontinuation of androgens immediately prior to initiating berotralstat should be avoided. These elevations, which were generally transient and asymptomatic and which improved with or without discontinuation of berotralstat, have not been associated with jaundice or signs of any synthetic dysfunction. No single electrocardiogram (ECG) in healthy participants or participants with HAE dosed with berotralstat has demonstrated a clinically significant abnormality. There are no data available for the use of berotralstat in patients with independent risk factors for corrected QT (QTc) prolongation such as electrolyte disturbances, known preexisting QTc prolongation (either acquired or familial), advancing age, or concomitant use of other medicinal products known to prolong the QTc.

Additional details on all berotralstat clinical studies can be found in the IB or SmPC.

4.4. Rationale

Berotralstat is approved for patients aged 12 years and above with HAE in the US, EU, UK, Japan, and other countries.

Studies 302 and 204 have met their objectives to generate sufficient efficacy and safety data to support marketing applications of berotralstat and are now closed. Study 304 was designed to collect safety and PK data in pediatric participants (aged 2 to < 12 years) and provide access for up to 144 weeks.

Berotralstat is not available in all countries where the clinical studies were or are being conducted. The current study allows enrollment of participants from Studies 302, 204, or 304 to provide continued access to berotralstat for participants who are benefiting from treatment and do not have another means of access to the appropriate dose of berotralstat and to collect additional long-term data on safety and growth in pediatric participants.

The sponsor has committed to provide berotralstat to participants from Studies 302 and 204 for up to 10 years or until another mechanism is available to provide berotralstat (eg, market access) and to participants from Study 304 until 16 years of age and has access to berotralstat via another mechanism; or up to 5 years, whichever comes first.

4.4.1. Rationale for Berotralstat Doses and Regimen

All participants enrolled in Studies 302 or 204 transitioned to berotralstat 150 mg QD. Marketing authorization applications for 150 mg QD as the recommended dose have been approved in major markets. Therefore, the current study will administer the 150 mg QD dose of berotralstat for participants ≥ 12 years of age, regardless of originating study. The investigational product will be used in accordance with the SmPC for participants ≥ 12 years of age.

All participants transitioning from Study 304 will receive the same dose levels studied in Study 304 (Table 3) with one modification based on Study 304 PK findings for participants < 12 years of age weighing ≥ 40 kg as described below.

Modeling conducted after the interim data cut of Study 304 suggests that a dose of 132 mg granules in participants < 12 years and weighing ≥ 40 kg results in exposure closer to adults administered the 150 mg capsules than the 150 mg dose evaluated in Study 304. As a result, participants who reach a weight of ≥ 40 kg and are increasing dose accordingly will adjust to 132 mg granules until they reach 12 years of age. Participants enrolling from Study 304 who are

< 12 years of age, weigh ≥ 40 kg, and receiving 150 mg capsules in Study 304 can remain on 150 mg capsules for the current study.

4.4.2. Rationale for Study Population

Studies 302 and 204 met their objectives and have closed. Study 304, conducted in patients aged 2 to < 12 years, has met its primary objective and will close after the last participant completes their last on-study visit. The current study will provide continued access to berotralstat for participants who have participated in Studies 302, 204, or 304, in alignment with regulatory and sponsor commitments. Study BCX7353-312 (Study 312) will enroll participants from Studies 302 and 204 in countries where other means of continued access to berotralstat (eg, market access) are not available, and from Study 304 to provide continued access and collect additional long-term data on safety and growth in pediatric participants. All participants will have a history of exposure to berotralstat and, in the opinion of the investigator, would continue to derive clinical benefit from berotralstat.

There are no or limited data from the use of berotralstat in pregnant women. Berotralstat is not recommended during pregnancy or in women of childbearing potential who are not using contraception.

Available pharmacodynamic/toxicological data in animals have shown excretion of berotralstat in milk. A risk to the newborn infants/infants cannot be excluded.

4.5. Benefit-Risk Analysis

Berotralstat has been approved in the US, EU, UK, Japan, and other countries for prevention of HAE attacks in adults and pediatric patients at least 12 years of age. Berotralstat has also been approved in Japan for suppression of the onset of acute hereditary angioedema attacks in adults and children aged 12 years and older. In clinical studies to date, berotralstat was safe and generally well tolerated. The most common adverse reactions were mild to moderate and consisted of GI reactions (including diarrhea, nausea, vomiting, and abdominal pain), nasopharyngitis, and headache.

Study 304 has completed the interim analysis that will support marketing authorization applications globally. Berotralstat was safe and well tolerated in Study 304 with no new safety signals and a safety profile consistent with that identified in patients ≥ 12 years of age. Similar to patients ≥12 years of age, pediatric participants < 12 years of age treated with berotralstat experienced a reduction in HAE attack rate compared to the SoC period.

Participants enrolling in this study will have been previously exposed to berotralstat in Studies 302, 204, and 304. They have tolerated the therapy sufficiently to continue therapy with berotralstat, and will, in the opinion of the investigator, continue to derive benefit from therapy with berotralstat. Therefore, the overall benefit-risk balance is considered acceptable.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of the study is to monitor the long-term safety of berotralstat.

5.2. Secondary Objectives

The secondary objectives of the study are:

- To provide continued access to berotralstat to subjects who have participated in Studies 302 and 204, are expected to continue benefiting from treatment with berotralstat, and do not have other means of access to berotralstat.
- To provide continued access to berotralstat to patients who have participated in BCX7353-304 (Study 304) and are expected to continue to benefit from treatment with berotralstat.

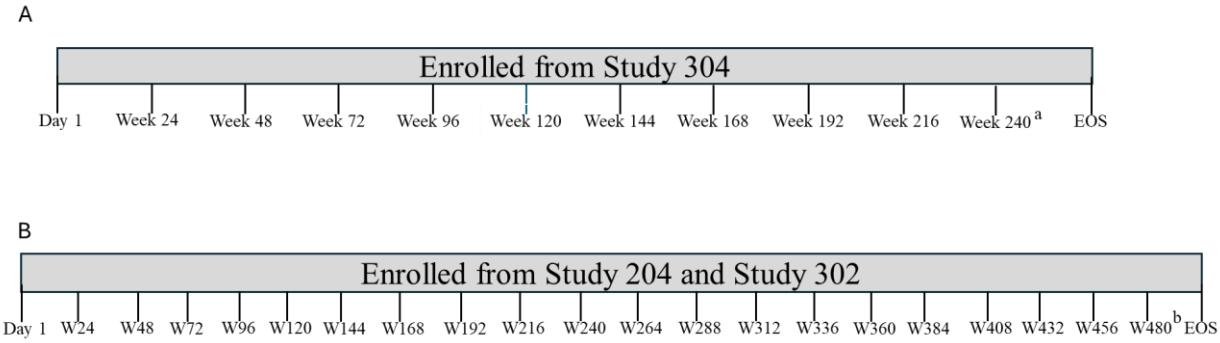
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Study 312 is a single-arm, open-label, multicenter study for participants who were enrolled in berotralstat Studies 302, 204, or 304. For participants in Studies 204 or 302, the study will be conducted in countries where berotralstat is not available either commercially or via another mechanism. The study is also planned to be conducted in countries where pediatric participants have been enrolled in Study 304 (eg, Austria, Canada, France, Germany, Israel, Italy, Poland, Spain, and UK) to enable continued access to berotralstat therapy. Enrolled participants at least 12 years of age and weighing ≥ 40 kg will receive the marketed dose of berotralstat, 150 mg QD, and participants < 12 years of age will receive the dose indicated by the appropriate dose weight band presented in Table 3.

The study schemas are presented in Figure 1.

Figure 1: Study Schema



Abbreviations: EOS = end-of-study; W = week.
[a] Participants from Study 304 may remain in the study until 16 years of age and has access to berotralstat via another mechanism or up to 5 years, whichever comes first.
[b] Participants from Studies 302 and 204 may remain in the study up to 10 years or another mechanism is available to provide drug to the subject (eg, market access).

All study endpoints will assess the safety and tolerability of berotralstat. Endpoints will include the following:

- Number and proportion of participants with a treatment-related TEAE
- Number and proportion of participants who experience an SAE
- Number and proportion of participants who experience a treatment-related Grade 3 or 4 TEAE
- Number and proportion of participants who experience a treatment-related Grade 3 or 4 treatment-emergent chemistry abnormality
- Number and proportion of participants who discontinue due to a TEAE

6.2. Number of Participants

Study 312 may enroll up to 139 participants.

6.3. Subject Numbers

All participants will retain their subject number from Study 302, 204, or 304 in Study 312.

6.4. Treatment Assignment

All participants from Studies 302 and 204, and participants from Study 304 who are ≥ 12 years of age and weigh ≥ 40 kg enrolled in Study 312 will be treated with open-label berotralstat 150 mg administered orally QD.

For participants from Study 304 who are < 12 years of age, open-label berotralstat will be orally administered QD based on participant weight.

Table 3: Dosing Weight Bands

Age (years)	Dose	Weight Band
≥12	150 mg capsule	≥ 40 kg[a]
2 to < 12	132 mg granules or 150 mg capsule[b]	≥ 40 kg
	108 mg granules	32 to < 40 kg
	96 mg granules	24 to < 32 kg
	78 mg granules	12 to < 24 kg

[a] Participants ≥ 12 years of age weighing < 40 kg should remain on previous dose until weight is ≥ 40 kg.
[b] Participants enrolling from Study 304 and receiving a dose of 150 mg will remain at that dose. All other participants who are < 12 years of age and weigh ≥ 40 kg will receive 132 mg.

6.5. Dose Adjustment Criteria

No dose adjustments for participants from Studies 302 or 204 will be permitted during the study.

Dose adjustments for participants from Study 304 may be made for the following reasons.

- For participants < 12 years of age, the dose of berotralstat will be adjusted based on the weight of the subject as shown in Table 3.
- Transition to 150 mg capsules after reaching 12 years of age, in accordance with product labelling (with weight ≥ 40 kg).
- Alignment with regulatory authority-approved commercial doses for patients < 12 years of age.
- As directed by sponsor via dosing clarification memo.

Study drug interruptions are discussed in Section 11.2.7.

6.6. Study Conduct

Each eligible subject who consents to participate in the study will receive orally administered berotralstat. Duration of treatment is based on the participant's clinical study history.

- Participants from Studies 302 and 204 may remain on study for up to 10 years or until another mechanism is available to provide drug to the subject (eg, market access).
- Participants from Study 304 may remain in the study until 16 years of age and has access to berotralstat via another mechanism or up to 5 years, whichever comes first.

Treatment would be discontinued if the sponsor discontinues all global commercialization and development of berotralstat for the prevention of angioedema attacks.

Participants will be required to attend a study visit every 24 weeks during the dosing period. More frequent clinic visits or telephone follow-up may be permitted as directed by local regulation, the physician's usual clinical practice, or under some special circumstances (eg, to accommodate drug expiry).

Participants may be enrolled once all eligibility criteria are met. Consistent with treatment guidelines that strongly support the position that all patients with C1-INH deficiency should have access to medications for treating attacks, all participants should have access to appropriate medications for the treatment of acute attacks of HAE, consistent with usual practice in their country (Marcus et al. 2018; Busse et al. 2021).

For participants with a break in treatment less than 24 weeks from Study 302, 204, or 304, the study assessments obtained at the final on-treatment visit in that study will serve as the baseline visit assessments in Study 312. Demographic data, medical history data, ongoing concomitant medications, and ongoing treatment-related TEAEs from Studies 302, 204, and 304 will be used as baseline data in Study 312. Participants who end participation in Study 302, 204, or 304 and choose to continue berotralstat treatment in Study 312 will not be required to have a follow-up/ end-of-study (EOS) visit 3 weeks after the last dose of berotralstat in Study 302, 204, or 304.

Participants who are eligible for and wish to participate in Study 312 and who have not continued with berotralstat administration for > 24 weeks after participation in Study 302, 204, or 304 will need to complete all baseline assessments except for the collection of demographic and medical history data. These data will be obtained from Study 302, 204, or 304. An assessment of prior and ongoing concomitant medications within 30 days of enrollment into Study 312 must be conducted, as well as an assessment of any ongoing treatment-related TEAEs from Studies 302, 204, and 304.

The following assessments will be performed at Baseline and all post-Baseline study visits: clinical chemistry, targeted physical examination, concomitant medications, treatment-related TEAEs, and SAEs regardless of causality. For participants from Study 304, height, weight, body mass index (BMI), and age of menarche (for the girls) will also be collected. All post-Baseline findings should be documented in source; however, post-Baseline only those laboratory, physical examination, or other findings meeting the definition of an SAE or treatment-related TEAE will be recorded in the case report form (CRF). SAEs must be reported on an ongoing basis in accordance with regulatory requirements (see Section 11.2.4). ECGs, hematology, coagulation, and urinalysis should be conducted in accordance with the investigator's usual practice for patients with HAE and documented; however, results should be recorded in the CRF only if a treatment-related TEAE or any SAE is identified. Pregnancy testing for women of childbearing potential will be conducted at Baseline. A pregnancy test should be conducted promptly for any woman suspected to have become pregnant during the study.

After completion of dosing in Study 312, participants will be required to attend a follow-up visit scheduled approximately 3 weeks following the last administration of study drug. Participants who continue to receive berotralstat via another mechanism after their last dose of study drug in Study 312 will not be required to complete a follow-up visit.

Written informed consent and assent (as applicable) must be obtained from each participant or parent/ legally designated representative before initiation of any assessments or procedures. Signing the informed consent form (ICF) may occur prior to the Baseline visit.

6.6.1. Schedule of Assessments

The schedule of assessments for this study is presented in Table 4 and procedures are described in Section 11.

Table 4: Schedule of Assessments

Assessment	Baseline	Clinic Visits (Every 24 Weeks) Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240*, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480 (± 12 days)	Follow-up/EOS[i] (3 weeks after last dose of study drug ± 7 days)
Informed consent/assent [a]	X		
Inclusion-exclusion criteria	X		
Demographics and medical history [b]	X		
Weight/height/BMI (participants < 18 years of age only)[c]	X	X	X
Targeted physical examination [d]	X	X	X
Pregnancy test [e]	X		
Clinical chemistry [f]	X	X	X
Concomitant medications	X[g]	X	X
Assessment of treatment-related TEAEs and all SAEs	X[g]	X	X
Study drug accountability/dispensing [h]	X	X	X[j]
Sexual counseling	X[k]	X[k]	

Abbreviations: BMI = body mass index; EOS = end-of-study; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

*Participants from Studies 302 and 204: current study duration is up to 10 years with the last clinic visit prior to the EOS at 480 weeks. Participants from Study 304: current study duration is until 16 years of age and has access to berotralstat or up to 5 years, whichever comes first, with a final clinic visit at Week 240.

[a] Signing of informed consent must occur in advance of any study procedures being performed and may occur prior to the Baseline visit. Assent will be collected for participants ≤ 18years of age per local regulatory requirements, as appropriate.

[b] Demographic and medical history data may be transferred from the Study 302, 204, or 304 databases. Limited new demographic information (eg, current age, Study 204/302/304 subject number) may also be collected.

[c] Height, weight, and BMI are to be recorded at each scheduled in-clinic visit for participants < 18 years of age.

[d] Abbreviated physical examinations targeted to signs and symptoms will be performed at all visits.

[e] Urinary pregnancy tests will be assessed at Baseline for all women of childbearing potential. Demonstration of a negative urine pregnancy test will be required prior to the subject taking berotralstat on Day 1. Participants who reach menarche while enrolled will begin pregnancy tests as appropriate from that point. A urine pregnancy test should be conducted promptly for any subject suspected to have become pregnant. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test.

[f] Parameters to be assessed are provided in Table 5. Relevant laboratory assessments from the final visit of Study 302, 204, or 304 will serve as the Baseline assessment for Study 312 for participants with a break in treatment less than 24 weeks from Study 302, 204, or 304. For participants with a break in treatment > 24 weeks, laboratory assessments described in Table 4 must be conducted at the Study 312 Baseline visit.

[g] For participants with a break in treatment > 24 weeks, an assessment of prior and ongoing concomitant medications within 30 days of enrollment into Study 312 and an assessment of ongoing treatment-related TEAEs from Studies 302, 204, and 304 must be conducted at the Baseline visit.

[h] Berotralstat should be taken at approximately the same time each day, with food. Participants are not required to take their doses at clinic visits. In some cases, more frequent (unscheduled) clinic visits may be required to accommodate drug expiry.
[i] Conducted 3 weeks after last dose of study drug for participants who reach end-of-study or participants who terminate participation prior to the end-of-study. Participants who discontinue participation in Study 312 but will continue to receive berotralstat via another mechanism are not required to have a follow-up/EOS visit.
[j] Study drug accountability only. No study drug dispensing will occur at the EOS visit.
[k] To be provided to participants from Study 304 once they reach 12 years of age or age of menarche if earlier for females (Section 11.1.7). Date of menarche will be recorded for female participants < 18 years of age.

6.7. Study Visits

6.7.1. Baseline Visit

For participants with a break in treatment less than 24 weeks from Study 302, 204, and 304, the following assessments will be recorded from the last visit on Study 302, 204, or 304. Those assessments not available from the prior study will be completed for this study.

- Written informed consent and assent, if applicable
- Inclusion and exclusion criteria
- Demographics, including previous subject number and medical history
- Weight, height, and BMI (participants < 18 years of age only)
- Targeted physical examination
- Clinical chemistry
- Urine pregnancy test for women of childbearing potential (WOCBP) only
- Sexual counseling for Study 304 participants, as appropriate
- Concomitant medications
- Assessment of SAEs and treatment-related TEAEs
- Study drug dispensing

For participants where the break in treatment is > 24 weeks between Studies 302, 204, or 304 to Study 312, all assessments listed above must be conducted, except for the collection of demographic and medical history data which will be taken from Study 302, 204, or 304 and used as Baseline data in Study 312.

6.7.2. On-treatment Visits: every 24 weeks

Participants will have the following assessments performed every 24 weeks at each on-treatment visit.

- Weight, height, and BMI (participants < 18 years of age only)
- Targeted physical examination
- Clinical chemistry (local laboratory)
- Concomitant medications

- Assessment of SAEs and treatment-related TEAEs
- Study drug accountability/dispensing
- Sexual counseling for Study 304 participants, as appropriate

6.7.3. Follow-up / End-of-Study Visit

The following assessments will be performed at the end of the study or in the case of early discontinuation from study. Participants who discontinue participation in Study 312 but will continue to receive berotralstat via another mechanism are not required to have a follow-up/EOS visit.

Follow-up/EOS assessments should be conducted 3 weeks after the last dose of study drug (±7 days).

- Weight, height, and BMI (participants < 18 years of age only)
- Targeted physical examination
- Clinical chemistry (local laboratory)
- Concomitant medications
- Assessment of SAEs and treatment-related TEAEs
- Study drug accountability

6.8. Study Termination and Site Closure

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

- Changes in scientific knowledge that lead to a negative impact on the benefit-risk profile for participants
- Request of BioCryst or competent public authorities/institutional review board (IRB)/ independent ethics committee (IEC)
- If the permit to manufacture or import investigational medicinal product (IMP) is revoked
- Another mechanism to provide berotralstat to study participants becomes available (eg, market access)

BioCryst reserves the right to discontinue the study prior to inclusion of the intended number of participants but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating participants immediately after notification. As directed by BioCryst, all study materials must be collected and all CRFs completed to the greatest extent possible.

An individual study center that is determined to be unsuitable by the sponsor, competent public authorities, or IRB/IEC may be terminated without affecting the other study sites.

Except for those situations outlined in Section 7.3, no other formal stopping rules for individual participants, parts of the study, or the entire study will be defined. Individual participants will be

discontinued from the study following the emergence of any laboratory abnormality or adverse event (AE) that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Subject Inclusion Criteria

Participants must meet all the following inclusion criteria to be eligible for participation in this study.

1. Males and non-pregnant, non-lactating females who are currently enrolled as a subject or were previously enrolled and did not discontinue due to an AE or due to noncompliance in BioCryst-sponsored Study 302, 204, or 304.
2. Participant or parent/ legally designated representative (for participants < 18 years of age) able to provide written informed consent. For participants < 18 years of age, based on the child's age and local regulatory requirements, participant assent will be collected as appropriate.
3. Would benefit from continued berotralstat treatment in the opinion of the investigator.
4. Female participants must meet at least 1 of the following requirements:

    a. Be a WOCBP (defined as a female following menarche and prior to becoming post-menopausal who has not had a hysterectomy or bilateral salpingectomy and bilateral oophorectomy) who agrees to use at least an acceptable effective contraceptive method during the study and for at least 1 month after the last dose of berotralstat. One or more of the following methods are acceptable:
        - Surgical sterilization (ie, bilateral tubal occlusion or vasectomy of male partner).
        - 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.
        - Male or female condom with or without spermicide.
        - Use of an occlusive cap (diaphragm, or cervical/vault caps) with spermicide (foam/gel/film/cream/suppository).

    Female participants are considered postmenopausal if they have had no menses for at least 12 months without an alternative medical cause.
    WOCBP who declare themselves as either sexually abstinent or exclusively having female sexual partners do not need to use an acceptable method of contraception. Abstinence in this study is defined as "true abstinence: when this is in line with the preferred and usual lifestyle of the subject." This declaration should be reviewed with the subject throughout the study to ensure continued accuracy.
    Adolescent participants who reach menarche while enrolled in the study will receive appropriate sexual counseling (Section 11.1.7).

    b) Be a woman of nonchildbearing potential (defined as postmenopausal [no menses for at least 12 months without an alternative medical cause], has had a hysterectomy or a bilateral salpingectomy and bilateral oophorectomy, or has not reached menarche).

5. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures.

7.2. Subject Exclusion Criteria

The subject may meet none of the following exclusion criteria.

1. Any condition or situation, including medical history or changes in medical history, which, in the opinion of the investigator or sponsor, would interfere with the subject's safety or ability to participate in the study.
2. Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
3. Hypersensitivity to the active substance or to any of the excipients listed in Section 9.1.
4. Use of other medications for long-term prophylaxis of HAE attacks at the Baseline visit or any time during the study. These include: C1-INH, tranexamic acid, androgens, or lanadelumab.
5. Use of any other IMP at the Baseline visit or any time during the study.
6. Pregnancy or breastfeeding.
7. Participants with an immediate family relationship to either sponsor employees, the investigator, or employees of the study site who are named on the delegation log.
8. Participants who are held in an institution by a government or judicial order.

7.3. Subject Withdrawal Criteria

Participation in the study is strictly voluntary; a subject may withdraw consent to contribute additional study information at any point. A subject who withdraws consent or is discontinued from berotralstat will be requested to attend a follow-up visit three weeks after the date of last dose with berotralstat to complete all end-of-study evaluations.

Although a subject may withdraw from the study at any time without specifying a reason for withdrawal, if known, the reason for withdrawal will be recorded in the subject's medical records (source documents) and also in the CRF. If the reason for subject withdrawal is not known, the subject must be contacted to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 11. If at any point in the study the clinic is unable to contact the subject after appropriate attempts have been made, the subject will be considered lost to follow-up.

A subject will be permanently discontinued for any of the following reasons, which will be recorded in the source documents and CRF. Participants who permanently discontinue berotralstat should complete all scheduled procedures for the EOS visit outlined in Section 6.7.3.

- End-stage renal disease requiring hemodialysis.
- Moderate or severe hepatic impairment (Child-Pugh Class B or C).

- Emergence of any laboratory abnormality or AE that in the judgment of the investigator 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.

Participants enrolled from Studies 302 and 204 will be discontinued from the study if another mechanism to access berotralstat is available in the subject's country of residence (eg, market access). Participants enrolled from Study 304 will discontinue from the current study when they reach the age of 16 and have another mechanism to access berotralstat.

Once participants have discontinued the study, the sponsor will no longer provide treatment through the study. Following discontinuation, a subject will be able to receive further treatment as recommended by their treating physician and according to local clinical practice for HAE.

Participants who withdraw from the study will not be replaced.

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 the study be terminated early.

8. TREATMENT OF PARTICIPANTS

Each participant will receive the appropriate dose of berotralstat QD (Section 9). Specifications for treatment assignments are provided in Section 6.4, with guidance for dose level modification presented in Section 6.5.

8.1. Concomitant Medications

All participants in the study must refrain from taking prohibited concomitant medications as outlined in Section 8.1.1.

Berotralstat is a moderate inhibitor of cytochrome P450 (CYP)2D6 and CYP3A4, a weak inhibitor of CYP2C9, and at 300 mg is a weak inhibitor of P-glycoprotein (P-gp). The following medications are permitted on study; however, appropriate dose monitoring and dose titration are recommended for daily use of the following medications:

- Medications that are P-gp substrates, particularly those with a narrow therapeutic index (eg, digoxin) or whose prescribing information recommends therapeutic monitoring (eg, dabigatran). Dose adjustments of these medications may be required.
- Medications that are predominantly metabolized by CYP2D6 or CYP3A4, particularly those with a narrow therapeutic index or whose prescribing information recommends therapeutic monitoring. Dose adjustments of these medications may be required. These include: thioridazine, pimozide, tricyclic antidepressants, desipramine, amlodipine, cyclosporine, and fentanyl.

Consistent with treatment guidelines that strongly support the position that all patients with C1-INH deficiency should have access to medications for treating attacks, all participants should have access to appropriate medications for the treatment of acute attacks of HAE, consistent with usual practice in their country (Cicardi et al. 2012; Busse et al. 2021).

All current concomitant medication use (including herbal supplements), through the follow-up/EOS visit, including all medications administered for the treatment of AEs, will be recorded in the source documentation/CRFs.

8.1.1. Prohibited Medications

The following medications are excluded during the study:

- 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 Baseline visit or initiation during the study.
- Use of oral androgens within 28 days of the baseline visit or planned initiation during the study (eg, danazol, stanozolol, oxandralone, methyl-testosterone). Note: Use of testosterone replacement therapy is oral androgens for long-term prophylaxis.
- Use of other medications for long-term prophylaxis of HAE. These include C1-INH, tranexamic acid, or lanadelumab. Note: Use of these therapies for treatment of attacks is not excluded at any time, nor is pre-procedure prophylaxis.

- Berotralstat is a substrate of P-gp and BCRP (breast cancer resistance protein). P-gp and BCRP inducers (eg, rifampicin, St. John's wort) may decrease berotralstat plasma concentration, leading to reduced efficacy of berotralstat. The use of P-gp inducers is not recommended with berotralstat.

Any changes to the prohibited concomitant medications in Study 312 resulting from the IB or SmPC will be communicated to all clinical sites via a memo specifying the relevant changes.

8.2. Treatment of Participants with Risk Factors for QTc Prolongation

There are no data available for the use of berotralstat in patients with independent risk factors for QT prolongation such as electrolyte disturbances, known preexisting QT prolongation (either acquired or familial), advancing age or concomitant use of other medicinal products known to prolong the QT. Appropriate monitoring (eg, ECGs) should be considered in these patients.

8.3. Treatment Compliance

Accountability of study drug dispensed and returned (as applicable) will be performed at each study visit. Returned study drug bottles and kits of granule packets must be retained and reviewed during monitoring visits by the clinical research associate (CRA) (Section 13.1).

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

At the end of the study or at other times as agreed by all involved parties, all study drug not dispensed or administered will either be collected 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.

8.4. Randomization and Blinding

Randomization and blinding are not applicable to this open-label, single-arm study (Section 6).

8.5. Lactation

Berotralstat can pass into breastmilk and the effects on the infant are unknown. Feeding an infant with breastmilk produced while on berotralstat is strictly prohibited.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Study drug in this study consists of berotralstat capsules or granules. Berotralstat is an oral small-molecule inhibitor of plasma kallikrein. Participants will receive berotralstat 150 mg capsules or granules (dose based on weight; see Table 3) for oral administration QD for up to 480 weeks (Studies 302 and 204); or up to 240 weeks or age 16 (Study 304).

The capsules are composed of the active pharmaceutical ingredient (berotralstat) blended with the excipients pregelatinized starch, crospovidone, colloidal silicon dioxide, and magnesium stearate in a gelatin capsule. Berotralstat oral granules (6 mg free base per granule) consist of the active ingredient blended with pregelatinized starch, crospovidone, colloidal silicon dioxide, and magnesium stearate in the same proportions as the capsule formulation and is coated with taste masking material, Eudragit E PO ReadyMix White, a preformulated blend of compendial excipients. All ingredients are considered safe for use in the pediatric population.

Additional details for the chemical and physical characteristics of berotralstat may be found in the IB or SmPC.

9.2. Study Drug Packaging and Labeling

Berotralstat capsules will be packaged in bottles and granules will be packaged in packets as described in the IMP manual. Participants will be dispensed a sufficient number of bottles and capsules or kits of granule packets to cover at least a 3-month and up to a 6-month dosing period. Additional visits for dispensing of study drug supply in between scheduled clinic visits may occur as needed.

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

9.3. Study Drug Storage

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

Details on the study drug packaging, labeling, shipment, storage, allowed temperature excursions, and dispensing will be provided in the IMP manual.

9.4. Study Drug Preparation

Not applicable.

9.5. Administration

Participants will take either a single capsule or the appropriate granule dose of berotralstat daily according to dosing instructions (Section 6.4). Participants will be instructed to take study drug at approximately the same time each day, with food. It is recommended that the study drug be administered with food to help minimize GI effects. If GI-related symptoms are noted as a

treatment-related TEAE, the site should query the subject and record whether the drug is being taken as instructed (ie, with food).

Participants 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 parent/ legally designated representative should ensure that all of the granules were dispensed and that all of the granules were consumed by the participant.

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

Participants will be instructed to bring all drug bottles/kits (including both unused and used) with them for each study visit. Accountability and adherence will be reviewed at clinic visits. Participants do not need to withhold any doses on clinic days or take a dose in the clinic.

9.6. Study Drug Accountability

See Section 8.3.

9.7. Study Drug Handling and Disposal

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

10. ASSESSMENT OF EFFICACY

There will be no assessment of the efficacy or effectiveness of berotralstat in this study.

11. ASSESSMENTS OF SAFETY

The schedule of procedures and assessments of safety to be conducted throughout the study are outlined in Table 4 with details on the conduct of the procedures/assessments provided below. Even if not provided by the investigator, routine and appropriate preventative care such as mammograms, cervical and testicular cancer screenings, etc., should be obtained by the subject via their usual mechanisms of care to demonstrate ongoing general health due to the longstanding nature of this trial.

11.1. Safety Parameters

11.1.1. Demographic/Medical History

Demographic information, including month (for Study 304, as permissible by country requirements), year of birth, sex, race, and medical history data will be collected.

Relevant demographic and medical history will have been obtained in Study 302, 204, or 304. The source documentation for demographics and medical history from Study 302, 204, or 304 should be re-verified, dated, and may be used as source documentation for the current study. Where possible, CRF data from Studies 302, 204, or 304 will be imported into the current study database for update and source data verification.

11.1.2. Weight and Height

Weight and height will be captured at all study visits for participants < 18years of age.

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

Body mass index (BMI) will be calculated from height and weight measures at each visit using the following formula: body weight (kg) / height $(m)^2$.

11.1.3. Targeted Physical Examination

The last targeted physical examination from the prior study will be used as the baseline examination for participants with a break in treatment less than 24 weeks from Studies 302, 204, or 304. A targeted physical examination must be conducted at the Baseline visit for participants where the break in treatment is > 24 weeks between Studies 302, 204, or 304 prior to Study 312. All physical examinations will be abbreviated (ie, targeted or symptom-directed) to include, at a minimum, evaluation of any new signs or symptoms. All subsequent physical examination findings will be recorded in the CRF only if a treatment-related TEAE is identified.

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

11.1.4. Electrocardiogram

ECGs should be conducted in accordance with the investigator's usual practice for patients with HAE. Results should be recorded in the CRF only if a treatment-related TEAE or any SAE is identified.

11.1.5. Laboratory Assessments

Blood samples will be obtained per the schedule of events. Individual laboratory tests to be performed are provided in Table 5. Any individual assessments that are not available at a site's local laboratory will not be recorded as protocol deviations.

Urinalysis, hematology, and coagulation assessments should be conducted in accordance with the investigator's usual practice for patients with HAE; however, results should be recorded in the CRF only if a treatment-related TEAE or any SAE is identified.

All laboratory samples will be drawn and resulted locally.

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 meeting the definition of a treatment-related TEAE in the opinion of the investigator should be recorded as such and handled as described in Section 11.2.

Table 5: Clinical Laboratory Evaluations

Chemistry	Pregnancy Test
• Albumin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Bilirubin (total and direct) • Blood glucose • Blood urea nitrogen (BUN) • Electrolytes (sodium, potassium, chloride) • Creatinine • Gamma-glutamyltransferase (GGT) • Lactate dehydrogenase (LDH) • Total serum protein	• Urine (Baseline) β-human chorionic gonadotropin for WOCBP only

11.1.6. Pregnancy Screen

Urinary pregnancy tests will be assessed at Baseline for WOCBP. Participants who reach menarche during the study will be given sexual counseling (Section 11.1.7) and pregnancy tests as required. A urine pregnancy test should be conducted promptly for any subject suspected to have become pregnant. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test.

Pregnancy tests will be resulted locally.

If a female subject becomes pregnant during the study, study drug/IMP will be stopped immediately and pregnancy reporting and follow-up will be conducted as described in Section 11.2.5.

11.1.7. Sexual Counseling

Age-appropriate sexual counseling will be provided to all participants, male and female, from Study 304 by a qualified healthcare professional to determine the adherence to inclusion criterion #4 in Section 7.1. The counseling will be provided at the baseline visit or first Study 312 visit for participants who are at least 12 years of age at enrollment. All other participants will receive counseling when they turn 12 years of age or at the age of menarche if earlier for females.

11.2. Adverse Events and Serious Adverse Events

AEs will be assessed from the time of signing the informed consent through the appropriate follow-up period. For the purpose of this protocol, only TEAEs assessed as related to berotralstat and all SAEs will be recorded in the CRF.

11.2.1. Definitions

11.2.1.1. Adverse Event

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 11.2), including medical triggers resulting in an HAE attack. Emotional stress will not be considered an AE unless it results in a medical diagnosis or requires medical treatment.
- Findings from protocol-mandated interventions. This can include laboratory assessments performed in the course of the trial. AEs are abnormalities that are changes from baseline and are clinically significant as described above.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period. When recording such events on an AE/SAE CRF page, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, “more frequent headaches”).

An adverse reaction is defined as follows: all untoward and unintended responses to a study drug/IMP related to any dose administered. The definition also covers medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the

product. The definition implies a reasonable possibility of a causal relationship between the event and the study drug/IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

For the purposes of this protocol, HAE attacks and their associated symptoms are not defined as AEs. HAE attacks and associated symptoms are a reflection of the disease under study. The events that may trigger an HAE attack, such as an infection or trauma, are considered AEs.

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

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

11.2.1.2. Serious Adverse Event

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

- Death
- Is life-threatening (subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires subject hospitalization or prolongation of existing hospitalization
- 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 SAEs 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 include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization.

In addition, the sponsor considers events of abortion (spontaneous or induced), fetal demise, and still birth as SAEs for reporting purposes. 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 a routine dental procedure in an HAE patient).

- Receive routine treatment for an HAE attack, in accordance with usual standard of care in the country.
- 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 11.2.2). Details of signs or symptoms, clinical management, and outcome should be reported if available. Overdose without associated signs or symptoms should not be recorded as AEs but should be recorded as protocol deviations.

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

Reports of all SAEs, regardless of investigator attribution, and treatment-related TEAEs are to be collected and recorded in the CRF from the time of signing of the study informed consent through to the last study visit (ie, through the post-treatment EOS visit).

SAEs and treatment-related TEAEs should be documented on CRFs as investigators become aware of them. At each study visit, the investigator will inquire about the occurrence of SAEs/treatment-related TEAEs since the last visit. Events are to be followed until they resolve. If a treatment-related TEAE is ongoing at the EOS visit, Grade 1 and 2 events do not need to be followed. For all Grade 3 and 4 events, the event should be followed until the treatment-related TEAE is resolved or the subject is in a clinically stable condition with regard to the treatment-related TEAE.

The investigator shall report all SAEs immediately to the sponsor in accordance with Section 11.2.4, without undue delay but not later than within 24 hours of their knowledge of the event. The SAE report form is a detailed, written report on the SAE provided by the sponsor or designee. The investigator should follow all unresolved SAEs observed during the study until they are resolved, or are judged medically stable, or are otherwise medically explained.

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

11.2.3. Definition of Severity

All SAEs and treatment-related TEAEs will be assessed (graded) for severity and classified using the Division of Acquired Immunodeficiency Syndrome (DAIDS; Publish date July 2017, see Appendix 1). Any events not covered by the DAIDS criteria will be assessed and classified into 1 of 4 clearly defined categories as follows:

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

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

11.2.3.1. Definition of Relationship to Study Drug

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

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

Upon receipt of an SAE record, the sponsor will also make an assessment of relationship to study drug. The sponsor may upgrade causality if deemed appropriate.

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

mailto: safety@biocryst.com

SAEs should be reported to the BioCryst medical monitor and via the AE/SAE eCRFs within the electronic data capture (EDC) system. 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 as soon as information becomes available by amending the eCRFs. The SAE notifications from the EDC system will trigger a notification email to the following email address:

Email: safety@biocryst.com

In the event the EDC system is not functioning, the reporting of an SAE must not be delayed. Sites will have back-up SAE report forms (electronic Word document) to be completed and emailed to the above BioCryst email address. As soon as the EDC system is functioning, the SAE information must be entered into the AE/SAE eCRF.

Immediate reporting should allow BioCryst to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the initial report should be submitted by the investigator as soon as possible and no more than 24 hours following awareness of the SAE.

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

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 SmPC) in their files.

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

BioCryst or designee shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the relevant authorities and as warranted as well as to the IECs/IRBs, and in any case no later than 7 days after knowledge by BioCryst of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned and to the IECs/IRBs concerned, as applicable, as soon as possible but within a maximum of 15 days of first knowledge by BioCryst. BioCryst or 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.

11.2.5. Pregnancy

Any female subject who becomes pregnant during the course of the study should stop taking study drug immediately and must be followed through to 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 are to be reported immediately to BioCryst. The Pregnancy Notification Form and Pregnancy Outcome Form should be sent to the following email address:

Email: safety@biocryst.com

Information related to the pregnancy must be given on “Pregnancy Notification” and “Pregnancy Outcome” forms that will be provided by the sponsor so that the pregnancy may be followed and an outcome determined. Any SAEs or any TEAEs experienced by a pregnant subject are to be reported as directed in Section 11.2. 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.

11.2.6. Serious Breaches of Good Clinical Practice

It is the responsibility of the sponsor to notify the licensing authority, as applicable, of any serious breach of GCP that is likely to affect, to a significant degree, the safety or mental integrity of the participants of the study or the scientific value of the study, in accordance with local regulations. The reporting to the sponsor will be performed by the party who suspects the serious breach.

11.2.7. Treatment Interruptions

Any treatment interruption will be recorded in source documents, including the reason for the interruption.

If a subject has a treatment interruption due to pregnancy, and if the subject desires to do so and the investigator considers it in the best interest of the mother and baby, the subject may re-start study drug after the pregnancy reaches its outcome (see Section 11.2.5).

11.2.8. Overdose

To date, there is no experience with overdose of oral berotralstat in adult participants. 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 participants in Study BCX7353-101. Safety data generated in Study BCX7353-203 with 28-day dosing of up to 350 mg/day revealed no clinically significant safety concerns in participants with HAE. Subsequently, participants enrolled in Study BCX7353-106 were exposed to berotralstat 450 mg QD for 14 days without any unexpected AEs or increased severity of reported AEs.

In the event that study personnel become aware of an overdose of study drug/IMP (≥ 2 doses per calendar day) that is associated with a treatment-related TEAE, both the overdose and the resultant event should be reported as AEs. Overdose without any symptoms (ie, AEs) does not need to be reported as an AE. If overdose occurs with or without associated AEs, participants should undergo clinical and laboratory monitoring as appropriate for their clinical condition and, if indicated, should receive clinically indicated supportive therapy. Overdose without associated signs or symptoms should not be recorded as an AE but should be recorded as a protocol deviation.

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 11.2.1). Details of signs or symptoms, clinical management, and outcome should be reported, if available.

11.2.9. 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 site 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.

Berotralstat administration is not considered to place a subject at higher risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The prevention of HAE attacks in a subject should allow him or her to require less emergency room treatment and be at less risk of requiring respiratory intervention following a laryngeal attack.

12. STATISTICS

No formal statistical hypothesis will be tested. Data will be listed and summarized using descriptive statistics.

12.1. Statistical Methods

A detailed statistical analysis plan (SAP) will be developed to describe in detail the methods of analyses. Deviations from the analyses outlined in the SAP will be described in the clinical study report.

12.1.1. Analysis Populations

The analysis population is defined below.

12.1.1.1. Safety Population

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

12.1.2. General Considerations for Data Analysis

In general, descriptive summaries will include n, mean, standard deviation, standard error, median, minimum, and maximum for continuous variables and n and percent for categorical variables. Summaries will be presented by study visit. There will be no assessment of the efficacy or effectiveness of berotralstat in this study. All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, North Carolina, US).

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

12.1.3. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race, and height, weight, and BMI (participants < 18 years of age), will be summarized for all participants. Separate summaries will also be presented by participants from Study 304. Participants from Study 304 will be included in the overall summary.

Subject disposition will be presented for all participants. Separate summaries will also be presented by participants from Study 304. Participants from Study 304 will be included in the overall summary as well. The number of participants who complete the study and those who discontinue from the study will be provided. The reasons for early discontinuation also will be presented, including discontinuation due to lab abnormality or AE. A tabulation of the number of participants exposed to study drug and duration of exposure will also be presented for each treatment group. Treatment compliance, as determined from pill/packet counts, will be summarized or listed as appropriate.

12.1.4. Analysis of Efficacy Variables

There are no evaluations of efficacy or effectiveness planned for this study.

12.1.5. Analysis of Safety Variables

Safety endpoints that will be summarized include, at a minimum, the number and proportion of participants: 1) with a treatment-related TEAE; 2) who experience a SAE; 3) who experience a treatment-related Grade 3 or 4 TEAE; 4) who experience a treatment-related, treatment-emergent Grade 3 or 4 chemistry abnormality; and 5) TEAEs leading to discontinuation of study drug.

SAEs and treatment-related TEAEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA, Version 24 or higher) PT and SOC. The occurrence of treatment-related TEAEs will be summarized using MedDRA PTs, SOCs, and severity. Separate summaries of treatment-emergent SAEs, treatment-related TEAEs, and AEs leading to study drug discontinuation will be generated. All AEs considered related to study drug will be listed for individual participants showing both MedDRA verbatim and preferred terms.

Laboratory abnormalities will be graded according to the DAIDS for Grading the Severity of Adult and Pediatric Adverse Events (Publish Date: July 2017; Appendix 1).

Concomitant medications will be coded using the WHO drug dictionary and summarized.

As applicable, all safety data will be summarized. Separate safety summaries will also be presented by participants from Study 304. Participants from Study 304 will be included in the overall summary as well.

No tests of hypothesis are planned for safety data.

12.1.6. Interim and Final Analyses

No formal interim analysis will be conducted although data may be analyzed as needed (eg, for regulatory filings or annual reports). The final analysis will be performed when the last subject has completed the final study visit, the data are cleaned, and the database has been authorized for analysis.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

During trial conduct, BioCryst or its designee may conduct periodic monitoring visits to ensure that the protocol and GCP are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. A targeted approach to monitoring study data may be used and details will be contained in a Clinical Monitoring Plan. The investigator and institution will allow BioCryst representatives, monitors, or its designees direct access to source documents to perform this verification.

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

13.2. Audits and Inspections

Authorized representatives of BioCryst, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a BioCryst audit 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, ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact BioCryst immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board and Independent Ethics Committee

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

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

Written reports of clinical study status will be submitted to the IRB/IEC as locally required. A final study notification will also be forwarded to the IRB/IEC after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations. The study will be considered to be completed once the last subject completes their last study visit. Copies of all contact with the IRB/IEC should be maintained in the study file. Copies of clinical study status reports (including termination) should be provided to BioCryst.

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, BioCryst may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

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

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

15. ETHICS

15.1. Regulatory Authority Approvals

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

15.2. Ethics Review

Refer to Section 13.3.

15.3. 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 policy on bioethics.

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

15.4. Written Informed Consent

The investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

15.4.1. Subject Informed Consent: Adults

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

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

The investigator must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Participants will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice

future treatment. They will also be told that their records may be examined by competent authorities and authorized persons, but that personal information will be treated as strictly confidential and will not be publicly available. Participants must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's dated signature. The subject should receive a signed and dated copy of the ICF. The original signed ICF should be retained in the study files. The investigator shall maintain a log of all participants who sign the ICF and indicate if the subject was enrolled into the study or reason for non-enrollment.

15.4.2. Participant Informed Consent: Participants < 18 years of age

Signed informed consent must be obtained from a parent/ legally designated representative, in accordance with local regulations, prior to performing any study-related procedures. Similarly, participant assent by participants < 18 years will be obtained prior to performing any study-related procedures. If the local requirements limit the age of assent, then assent will be obtained based on those requirements. Each parent/ legally designated representative and 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 parent/ legally designated representative has adequate time to consider the risks and benefits associated with his/her child's participation in the study. Participants will not be screened or treated until the parent/ legally designated representative and subject have signed an approved ICF and assent form written in a language in which the subject is fluent. The ICF and assent forms that are used must be approved both by BioCryst and by the reviewing IRB/IEC. The ICF and assent forms should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policy.

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

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

Participants who reach the age of 18 years, or as otherwise determined by local law, whilst participating in the study, will be provided with the adult information and informed consent, and asked to provide written informed consent that they wish to continue in the clinical study.

16. DATA HANDLING AND RECORDKEEPING

16.1. 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.

16.2. Retention of Records

To enable evaluations and/or audits from regulatory authorities or BioCryst, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, CRFs, and medical/hospital records), all original signed ICFs, all original signed assents (if applicable), all CRFs, and detailed records of study drug accountability and treatment disposition. The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to BioCryst. The investigator must obtain BioCryst's written permission before disposing of any records and must notify BioCryst before transferring any records to another facility.

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

16.3. 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 EMA 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 requirements of the Data Protection Regulation in the European Union, where applicable. A valid authorization and consent must meet the specifications of the applicable laws and regulations relating to such personal data and health information. It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual. Investigator and associated organizations will be responsible for the technical requirements to ensure the security, integrity and restricted access to participant data. Measures will include password protection, access roles with restrictions and restricted physical access for both paper and electronic documentation. The investigator will report any data breaches affecting participant data to the sponsor, without delay. Sponsor has processes and

procedures available to ensure the timely notification of authorities and participants, as required, of any data breaches.

16.4. Publication Policy

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 prior 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.

17. LIST OF REFERENCES

Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol [Internet]. 2012;130(3):692–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22841766

Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9:132-150.e3.

Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy [Internet]. 2012;67(2):147–57. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22126399

ICH. E11A Pediatric Extrapolation [Internet]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2024 [cited 2025 Jan 10]. Available from: https://database.ich.org/sites/default/files/ICH_E11A_Guideline_Step4_2024_0821.pdf

Longhurst H, Cicardi M. Hereditary angio-oedema. Lancet [Internet]. 2012;379(9814):474–81. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22305226

Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc [Internet]. 2010;31(5):407–14. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20929608

Marcus M, Markus M, Ignacio A, Emel AP, Stephen B, Konrad B, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. World Allergy Organization Journal. 2018;11(1):5.

Zuraw B, Christiansen S. Pathophysiology of hereditary angioedema. Am J Rhinol Allergy [Internet]. 2011;25(6):373–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22185738

APPENDIX 1. DAIDS ADULT AND PEDIATRIC ADVERSE EVENTS TABLE (PUBLISH DATE: JULY 2017)

For the purposes of this protocol, the title of the DAIDS table to be used to grade adverse events is referred to as the 'DAIDS Adult and Pediatric Adverse Events Table'. The criteria contained in the 'DAIDS Adult and Pediatric Adverse Event Table' have been unaltered from the published DAIDS table under the name 'DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Publish Date: July 2017).'

Copies of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events will be available to the medical staff throughout the project.

NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY

Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting

APeX-N

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PASS Information

Title	Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting
Protocol version identifier	Final v. 3.0
Date of last protocol version	06 December 2023
EU PAS Register number	EUPAS43575
Active substance	(*R*)-1-(3-(aminomethyl)phenyl)-*N*-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide
Medicinal product	berotralstat, ORLADEYO™
Procedure number	EMEA/H/C/005138
Marketing authorisation holder(s)	BioCryst Ireland Limited
Joint PASS	No
Research question and objectives	As the long-term safety of berotralstat cannot be addressed during clinical trials, this non-interventional PASS is designed to further characterize the safety profile of berotralstat. **Primary objective:** • To monitor safety and tolerability of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients during long-term administration in a real-world setting **Secondary objectives:** • To assess growth and development in adolescent patients 12 to 17 years of age • To evaluate the effectiveness of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients in a real-world setting • To assess quality of life during long-term administration of berotralstat in a real-world setting
Country (-ies) of study	Multiple centres in Europe and the UK
Author	Kristin Buske (KBuske@biocryst.com)

Marketing Authorisation Holder(s)

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AE-QoL	Angioedema Quality of Life Questionnaire
AECT	Angioedema Control Test
AMS	Advanced Medical Services GmbH (CRO)
C1-INH	C1-Inhibitor
cATU	French Autorisation Temporaire d'Utilisation de cohorte
CDMS	Clinical Data Management System
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organization
EAMS	UK Early Access to Medicines Scheme
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FPI	First Patient In
GAMP	Good Automated Manufacturing Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GPP	Good Pharmacoepidemiological Practices
GVP	Good Pharmacovigilance Practice
HAE	Hereditary Angioedema
IC	Informed Consent
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MHRA	Medicines and Healthcare products Regulatory Agency
NI-PASS	Non-interventional Post-Authorisation Safety Study
NIS	Non-interventional Study
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error

Abbreviation	Definition
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SSL	Secure Sockets Layer
STIAMP	Suspected transmission of infectious agent via medicinal product
TEAE	Treatment-Emergent Adverse Event
UK	United Kingdom
V1	Visit 1
WHO	World Health Organization

3 RESPONSIBLE PARTIES

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BioCryst Signature Page

Study Title: Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting- APeX-N

Protocol Code: BCX7353-401

Protocol Version and Date: Final v. 3.0, 06th December 2023

Registry Number: EUPAS43575

Sponsor/ Marketing Authorisation Holder (MAH): BioCryst Ireland Limited

This protocol has been reviewed and approved by:

DocuSigned by:
Kristin Buske
Signer Name: Kristin Buske
Signing Reason: I have reviewed this document
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Date		Signature
18 January 2024 | 05:11:33 EST	Rachel Wallace Qualified Person for Pharmacovigilance (QPPV) Eimer Darley signed on behalf of Rachel Wallace	

Treating Physician Signature Page

Study Title: Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting – APeX-N

Protocol Code: BCX7353-401

Protocol Version and Date: Final v. 3.0, 06th December 2023

Registry Number: EUPAS43575

Sponsor/ Marketing Authorisation Holder (MAH): BioCryst Ireland Limited

I have read the above-mentioned protocol and its attachments. I agree to conduct the study in compliance with all stipulations of the protocol, regulations and guidelines.

Name: _____

(Please print)

Affiliation: _____

City: _____

Country: _____

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Date Signature

4 ABSTRACT

Title	Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting, APeX-N
Protocol No.	BCX7353-401
Observational drug	Berotralstat, ORLADEYO™
Indication	Hereditary Angioedema (HAE)
Rationale and background	Berotralstat is an oral kallikrein inhibitor indicated for routine prevention of attacks of hereditary angioedema (HAE) in adult patients and adolescent patients aged at least 12 years. Berotralstat is approved by the European Medicines Agency (EMA) (30 April 2021) and the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) (12 May 2021). The purpose of this study is to evaluate long-term safety of berotralstat in a category 3 Post-Authorisation Safety Study (PASS). It is a voluntary commitment in the risk management plan by BioCryst to the EMA to conduct this PASS as an additional pharmacovigilance activity. It is of significant interest to the marketing authorisation holder (MAH) to collect data on routine use of berotralstat in a real-world setting outside of a controlled trial setting and in accordance with EMA- and MHRA-approved labelling. With this non-interventional Post-Authorisation Safety Study (NI-PASS), the MAH plans to collect further long-term data to evaluate safety, tolerability and effectiveness of berotralstat.
Study Design	A prospective, multicentre, non-interventional PASS (NI-PASS).
Research question and objectives	The objectives of this study are to further characterize the safety profile of berotralstat, including the long-term impact of berotralstat administration on the growth of adolescents with HAE. Study BCX7353-401 is a non-interventional PASS to evaluate the long-term safety, tolerability, and effectiveness of berotralstat in HAE patients receiving berotralstat prophylaxis over a long-term. **Primary objective:** • To observe safety and tolerability of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients during long-term administration in a real-world setting **Secondary objectives:** • To assess growth and development in adolescent patients 12 to 17 years of age • To evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting • To assess quality of life during long-term administration of berotralstat in a real-world setting
Participating countries	It is planned to include multiple study sites in Europe and the UK.
Number of study sites	30-40 sites

Population	It is planned to enrol approximately 150 patients with HAE in this study. The estimated prospective observation period for each patient whilst on berotralstat treatment according to the approved label is anticipated to be up to 60 months or at least 24 months after the last patient was enrolled or until the study is completed. Patient's berotralstat treatment according to the approved label may be documented retrospectively at study inclusion. Limited medical history data as well as treatment with berotralstat according to the approved label prior to informed consent (and e.g., retrospective attack rate, when available) will be documented retrospectively. Routine clinical care is at the discretion of the responsible physician. Visit frequency occurs according to routine clinical practice for HAE patients If patient visits occur once a year, one or more additional patient contact which can either be another visit to study site or contact via phone, e-mail etc., are recommended in order to collect and assess any safety event.
Inclusion criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study. • Confirmed diagnosis of hereditary angioedema (HAE). • Adult and adolescent patients who are 12 years of age and older. • Initiation of treatment with berotralstat in accordance with the current EMA- or MHRA-approved labelling. The decision to start treatment with berotralstat must be made before and be independent from enrolment in this study. Patients who received berotralstat via early access programs such as the UK Early Access to Medicines Scheme (EAMS), or the French Autorisation Temporaire d'Utilisation de cohorte (cATU) and who continued treatment with commercial berotralstat are eligible to participate. • Ability to provide informed consent / confirmation of non-opposition to participate in the study as required per country. Adolescent patients must be able to read, understand, and be willing to sign an assent form / confirm their non-opposition to participate in the study. Depending on local requirements, it might be necessary for the legal caregiver(s) to provide informed consent / confirm the non-opposition to the adolescent's participation in the study.
Exclusion criteria	Patients will not be included in the study if one or more of the following criteria apply: • Contraindication to treatment with berotralstat according to current product labelling. • Current participation in any interventional clinical trial.

Study duration per patient	The estimated prospective observation period for each patient is anticipated to be up to 60 months or at least 24 months after the last patient was enrolled, whilst on berotralstat treatment according to the approved label. For patients who are already treated with berotralstat according to the approved label at time of informed consent, treatment data may be collected retrospectively, if available.
Planned study period	The study duration is 5 years. It is planned to recruit eligible patients for at least 3 years from the date the first patient is consented (First Patient In, FPI). Estimated date first patient enrolled: Q4 2021 Estimated end of data collection: Q4 2026 The study may be discontinued if ongoing regulatory or institutional review board / ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the conduct of the study.
Study endpoints/ Variables for evaluation	The following **primary** endpoints are to be assessed within this NI-PASS: • Incidence of adverse drug reactions (ADRs) • Duration of exposure to berotralstat according to the approved label The following **secondary** endpoints are to be assessed within this NI-PASS: • Height and weight in patients starting berotralstat treatment according to the approved label. This is applicable to adolescents (12 to < 18 years of age) only • Rate of patient-reported HAE attacks during observation period • Rate of HAE attacks requiring treatment with standard of care medication • Change in severity of disease compared to Visit 1 (V1), measured by the Angioedema Control Test (AECT) • Number of days per month with HAE symptoms • Change of Quality of life compared to V1, measured by the Angioedema Quality of Life Questionnaire (AE-QoL) assessed according to standard of care of the respective participating country. **Variables for evaluation** All treatments and measures are up to the investigators' discretion and performed according to standard of care. Visit frequency occurs according to routine clinical practice for HAE patients. If patient visits occur once a year, one or more additional patient contacts, which can either be another visit to study site or contact via phone, e-mail etc., are recommended in order to collect and assess any safety events.

	The following data will be collected during routine visits in the patients' medical records and will be transferred to the electronic Case Report Form (eCRF).
	• Serious Adverse Events (SAEs)
	• Non-Serious Adverse Drug Reactions (ADRs)
	• Height and weight for all patients starting commercial use of berotralstat between the ages of 12 to < 18 years through completion of study. In addition, date of menarche for adolescent females will be collected, if applicable
	• Variables reported by the patient to the investigator at routine visits based on patient-recorded diary:
	  ○ Number and location of attacks
	  ○ Attack severity
	• Use of standard of care required to treat HAE attacks
	• AE-QoL
	• AECT
	• Concomitant medications and comorbidities
	
	The following assessments may be performed in accordance with local clinical practice. Results for these assessments should be documented in the patient's medical record but will only be transferred to the eCRF if they meet the criteria of an SAE or a non-serious ADR.
	• Clinical chemistry and haematology
	• Electrocardiogram
	• Physical examination (targeted exams post-baseline)
	• Vital signs
	
	Safety and tolerability will be evaluated through assessment of ADRs and SAEs.

Data source	Data from patient medical records and patient-reported outcomes such as AE-QoL and AECT questionnaires will be analysed. All data obtained during this study are captured electronically in a project-specific programmed Electronic Data Capture (EDC) application, also referred to as eCRF.
Data analysis	Data will be summarized using descriptive statistics or provided in listings. Adverse drug reaction data and serious adverse event data will be coded using the most current version of Medical Dictionary for Drug Regulatory Affairs (MedDRA). Interim analyses of accumulating data may be done. Growth in paediatric patients will be described.

Milestones	Estimated study duration: 60 months Estimated enrolment period: 36 months Estimated prospective observation period: up to 60 months or at least 24 months after the last patient was enrolled. Estimated date first patient enrolled: Q4 2021 Estimated date of last patient in: Q4 2024 Estimated end of data collection: Q4 2026 Estimated final study report: Q2 2027

5 AMENDMENTS AND UPDATES

Protocol version	Date	Section of protocol	Amendment or update	Reason
1.0	19 July 2021	N/A	N/A	N/A
2.0 (internal version only)	29 August 2023	PASS Information / Marketing Authorisation Holder(s) 3 Responsible Parties	QPPV: ~~Dr. med. Edgar J. Fenzl~~ ~~Edgar.fenzl@fgk-cro.com~~ ~~FGK Clinical Research GmbH~~ ~~Heimeranstr. 35~~ ~~80399 Munich~~ ~~Germany~~ Rachel Wallace EUQPPVOffice@BioCryst.com BioCryst Ireland Limited Block 4, Harcourt Centre Harcourt Road Dublin 2 D02 HW77 Ireland Author / Sponsor Project Responsible: Kristin Buske ~~Zlatko Sisic~~	Administrative changes of QPPV and sponsor project responsible person
		3 Responsible Parties	Responsible Statistician: Lavinia Suberg ~~Sandra Roldan~~	Administrative change of responsible statistician
		PASS Information Signature Pages	~~Not yet registered~~ EUPAS43575	Study was registered before study start
		BioCryst Signature Page	~~Kavita Aggrawal, Pharm D~~ Kristin Buske, Medical Affairs Europe Sylvia Dobo, MD Senior ~~Medical and Safety Science~~ Vice President, Global Drug Safety and Pharmacovigilance ~~QPPV~~ Rachel Wallace~~Dr. Med. Edgar J. Fenzl~~ Qualified Person for Pharmacovigilance (QPPV)	Administrative changes
		2 Abbreviations	Abbreviations deleted from list of abbreviations: ~~AGES, BASG, BfArM, GKV, KBV, PEI, PKV, GCP, GMP, ICF, ICH, ICH-GCP, LPI, LPO~~. Abbreviations included in list of abbreviations: ENCePP, IC, PRAC, SADR, STIAMP, TEAE, V1.	In section 10.1 country specific notifications, which included these abbreviations, were deleted Further update of the list of abbreviations

Protocol version	Date	Section of protocol	Amendment or update	Reason
				List of Abbreviations sorted alphabetically
		4 Abstract	The purpose of this study is to evaluate long-term safety of berotralstat in a category 3 Post-Authorisation Safety Study (PASS) ~~study as requested by EMA/PRAC~~. It is a voluntary commitment in the risk management plan by BioCryst to the EMA to conduct this PASS as an additional pharmacovigilance activity.	Clarification that the PASS is voluntary and not mandated
		4 Abstract 9.2.1 Planned Number of Study Sites	**Participating countries:** It is planned to include multiple study sites in Europe and the UK ~~Germany, France, Austria, Sweden and the UK~~. **Number of study sites:** ~~To be determined~~ 30- 40 sites. The sites will be located in ~~Germany, France, Sweden and the UK~~ Europe and the UK. The planned number of sites ~~is yet to be determined~~ is 30-40 sites in total.	Multiple European countries instead of naming every single country Update of the planned number of study sites
		4 Abstract 9.2.2 Patient Population and Selection Criteria	**Inclusion criterion 4:** Ability to provide ~~written~~ informed consent / confirmation of non-opposition to participate in the study as required per country. Adolescent patients ~~who are aged 12 to 17 years of age~~ must be able to read, understand, and be willing to sign an assent form / confirm their non-opposition to participate in the study ~~in addition to the legal caregiver providing informed consent~~. Depending on local requirements, it might be necessary for the legal caregiver(s) to provide informed consent / confirm the non-opposition to the adolescent's participation in the study.	Changes to inclusion criterion 4 in order to include the country specific requirements for all countries. Rewording is done for the purpose of clarification only; there are no changes to the content
		6 Milestones	**Registration in the EU PAS Register:** ~~Study is not yet registered~~ 08 October 2021	Study was registered before study start
		9.3 Variables	**End of Study:** If premature termination [reasons…., ~~Unsatisfactory efficacy level~~ Discontinuation of treatment with berotralstat, …]	At the end of study visit, the unsatisfactory efficacy level will not be assessed by the discontinuation of berotralstat
		9.7 Data Analysis	Interim analysis will be performed ~~annually~~ using the data collected so	Interim analysis will be based on the

Protocol version	Date	Section of protocol	Amendment or update	Reason
			far up to the time of the interim analysis. The first interim analysis will be performed once 50 patients have been enrolled, the second one will be performed at 100 patients, and the last one at 150 patients. For annual safety reports, data snapshots will be taken each 3rd December (or if this date falls on a weekend, it will be taken at the next business day).	number of recruited patients rather than annually. Definition of data snapshot time for annual safety reports
		10.1 Ethical, Legal and Administrative Aspects	~~Details on registration and notifications are described in a study specific Submission Plan~~ ~~In Germany this PASS will be notified pursuant to AMG §63f (voluntary PASS) to the BfArM (Federal Institute for Drugs and Medical Devices, Bundesinstitut für Arzneimittel und Medizinprodukte), the National Association of Statutory Health Insurance Physicians (KBV, Kassenärztliche Bundesvereinigung), the Confederation of Statutory Health Insurance Providers (GKV, Spitzenverband der Krankenversicherungen) and the Association of Private Health Insurers (PKV, Verband der privaten Krankenversicherungen) by the MAH. The names and unique lifetime IDs of participating investigator will be submitted to KBV, PKV and GKV. Fees paid to participating investigator will be reported (quarterly and annually) to KBV, and GKV. Moreover, after completion of the study, a final list indicating the number of enrolled patients and the sum of fees paid per investigator will be provided to KBV, PKV and GKV.~~ ~~In Austria every non-interventional study (NIS) has to be notified electronically to the Austrian Federal Office for Safety in Healthcare (Bundesamt für Sicherheit im Gesundheitswesen, BASG) according to the Ordinance on the Conduct of Non-Interventional Studies (Federal Law Gazette II No. 180/2010) and registered in the Austrian Agency for Health and Food Safety Ltd. (AGES) NIS registry. After completion of the NIS, a final report as well as a shortened lay summary of the final report must be submitted electronically to the BASG NIS register according to §11 of the NIS MeldeVO within 12~~	No need to mention submission in single countries, as multiple European countries are to be included and submissions are performed according to local legal obligations

Protocol version	Date	Section of protocol	Amendment or update	Reason
			~~months after completion of the data collection at the latest. The shortened version of the final report is published electronically by BASG~~	
		10.2 Patient Information and Informed Consent	Informed consent will be obtained from all patients in accordance with local legislation and guidelines. Patients and for adolescent patients ~~(12 - 17 years of age)~~ also their legal caregivers must sign and date the most recent informed consent form that has been previously assessed by an independent EC, before any study-specific data will be collected. Informed consent will be obtained from the patient him/herself. The investigator or a delegate will inform the patients and legal caregivers (for adolescent patients ~~12 - 17 years of age~~) that they are completely free to refuse to enter the study or to withdraw from it at any time, and that they are not obliged to state their reasons. After withdrawal of consent, no additional data can be collected. Data already collected prior to withdrawal must be deleted at the patient's request. […] All patients and legal caregivers (for adolescent patients ~~12 - 17 years of age~~) should be given sufficient time to request further details about the study before signing the informed consent form. Patients and for adolescent patients ~~(12 - 17 years of age)~~ also their legal caregivers will personally sign and date the informed consent form. The informed consent will be documented in the source data. […] Patients and for adolescent patients ~~(12 - 17 years of age)~~ also their legal caregivers give informed consent to direct access to their original records for the purpose of monitoring, audits and regulatory inspections. […]	'12-17 years of age' removed in order to meet all country specific requirements.
		10.3 Confidentiality of Study Documents and Patient Records	With his/her consent the patient and legal caregivers (for adolescent patients ~~12 - 17 years of age~~) gives his/her/their agreement to the documentation of clinical data in the bounds of the study and to their transmission to the sponsor. […]	'12-17 years of age' removed in order to meet all country specific requirements
		11.1.3 Special Situations	In this study, the following are considered special situations: off-label use (e.g., unapproved indication or age group), overdose, abuse, misuse, medication error, product technical complaints, lack of therapeutic efficacy, drug exposure	Further specifications of special situations

Protocol version	Date	Section of protocol	Amendment or update	Reason
			during pregnancy or lactation, drug exposure via father, occupational or accidental exposure, falsified medicinal product suspected transmission of infectious agent via medicinal product (STIAMP), drug interaction	
		11.3.2 Pregnancy / Drug Exposure via Parent	E-mail address updated and second e-mail address added: PM_Safety@biocryst.com; cc APeX-N-Safety@ams-europe.com	Update of e-mail addresses for the reporting of pregnancy / drug exposure via parent
		Various sections	Correction of typos	Consistency
3.0	14 December 2023	Abstract	The estimated prospective observation period for each patient whilst on berotralstat treatment according to the approved label is anticipated ~~for~~ to be up to 60 months or ~~and~~ at least 24 months ~~from the time~~ after the last patient was enrolled or until the study is completed. Estimated prospective observation period: up to 60 months or at least 24 months after the last patient was enrolled.	Addition of **'prospective'** prior to observation period to clarify that each patient will be observed prospectively for up to 60 months or at least 24 months after the last patient was enrolled
		Section 9.1.1	The planned study duration is 5 years, starting in Q4 2021 (estimated First Patient In, FPI) with a recruitment period of up to 36 months and ~~an~~ prospective observation period whilst on berotralstat treatment according to the approved label of up to 60 months or at least 24 months after the last patient was enrolled. Each patient will be prospectively observed for up to 60 months or at least 24 months after the last patient was enrolled whilst on berotralstat treatment according to the approved label. Figure 1 adapted to changes mentioned above	Addition of **'prospective'** prior to observation period to clarify that each patient will be observed prospectively for up to 60 months or at least 24 months after the last patient was enrolled
		PASS Information	QPPV Rachel Wallace EUQPPVOffice@BioCryst.com ~~wallace@biocryst.com~~	Contact e-mail address revised
		3 Responsible Parties	Responsible Statistician: ~~Lavinia Suberg~~ Miguel Rua del Barrio	Administrative change

Protocol version	Date	Section of protocol	Amendment or update	Reason
		11.1.5 Pre-existing Medical Conditions	(…) However, baseline medical conditions, other than the disease under study, that worsen in severity or frequency during the study and suspected to be due to Orladeyo use ~~assessed as~~ should be recorded and reported as ~~SAE~~ an ADR.	Correction that any worsening of baseline conditions shall only be recorded and reported if suspected due to Orladeyo use and therefore constitute an ADR.
		11.2.3 Classification of Causality	All SAEs and ~~O~~only related AEs not meeting seriousness criteria defined as ADRs and ~~all SAEs~~ are to be recorded in the eCRF AE Form.	Sentence structure revised
		11.3 Reporting of Drug Safety Information	E-mail: APeX-N-Safety@ams-europe.com ~~BioCryst.Pharmacovigilance@propharmagroup.com~~	Contact E-Mail address revised
		11.3.2 Pregnancy	E-mail: PM_Safety@biocryst.com; cc APeX-N-Safety@ams-europe.com ~~BioCryst.Pharmacovigilance@propharmagroup.com~~	Contact E-Mail address revised

6 MILESTONES

Milestone	Planned date
Start of data collection	*Q4 2021*
End of data collection	*Q4 2026*
Registration in the EU PAS Register	*08 October 2021*
Final report of study results	*Q2 2027*

7 RATIONALE AND 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 reported prevalence of HAE varies widely, from 1:50,000 to 1:100,000. The frequency of attacks varies among patients, 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 increased estrogen) and are typically rapid in onset, with symptoms subsiding gradually over the following 3 to 5 days in the absence of treatment (Zuraw and Christiansen 2011). Oropharyngeal swelling can be life-threatening (Bork, Hardt et al. 2012), whilst attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring, and have a significant impact on functionality and quality of life (Lumry, Castaldo et al. 2010). Although mortality risk from asphyxiation is much higher in undiagnosed patients with HAE, deaths still occur in patients who have been diagnosed with HAE and have access to healthcare at centres of excellence (Bork, Hardt et al. 2012).

Berotralstat (ORLADEYO™) is a potent, synthetic, small molecule inhibitor of plasma kallikrein. In contrast to parenterally administered options commercially available for treatment of HAE attacks, inhibition of kallikrein with an orally bioavailable small molecule such as berotralstat offers the advantage of oral administration. Inhibition of plasma kallikrein with berotralstat has significant benefits for patients with HAE by reducing the duration and/or severity of attacks.

In previous clinical studies, the efficacy and safety of berotralstat was demonstrated in patients with HAE type I or II. A Phase 2 study (APeX-1; NCT02870972) confirmed a significantly lower rate of angioedema attacks during berotralstat treatment compared to placebo for 75 randomized patients. Mild GI symptoms were the principal adverse event (AE). (Aygoren-Pursun et al. 2018). A Phase 3 study (APeX-2, NCT03485911) was performed in 11 countries and enrolled 121 patients. A total of 120 patients were randomized to either 110 mg (n = 41), 150 mg (n = 40), or placebo (n = 39). Berotralstat demonstrated a significant reduction in attack rate at both 110 mg (1.65 attacks/month; p = .024) and 150 mg (1.31 attacks/month; p < .001) relative to placebo (2.35 attacks/month). The most frequent treatment-emergent adverse events (TEAEs) that occurred more with berotralstat than with placebo were abdominal pain, vomiting, diarrhoea, and back pain. No drug-related serious treatment-emergent AEs occurred (Zuraw et al. 2020).

In another Phase 3 study with a similar design (APeX-J, NCT03873116) conducted in Japan, 19 HAE patients were randomized to receive once-daily berotralstat 110 mg (n = 6) or 150 mg

(n = 7) or placebo (n = 6). Treatment with berotralstat 150 mg significantly reduced HAE attacks relative to placebo (1.11 vs. 2.18 attacks/month, p = .003). The most frequently reported treatment-emergent adverse events (TEAEs) in berotralstat-treated patients (n = 13) were nasopharyngitis (n = 4, 31%), abdominal pain, cough, diarrhoea, and pyrexia (n = 2 each, 15%) (Ohsawa et al. 2020).

Berotralstat was first approved in the USA (03 December 2020) for prophylaxis to prevent attacks of HAE in adults and paediatric patients aged 12 years or older (Lee 2021). On 22 January 2021 the Japanese Pharmaceuticals and Medical Devices Agency approved berotralstat for the suppression of the onset of acute hereditary angioedema attacks in adults and children aged 12 years and older (PMDA 2021).

On 25 February 2021, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending marketing authorisation for berotralstat for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older (CHMP 2021). This was approved by the European Commission on 30 April 2021. On 12 May 2021 the UK's Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisation for oral, once-daily berotralstat for the routine prevention of recurrent HAE attacks in HAE patients aged 12 years and older. A category 3 non-interventional Post-Authorisation Safety Study (NI-PASS) was recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to further evaluate the long-term safety of berotralstat in paediatric patients as an additional pharmacovigilance activity.

As soon as berotralstat becomes commercially available in the respective country and these patients decide to start berotralstat or continue berotralstat treatment from the existing early access programs, these patients will be invited to participate in this NI-PASS which aims to monitor long-term safety and tolerability as well as effectiveness of berotralstat in a real-world setting.

8 RESEARCH QUESTION AND OBJECTIVES

This study (BCX7353-401) aims to collect long-term data on the safety, tolerability, and effectiveness of berotralstat in HAE patients receiving berotralstat for long-term prophylaxis in a real-world setting. In addition, the long-term effects of berotralstat administration on the growth of adolescent patients is of particular interest.

The **primary objective** of this NI-PASS is:

- To observe the safety and tolerability of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients during long-term administration in a real-world setting

Secondary objectives are:

- To assess growth and development in adolescent patients 12 to 17 years of age
- To evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting
- To assess quality of life during long-term administration of berotralstat in a real-world setting

9 RESEARCH METHODS

9.1 Study Design

This study is designed as a prospective, multicentre NI-PASS.

The planned study duration is 5 years, starting in Q4 2021 (estimated First Patient In, FPI) with a recruitment period of up to 36 months and a prospective observation period whilst on berotralstat treatment according to the approved label of up to 60 months or at least 24 months after the last patient was enrolled. The estimated end of data collection is in Q4 2026.

The study may be discontinued if ongoing regulatory or institutional review board/ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the conduct of the study.

A patient's berotralstat treatment according to the approved label can be documented retrospectively at study inclusion.

The first date on berotralstat treatment according to the approved label, which can either be within an early access program or at the start of commercial use, is defined as Visit 1 (V1).

Each patient will be prospectively observed for up to 60 months or at least 24 months after the last patient was enrolled whilst on berotralstat treatment according to the approved label (Fig. 1).

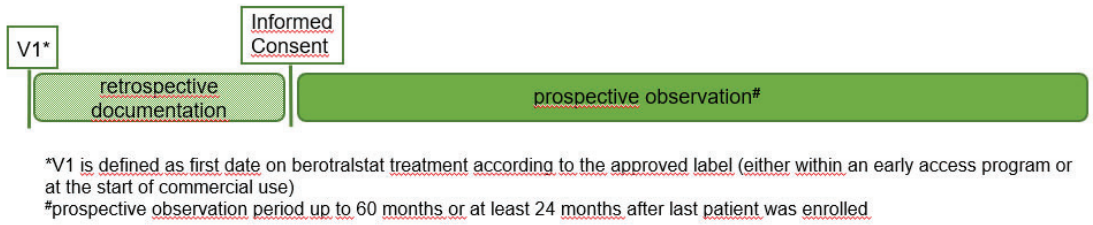

Figure 1: *Study Design*

As this is a NI-PASS no stipulations regarding patient treatment, or monitoring will be provided by this protocol. Investigators will treat patients in accordance with their medical judgment and standard of care. Any treatments and tests have to be administered at the discretion of the treating physician and treatments have to be in accordance with the approved Summary of Product Characteristics (SmPC).

The participating sites will offer participation in this study to all patients, who receive berotralstat treatment as part of routine clinical practice according to the current SmPC. Of patients who were in early access programs (such as EAMS, cATU) prior to this NI-PASS and who continued treatment with commercially available berotralstat prior to signing informed consent, treatment data may be collected retrospectively.

9.1.1 Endpoints

The **primary endpoints** are:

- Incidence of adverse drug reactions (ADRs)
- Duration of exposure to berotralstat

The **secondary endpoints** are:

- Height and weight in patients starting berotralstat treatment according to the approved label. This is applicable to adolescents (12 to < 18 years of age) only
- Rate of patient-reported HAE attacks during observation period
- Rate of HAE attacks requiring treatment with standard of care medication
- Change in severity of disease compared to V1, measured by the Angioedema Control Test (AECT)
- Number of days per month with HAE symptoms
- Change of Quality of life compared to V1, measured by the Angioedema Quality of Life Questionnaire (AE-QoL), assessed according to standard of care of the respective participating country

The described tests/assessments will only be performed if they represent standard of care for HAE patients in the respective participating country.

The AE-QoL questionnaire used in this study is validated for adult patients (> 18 years) but will also be used for adolescent patients in this NI-PASS.

9.2 Study Setting

9.2.1 Planned Number of Study Sites

The sites will be located in Europe and the UK. The planned number of sites is 30 - 40 sites in total.

9.2.2 Patient Population and Selection Criteria

It is planned that approximately 150 patients diagnosed with HAE will be observed in this NI-PASS. If a patient fulfils all of the inclusion criteria and none of the exclusion criteria, he/she will be enrolled.

The investigator will verify that all inclusion criteria are met and no exclusion criterion is met and all other requirements of the study protocol are fulfilled. He/she will confirm that according to his/her judgment the respective patient is eligible for participation in the study.

Inclusion Criteria

Patients have to meet all of the following criteria to be included:

- Confirmed diagnosis of hereditary angioedema (HAE).
- Adult and adolescent patients who are 12 years of age and older.
- Initiation of treatment with berotralstat in accordance with the current EMA- or MHRA-approved labelling. The decision to start treatment with berotralstat must be made before and be independent from enrolment in this study. Patients who received berotralstat via early access programs such as the UK Early Access to Medicines Scheme (EAMS), or the French Autorisation Temporaire d'Utilisation de cohorte (cATU) and who continued treatment with commercial berotralstat are eligible to participate.
- Ability to provide informed consent / confirmation of non-opposition to participate in the study as required per country. Adolescent patients must be able to read, understand, and be willing to sign an assent form / confirm their non-opposition to participate in the study. Depending on local requirements, it might be necessary for the legal caregiver(s) to provide informed consent / confirm the non-opposition to the adolescent's participation in the study.

Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Contraindication to treatment with berotralstat according to current product labelling.
- Current participation in any interventional clinical trial.

9.3 Variables

The variables listed in this section will be recorded during routine visits for all included patients. All treatments and measures are up to the physicians' discretion and performed according to standard of care. Data will be collected during routine visits in the patient's medical record and will be transferred to the electronic Case Report Form (eCRF). Visit frequency occurs according to routine clinical practice for HAE patients. If patient visits occur once a year, one or more additional patient contact which can either be another visit to study site or contact via phone, e-mail etc., are recommended in order to collect and assess any safety event.

For the day of **patient enrolment in NI-PASS** the following variables will be documented

- Eligibility according to SmPC/ in- and exclusion criteria
- Written informed consent

Demographic data

- Age [years]
- Sex [male/female]
    - If female: Pregnancy [test results, if available] / lactation
- Ethnicity [Caucasian, Asian, African, Other]
- Height [cm], weight [kg]; BMI [kg/m^2 calculated on backend by EDC]; in all adolescent patients starting berotralstat treatment according to the approved label; and menarche in adolescent females [Yes/No, if Yes, date of onset]

Medical history and HAE specific variables

- Diagnosis: HAE
- C1-Inhibitor concentration [g/L]
- C1 functional activity [%]
- Drugs with narrow therapeutic range metabolised by CYP2D6 (e.g., pimazide), CYP3A4 (e.g., ciclosporin, fentanyl), CYP2C19 (e.g., desogestrel) or p-glycoprotein substrates (e.g., digoxin) [if Yes, to be specified]
- Age at diagnosis [age in years]
- Family history of HAE [Yes/No]
- Prior preventive treatments [if Yes, treatment name and duration in months]
- Time since last attack [days]
- Number of HAE attacks in the last 6 months [#]
- AECT score [score]
- AE-QoL score [score]
- Comorbidities [if Yes, to be specified]
- Concomitant medications [if Yes, to be specified]

Visit 1:

The following variables will be documented for **Visit 1 (V1),** which is defined as the first date on berotralstat treatment according to the approved label.

Safety variables:

- Berotralstat treatment regime [to be specified]

Patient characteristics

- Height [cm], weight [kg]; BMI [kg/m^2 calculated on backend by EDC]; in all adolescent patients starting berotralstat treatment according to the approved label; and menarche in adolescent females [Yes/No, if Yes since when]

HAE specific variables

- Time since last attack [days]
- Number of attacks in the last 6 months [#]
- Number of on-demand treatments use in the last 6 months [#]
- AECT score [score]
- AE-QoL score [score]

Observation Period:

The following variables will be assessed at every routine visit during the **observation period**.

Safety variables:

- Adverse Drug Reactions (ADRs) [if Yes, to be specified in Adverse event Form in eCRF]
- Serious adverse events (SAEs) [if Yes, to be specified in Adverse event Form in eCRF]
- Berotralstat treatment [if changes, to be specified]
- Height [cm], weight [kg], BMI [kg/m^2 calculated on backend by Electronic Data Capture (EDC)]; in all adolescent patients starting berotralstat treatment according to the approved label; and menarche in adolescent females [if not answered with Yes before; Yes/No, if Yes date of onset]. To be assessed until adulthood (18 years of age)

Effectiveness variables:

- Disease severity measured by AECT [score]
- HAE attacks [if Yes; duration, location, severity, risk factors, standard of care treatment, hospitalisation; time to resolution of the attack]

Variables pertaining to quality of life:

- Quality of life as measured by the AE-QoL [score]

Further variables:

- Change in comorbidities [if Yes, to be specified]
- Change in concomitant medications [if Yes, to be specified]

- If any vital signs, laboratory values (i.e., clinical chemistry or haematology values), electrocardiogram results or physician examination results performed as part of routine care meet the criteria of an SAE or a non-serious ADR, they should be documented on the SAE/ADR form in the eCRF.

Treatment Discontinuation

In case of **treatment discontinuation**, the same variables will be assessed as during the observation period and in addition the following

- Last administration [Date]
- Reason for treatment discontinuation [to be specified; ADR, Unsatisfactory efficacy level, Pregnancy, Death, Medical decision, Other (specify choice)]
- Death [Date, Cause, Causal relationship to berotralstat treatment]

End of Study

At the **end of study**, the same variables will be assessed as during the observation period and in addition the following

- End of study [Date]
- Premature or regular termination [to be specified; Yes/No]
    - If premature termination [reason to be specified; ADR, Discontinuation of treatment with berotralstat, Lost to follow-up, Pregnancy, Withdrawal of consent, Death, Medical decision, Other (specify choice)]

9.3.1 Schedule of Data Collection (According to Standard of Care)

Visits are not scheduled by the study but will follow routine clinical care based on medical necessity. The documentation does not influence the individual course of treatment (Tab.1).

Table 1: *Schedule of Data Collection*

Study Phase	**Patient Enrolment in NI-PASS**	**Visit 1[1]**	**Visits during Observation period[2]**	**Treatment discontinuation**	**End of study**
Eligibility according to SmPC / in- and exclusion criteria	**x**				
Written informed consent	**x**				
Demographic data	**x**				
Pregnancy test results, if available	**x**				
Diagnosis of HAE / Age at diagnosis	**x**				
Medical history and family history of HAE	**x**				
Drugs with narrow therapeutic range	**x**				
Time since last HAE attack, Number of attacks in the last 6 months	**x**	**x**			
Number of on-demand treatments use in the last 6 months		**x**			
C1 functional activity	**x**				
Prior preventive treatments	**x**				
Comorbidities / concomitant medications	**x**				
C1-INH concentration	**x**				
Growth parameters for adolescent patients[#]	**x**	**x**	**x**	**x**	**x**
ADRs / SAEs / Special Situations			**x^**	**x**	**x**
Treatment with berotralstat according to the approved label		**x**	**x**	**x**	**x**
Disease severity (by AECT)	**x**	**x**	**x**	**x**	**x**
HAE attacks			**x**	**x**	**x**

Study Phase	Patient Enrolment in NI-PASS	Visit 1[1]	Visits during Observation period[2]	Treatment discontinuation	End of study
Quality of life score (by AE-QoL)	x	x	x	x	x
Change in concomitant medications and comorbidities			x	x	x
Vital signs[+]			x	x	x
Clinical chemistry and haematology[+]			x	x	x
Electrocardiogram[+]			x	x	x
Physical examination[+]			x	x	x
End of study date; if premature termination, reason to be specified					x
Reason for treatment discontinuation / Date of last administration				x	

[1]Visit 1 (V1) is defined as first date on berotralstat treatment according to the approved label
[2]Data collection at every routine visit at the study site (or at additional patient contacts) and retrospectively for patients being treated with berotralstat according to approved label prior signing Informed Consent (IC)
#Height, weight, onset of menarche
[+]Will only be documented if clinically significant and meeting criteria of an SAE or non-serious ADR on the SAE/ADR form
^ADRs / SAEs / Special Situations will be documented from the date of Informed Consent onwards
Abbreviations: ADR, Adverse Drug Reaction; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; C1-INH, C1-Inhibitor; HAE, Hereditary Angioedema; NI-PASS, Non-interventional Post-Authorisation Safety Study; SAE, Serious Adverse Event; SmPC, Summary of Product Characteristics.

9.4 Data Sources

In this non-interventional study, the main data source is the patient's medical record. Patient-reported outcomes such as patient questionnaires (AE-QoLs) serve as a second type of data source. At routine visits to the study site patients will report on HAE attacks and respective treatments, based on their entries in patient-recorded diaries. This information is to be entered in the patient's medical record by the investigator.

Data from medical records and questionnaires have to be recorded on electronic Case Report Forms (eCRFs) by the investigator and/or authorised site staff as soon as they become available. Questionnaires are to be used in local language, but the eCRF is in English only. Therefore, the investigator and/or authorised site staff will need to translate the patient-reported outcomes when transferring to eCRF.

No visits or measurements will be made mandatory by this protocol. The assignment of patients to berotralstat falls within current practice. Prescription of berotralstat occurred before and independently from the decision to include the patient in the study.

Collected ADRs and SAEs will be coded according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) and medications will be coded according to the World Health Organization (WHO) Drug Dictionary using the most current versions.

9.5 Study Size

All patients with HAE disease who meet the eligibility criteria may participate in the study. It is estimated that approximately 150 patients will be enrolled in the study. As no statistical hypotheses will be tested the sample size is based on feasibility considerations.

9.6 Data Management

Data management will be done in accordance with the Standard Operating Procedures (SOPs) of the Contract Research Organization (CRO) Advanced Medical Services GmbH *(**AMS**)*. All data obtained during this study will be captured electronically in a project-specific programmed Electronic Data Capture (EDC) application, also referred to as the eCRF. The eCRF is specifically designed for the collection of the data detailed in this study protocol. The EDC application used for this study is the Clinical Data Management System (CDMS) Clincase® (supplied by Quadratek Data Solutions Ltd.), which is fully validated according to Good Automated Manufacturing Practice (GAMP) 5 and compliant with United States Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) part 11.

The project-specific eCRF will be validated according to ***AMS*** SOPs and the above-mentioned regulations prior to going live. Only authorised staff will have access to the EDC system via a secure website (Secure Sockets Layer [SSL] encryption), using unique username and password. Data will be entered into eCRFs by the investigator and/or authorised site staff in accordance with instructions provided by ***AMS***.

Data from patient's routine visits, AE-QoL and AECT questionnaires and patient reports on HAE attacks and respective treatments, based on their entries in diaries will be transferred into the eCRF by the investigator and/or authorised site staff. Moreover, it is the responsibility of

the investigator to thoroughly check patient-reported outcomes for any potential ADRs and SAEs and to document reportable events in the eCRF in accordance with this protocol.

Each investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner and are assigned to the correct patient. The investigator confirms this by electronically signing the documentation, equivalent to a traditional handwritten signature. The eCRFs should be electronically signed on all required pages by the investigator after completion.

Each initial entry, each data modification (incl. reason for change), as well as all actions in the eCRF are tracked in an audit trail, including username, date and time. Patients' personal data will be gathered, stored and processed exclusively in a pseudonymous form according to national data protection laws.

Further details will be described in a project-specific Data Management Plan.

9.7 Data Analysis

All safety and effectiveness variables collected in this study will be analysed descriptively. For continuous data, the mean, sample size (n), standard deviation (SD), standard error (SE), median, minimum, maximum, 25th percentile (Q1) and 75th percentile (Q3) will be provided. Categorical data will be displayed by absolute and relative frequencies (percentages). For means or proportions, 95% confidence intervals will be provided where appropriate.

The incidence of ADRs and SAEs will be summarized according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) primary system organ classification (SOC) and preferred term (PT). Medications will be coded according to the WHO Drug Dictionary. Growth in paediatric patients will be described.

The analyses will be performed as observed-case analyses for all eligible patients included in the study who gave their informed consent.

Details / further analyses will be specified in a Statistical Analysis Plan (SAP), which will be approved prior to performance of any analyses. Statistical tests (if any) will be performed in exploratory fashion without adjustment for multiplicity.

Interim analyses will be performed using the data collected so far up to the time of the interim analysis. The first interim analysis will be performed once 50 patients have been enrolled, the second one will be performed at 100 patients, and the last one at 150 patients.

For annual safety reports, data snapshots will be taken each 3rd December (or if this date falls on a weekend, it will be taken at the next business day).

It is planned to organize a Data Review Meeting prior to database lock for the final analysis. This pre-analysis review will include review of data from patients who did not fulfil all inclusion and exclusion criteria or had no berotralstat treatment documented. Other topics may be discussed as well. Based on this review, the analysis defined in the SAP may need to be adapted, e.g., further sensitivity analyses or subgroup analyses may be defined. All decisions will be documented in the meeting minutes; the signed minutes can serve as an SAP amendment.

Analyses will be performed using Statistical Analysis System (SAS) 9.4 for Windows or higher.

9.8 Quality Control

9.8.1 Applicable Guidelines

This study will be performed in compliance with the guideline on good pharmacovigilance practices (GVP) module VIII by the European Medicines Agency (EMA) and the Guidelines for Good Pharmacoepidemiological Practices (GPP) by the International Society for Pharmacoepidemiology (ISPE).

The study protocol is developed according to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance on protocol development and the NI-PASS was registered in the EU PAS Register.

The study will be conducted and reported in accordance with the protocol, the applicable regulatory requirements and the applicable Standard Operating Procedures (SOPs) of **BioCryst** and ***AMS***.

The investigator will assure that he/she will conduct the study in accordance with the guidelines mentioned above and the prevailing local laws and that he/she accepts and observes all provisions of this study protocol. The study investigators should ensure that all the requirements of their professional code of conduct are met according to local regulatory requirements.

9.8.2 Study Monitoring

The investigator will permit a sponsor's representative (i.e., a 'study monitor') designated by the sponsor to monitor the study according to the relevant SOPs and to a separate study-specific Site Management Manual as frequently as deemed necessary by the sponsor to verify the correct entry of data and the conduct of the study in accordance with the protocol and with regard to factors such as the study design and site enrolment rate.

Monitors of the appointed CRO ***AMS*** will perform on-site initiation visits (including eCRF training). The site staff will be trained with special emphasis on collecting and reporting of adverse events

During the course of the study ***AMS*** will perform remote monitoring in each study site starting after recruitment of the first patient. This will be complemented with scheduled on-site monitoring visits. Please refer to Site Management Manual for precise information on monitoring frequencies.

The investigator must ensure that eCRFs are completed in a timely manner and must allow the study monitor access to patient records and all study-related material as well as internet access for the review of eCRFs during monitoring visits. During each monitoring visit the monitor will check the entries made in the eCRFs and compare these entries with the source data, e.g., the patient's medical records or patient questionnaires. The scope of this source data verification will be defined in the Site Management Manual.

The monitor will check the data for plausibility and completeness in collaboration with the investigator or his/her authorised site staff. It is understood that the investigator and his/her personnel will assist the monitor in every respect and provide them with all relevant study data.

9.8.3 Investigator's Files / Retention of Documents

The investigator must retain all study records required by BioCryst and by the applicable regulations in a secure and safe facility. The investigator must consult a BioCryst representative before disposal of any study records, and must notify BioCryst of any change in the location, disposition, or custody of the study files. The investigator/Institution must take measures to prevent accidental or premature destruction of essential documents such as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., patient charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The investigator/Institution should retain patient files and other source data in accordance with the country specific regulatory requirements for data retention. BioCryst must be notified and will assist with retention should the investigator/Institution be unable to continue maintenance of patient files for the term required. BioCryst is responsible for informing the investigator/Institution as to when these documents no longer need to be retained.

9.8.4 Audits and Inspections

For quality assurance reasons the sponsor or a third party on behalf of the sponsor may conduct quality assurance audits at any time during or following the study. Regulatory agencies may conduct inspections. The investigator must agree to allow auditors and inspectors direct access to all study-related documents including source documents, and must agree to allocate his/her time and the time of his/her study staff to the auditors/inspectors in order to discuss findings, issues and potential remedies. All persons involved are bound to maintain strict confidentiality concerning the identification of the patients.

9.8.5 Completion of Study

The completion of the study is defined as "last patient out of the study". The sponsor reserves the right at any time to discontinue inclusion of additional patients into the study, at any site or to discontinue the study for any reasons.

9.8.6 Control of Data Entered in the eCRF

During the electronic data entry in the eCRF, data are automatically checked for plausibility by programmed edit checks. Incomplete data fields in the eCRF are clearly labelled as incomplete (red symbols). Other discrepancies may be clarified by addressing manual queries to the site within the eCRF.

There will be a regular reconciliation between the adverse events documented in the study database and in the safety database. Due to the non-interventional nature of the study, missing values and/or implausibility may persist and will not be corrected.

9.9 Limitations of the Research Methods

Like any observational research, this study may be subject to the risk of various biases. A major potential bias is the selection bias, i.e., selective recruitment into the study of patients that are not representative of the exposure or outcome pattern in the source population. The target population of this study comprises patients diagnosed with HAE in a real-life setting in European countries and the UK. The inclusion of a large number of patients for a rare disease (approximately 150) is assumed to draw a representative sample of the target population. Patients are identified and recruited by their treating physicians/investigator.

The study will be non-comparative. The lack of an internal reference therapy is a limitation of this study and should be kept in mind when interpreting the data.

Information bias is caused by the collection of incorrect information about exposure or outcome or covariates. This bias as well as the limitation of missing data is supposed to be minimised as far as possible in a non-interventional study (NIS) by the planned measures of quality assurance (specifically study monitoring, see section 9.8.2). However, due to the non-interventional character of the study, missing values and/or implausibilities may persist at the end of the study.

In addition, data reporting / collection will be conducted in a consistent way to avoid bias in the data collection process (see section 9.6).

In non-interventional studies, the amount of data cleaning is limited. Therefore, missing values and/or implausible values are to be expected. The Statistical Analysis Plan will provide a detailed description on how to handle those values.

10 PROTECTION OF PATIENTS

10.1 Ethical, Legal and Administrative Aspects

This study is a Post-Authorisation Safety Study (PASS) according to European legal definition in GVP module VIII. The study will be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

Independent Ethics Committee

Prior to study start, the protocol, patient information, informed consent forms (for adults, legal caregivers and adolescents) and any information presented to potential study participants will be submitted to an independent ethics committee (EC) for assessment.

Each participating investigator may seek advice from her/his EC according to his/her code of medical ethics. For this purpose, the protocol, patient information, informed consent form and the assessment by the first EC may be disclosed.

Notifications / Registration

This voluntary NI-PASS will be conducted in several member states of the European Union and the UK and will therefore be notified to the Pharmacovigilance Risk Assessment Committee (PRAC). This study was listed in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register, see section 6 MILESTONES).

In the European countries participating in this NIS, registration of the study and required notifications will follow the local legal obligations.

10.2 Patient Information and Informed Consent

Informed consent will be obtained from all patients in accordance with local legislation and guidelines. Patients, and for adolescent patients also their legal caregivers, must sign and date the most recent informed consent form that has been previously assessed by an independent EC, before any study-specific data will be collected. Informed consent will be obtained from the patient him/herself.

The investigator or a delegate will inform the patients and legal caregivers (for adolescent patients) that they are completely free to refuse to enter the study or to withdraw from it at any time, and that they are not obliged to state their reasons. After withdrawal of consent, no additional data can be collected. Data already collected prior to withdrawal must be deleted at the patient's request.

If the patient withdraws his/her consent, no new study data will be collected about him/her. Data collected after withdrawal of consent must be deleted. The pseudonymised data collected until withdrawal of consent are necessary for scientific research and the withdrawal does not automatically lead to their deletion because this would make the objectives of data processing impossible or seriously impair them.

All patients and legal caregivers (for adolescent patients) should be given sufficient time to request further details about the study before signing the informed consent form. Patients, and for adolescent patients also their legal caregivers, will personally sign and date the informed consent form. The informed consent will be documented in the source data.

One copy of the consent form signed and dated by the patient and by the investigator who informed the patient will be kept at the study site; a second copy will be handed over to the patient. Each patient must receive a patient information sheet written in local language.

In case of new relevant information, all concerned patients should be informed and asked again for their consent in a timely manner, if applicable.

Patients, and for adolescent patients also their legal caregivers, give informed consent to direct access to their original records for the purpose of monitoring, audits and regulatory inspections. They also give informed consent to documentation of clinical data for the NI-PASS and to transmission of clinical data to the sponsor and applicable authorities.

In case a patient withdraws from the study, the treating investigator must document the discontinuation of study participation in the eCRF.

10.3 Confidentiality of Study Documents and Patient Records

With his/her consent the patient and legal caregivers (for adolescent patients) gives his/her/their agreement to the documentation of clinical data in the bounds of the study and to their transmission to the sponsor. They will, together with completed consent forms, be maintained by the investigator in strict confidence.

Neither the names of the patients nor any other records that may identify the patients will be made publicly available by the investigator or by the sponsor. The data collected as part of the study are subject to the provisions of the European General Data Protection Regulation (EU GDPR) 2016/679 and to applicable national laws.

The investigator must ensure that each patient's pseudonymity will be strictly maintained. On eCRFs or other documents submitted to the sponsor, patients must not be identified by their names, initials, addresses, complete dates of birth or any other information that may identify the patient, but by an unambiguous identification code consisting of the patient number. If patient names are included on copies of documents submitted to the sponsor, the names must be redacted and the assigned patient number must be added to the documents instead.

The investigator has to keep a separate patient identification list with patient numbers and patient names along with the completed informed consent forms. Documents, which contain the names associated with the patient numbers must not be submitted to the sponsor. They will be maintained by the investigator in strict confidence.

10.4 Substantial Changes to the Protocol

Any substantial change to the protocol can only be made in the form of a written amendment to the study protocol. Such amendments have to be signed by all roles who signed the previous protocol version and submitted to an EC prior to implementation.

Amendments, which might have an impact on the patients, have effects on the informed consent procedure and require the signature of the revised informed consent form by all patients enrolled in the study who are affected by the amendment.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Assessment of all adverse events will be performed throughout the course of the study from the time of patient's signature of Informed Consent (IC) onwards.

11.1 Definitions

11.1.1 Adverse Event (AE) and Adverse Drug Reaction (ADR)

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs are undesirable events not present prior to the observed medical treatment or an already present event that worsens either in intensity or frequency following the treatment.

An ADR is a response to a medicinal product which is noxious and unintended. An ADR, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

11.1.2 Serious Adverse Event (SAE) and Serious Adverse Drug Reaction (SADR)

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is any untoward medical occurrence or effect that at any dose:

- **results in death** (i.e., the AE/ADR causes or contributes to the death).
  Death cases due to the underlying disease are NOT considered as SAEs.
- **is life-threatening** (i.e., an AE/ADR in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- **requires inpatient hospitalisation or prolongation of existing hospitalisation** (i.e., the AE/ADR requires at least a 24-hour inpatient hospitalisation or prolongs a hospitalisation beyond the expected length).
  Hospital admissions planned before informed consent (where the condition requiring the hospitalisation has not changed post-medicinal treatment administration), for respite care, for social reasons or for normal disease management (administration of medicinal treatment or insertion of access for administration of medicinal treatment) are NOT to be considered as serious.
- **results in persistent or significant disability or incapacity** (i.e., the AE/ADR resulted in a substantial disruption of the patient's ability to conduct normal activities).
- **is a congenital anomaly or birth defect** (i.e., an adverse outcome in a child or fetus of a patient exposed to the Medicinal Product before conception or during pregnancy).
- **is a medically important condition** (medical and scientific judgment should be exercised in deciding whether an AE/ADR is serious in other situations. Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered as serious).

11.1.3 Special Situations

In this study, the following are considered special situations: off-label use (e.g., unapproved indication or age group), overdose, abuse, misuse, medication error, product technical complaints, lack of therapeutic efficacy, drug exposure during pregnancy or lactation, drug exposure via father, occupational or accidental exposure, falsified medicinal product, suspected transmission of infectious agent via medicinal product (STIAMP), drug interaction. All special situations should be recorded regardless of association with an adverse reaction.

Lack of therapeutic efficacy should only be captured when it was judged as such by the investigator. If lack of therapeutic efficacy is documented as special situation, batch number/expiry date should be documented in the eCRF.

If the investigator suspects drug interaction between drugs as cause of ADR or abnormal laboratory findings, this should be documented in the eCRF.

11.1.4 Abnormal Laboratory Findings and Other Objective Measurements

Abnormal laboratory findings and other objective measurements should not be routinely captured and reported as ADRs unless they are judged by the investigator to represent clinically significant changes from baseline values and are suspected of being causally related to Orladeyo use. If a routine laboratory value is abnormal, it is up to the investigator to determine whether the value constitutes an AE or ADR.

When reporting an abnormal laboratory finding on the AE section of the eCRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if this is available (for example, “anaemia” rather than “decreased red blood cell count” or “haemoglobin = 10.5 g/dL”).

11.1.5 Pre-existing Medical Conditions

Medical conditions present at the start of observation that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are not to be considered AEs. These medical conditions should be adequately documented on the medical history section of the eCRF. Any edema and signs and symptoms that are clear manifestations of the underlying disease should not be recorded as an AE except meeting any seriousness criteria or judged to be related to berotralstat (e.g., lack of effectiveness).

However, baseline medical conditions, other than the disease under study, that worsen in severity or frequency during the study and suspected to be due to Orladeyo use should be recorded and reported as an ADR.

11.2 Recording of Safety Data

11.2.1 Eliciting Adverse Events

Data on AEs will be obtained at all visits, based on the constant survey of the patient’s health status by the investigator and on information spontaneously provided by the patient and/or through questioning of the patient.

If a patient is seen by an investigator not involved in the study in relation to an AE, the study investigator should make every effort to contact the treating investigator in a timely manner in order to obtain all information necessary for appropriate reporting of the event.

11.2.2 Recording Adverse Events

Within this study, the following types of events are recorded in the eCRF

- any adverse drug reactions (ADRs)
- all serious adverse events (SAEs), regardless of their relationship to the observational drug
- special situations

Pregnancies are to be recorded on paper forms provided to the study sites.

The investigator should use the AE and ADR definitions provided in the above sections and should observe the following guidelines when completing the AE sections of the eCRF:

- Whenever possible, recognized medical terms should be used to describe an event rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.
- Events should be described using a specific clinical diagnosis, if this is available, rather than a set of signs and symptoms (for example, 'congestive heart failure' rather than 'dyspnoea, rales and cyanosis.')
- However, signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual event.
- Provisional diagnosis (e.g., "suspected myocardial infarction") are acceptable but should be followed up to a definite diagnosis if finally available.
- Events occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary event, if clearly identifiable, generally represents the most accurate clinical term to record. The investigator should be invited to provide his/her opinion of which is the primary event, or "Reporter's highlighted term".
- In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

It is important that each report includes a description of the event, whether it is considered serious (and if so, the criterion satisfied), its duration (onset and resolution dates), its relationship to the observational drug, any other potential causality factors, any treatment given or other action taken (including dose modification or discontinuation of the observational drug) and its outcome.

ADRs must be recorded on an ongoing basis from the day of written informed consent until discontinuation of study, withdrawal of consent or end of study.

SAEs must be recorded on an ongoing basis from the day of written informed consent until discontinuation of study, withdrawal of consent or end of study.

If ADRs / SAEs still persist at the end of the study, the events should be followed up with reasonable effort until they have resolved or, if resolution is unlikely, until they have stabilized. The length of follow-up depends on the severity and the progression of an SAE. If a patient is lost to follow-up, ongoing SAEs cannot be followed up.

Rationale for non-collection of safety data in this study.
AEs not meeting seriousness criteria that do not have a causal relationship with berotralstat will not be collected on the eCRF and subsequently captured in the EDC. The collection of non-serious, not related AEs is not required for the berotralstat NI-PASS. The characterization of very common (≥1/10) and common (≥1/100 to <1/10) non-serious reactions including gastrointestinal disorders, skin and subcutaneous disorders (rash) and headache is documented in the EU SmPC. The safety profile of berotralstat remained consistent across the pivotal clinical trials and the long-term safety study, across different regions and demographics. The sponsor concludes that the collection of non-serious ADRs and serious adverse events

(SAEs) for subsequent causality assessment to be sufficient to further elucidate the safety profile of berotralstat.

11.2.3 Classification of Causality

Every effort must be made by the investigator to categorize each AE according to its relationship to the study treatment by considering the following items:

- Temporal relationship of the onset of the AE to the initiation of the treatment.
- Discontinuation or reintroduction of treatment affecting the course of the AE.
- Known association of the AE with the treatment.
- Risk factors present in the study patient known to increase the occurrence of the AE.
- Non-treatment related factors known to be associated with the occurrence of the AE.

The following definitions apply:

Not related:
A causal relationship between the treatment with berotralstat and the AE is not a reasonable possibility. Reasons for this determination may include the presence of other factors such as the patient's clinical state, therapeutic interventions or concomitant products administered to the patient. The AE also does not follow a known response pattern to berotralstat.

Related:
A causal relationship between the treatment with the observational drug and the AE is a reasonable possibility.

All SAEs and only related AEs not meeting seriousness criteria defined as ADRs are to be recorded in the eCRF AE Form.

11.2.4 Grading of Severity

All AEs will be classified as

Mild:
The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate:
The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe:
Significant impairment of functioning: the patient is unable to carry out usual activities and/or the patient’s life is at risk from the event.

The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). This has to be clearly distinguished from the term "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligation.

11.2.5 Outcome of ADRs / SAEs

Outcome will be classified as

- Fatal (incl. date of death, cause of death)
- Recovered/Resolved (incl. recovery date)
- Recovering/Resolved with sequelae
- Not recovered/Not resolved
- Unknown

11.3 Reporting of Drug Safety Information

Any ADR; SAE, special situation; and/or clinically physical exam finding, vital sign result, electrocardiogram tracing, or laboratory result qualifying as an SAE or a non-serious ADR occurring during the course of the study must be reported to the sponsor by the investigator via the EDC system:

- SAEs within 24 hours of becoming aware
- all other events must be reported within 3 calendar days of becoming aware.

The investigator/reporter must provide as much detailed information as possible and complete associated relevant sections [e.g., concomitant medication, medical history, etc.]. It is important that each report includes a description of the event, whether it is considered serious, its duration [onset and resolution dates], its relationship to the observational drug, any other potential causality factors, any treatment given or other action taken [including dose modification or discontinuation of the observational drug] and its outcome.

In addition, the investigator/reporter must respond to any request for follow-up information or questions the sponsor may have regarding the safety information within the same timelines as for initial reports.

The investigator/reporter must ensure that the patient's pseudonymity will be maintained. The patient's name (and other information that may identify the patient) must be replaced by the patient number.

Paper AE and Special Situation reporting forms will be available as back-up in case of non-availability of eCRF for an extended period. If paper forms are used, they need to be faxed or emailed using the following contact:

- E-mail: APeX-N-Safety@ams-europe.com

As soon as the eCRF is accessible again, the site needs to subsequently document the ADR, SAE or special situation in the eCRF.

Only requested supporting documentation (e.g., discharge summary, laboratory results, autopsy report) should be sent to the same AE reporting contact. The investigator must ensure that the patient's pseudonymity will be maintained in these additional documents (e.g., blacking all sections that could enable identification of the patient).

ADRs will be reported by the sponsor to the competent authorities according the local and regional law. The format of these reports will follow the local and regional requirements.

11.3.1 Reporting Period

ADRs, SAEs and special situations will be recorded on an ongoing basis and independent of the visits throughout the patient's participation in the study. The collection starts from the time of patient's signature of Informed Consent and includes all ADRs, SAEs and special situations occurring since patient's consent to study participation.

In case of ongoing ADRs / SAEs at study termination, the events should be followed up with reasonable effort until they have resolved or until the degree of a permanent disability can be assessed. If a patient is documented as lost to follow-up, ongoing/unknown outcome of ADR / SAE will not be followed up.

If there is an ADR / SAE or special situation after completion of the observational period for the patient, which the investigator considers to be related to the observational drug, this should be reported as spontaneous case to the following contact:

- E-mail: PM_Safety@biocryst.com

11.3.2 Pregnancy / Drug Exposure via Parent

Only pregnancies considered related to study treatment by the investigator (i.e., resulting from a drug interaction with a contraceptive medication) are considered as ADRs. However, all pregnancies occurring from the date of informed consent signature until at least until end of observation must be recorded an a 'Pregnancy/Drug Exposure via Parent Data Collection Form', which is not part of the eCRF. Pregnancy outcomes are not recorded in the eCRF unless considered ADRs.

The investigator must notify the sponsor in an expedited manner of any pregnancy occurring during the above-mentioned period, by completing the first sections of the 'Pregnancy/Drug Exposure via Parent Data Collection Form'.

The completed 'Pregnancy/Drug Exposure via Parent Data Collection Form' should be emailed within 5 calendar days to the sponsor using the following contact:

- E-mail: PM_Safety@biocryst.com; cc APeX-N-Safety@ams-europe.com

The same reporting modalities apply in case the partner of a male study patient becomes pregnant at any time during the whole course of the study.

Investigators must actively follow-up, document and report the outcome of all these pregnancies to the sponsor, even if the patient was withdrawn from the study.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data and results of this study are the sole property of the sponsor and may be used world-wide for product documentation and publications. By conducting this study, the investigator affirms to the sponsor that he/she will maintain, in strict confidence, information provided to him/her by the sponsor, including data generated from this study, except as exempted for regulatory purposes.

In accordance with generally recognized principles of scientific collaboration, co-authorship with any personnel involved in this study will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

Design, progress and results of this study are planned to be presented at scientific conferences.

The final study report - all personal data redacted and regardless of outcome – will be published on the publicly accessible website of the respective competent authority in each participating country in accordance with the applicable laws and regulations.

13 REFERENCES

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

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

CHMP Committee for Medicinal Products for Human Use (2021): EMA/CHMP/86405/2021 ORLADEYO™, https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-orladeyo_en.pdf, accessed in May 2021

Lee, A (2021). ”Berotralstat: First Approval.” Drugs, 81:405–409, https://doi.org/10.1007/s40265-021-01475-4.

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

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

Ohsawa, I., D. Honda, Y. Suzuki, T. Fukuda, K. Kohga, E. Morita, S. Moriwaki, O. Ishikawa, Y. Sasaki, M. Tago, G. Chittick, M. Cornpropst, S. C. Murray, S. M. Dobo, E. Nagy, S. Van Dyke, L. Reese, J. M. Best, H. Iocca, P. Collis, W. P. Sheridan, M. Hide (2020). “Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial.” Allergy ahead of print, doi: 10.1111/all.14670

PMDA Pharmaceuticals and Medical Devices Agency (2021): https://www.pmda.go.jp/files/000239841.pdf

Zuraw, B., W. R. Lumry, D. T. Johnston, E. Aygoren-Pursun, A. Banerji, J. A. Bernstein, S. C. Christiansen, J. S. Jacobs, K. V. Sitz, R. G. Gower, R. Gagnon, H. J. Wedner, T. Kinaciyan, R. Hakl, J. Hanzlikova, J. T. Anderson, D. L. McNeil, S. B. Fritz, W. H. Yang, R. Tachdjian, P. J. Busse, T. J. Craig, H. H. Li, H. Farkas, J. M. Best, D. Clemons, M. Cornpropst, S. M. Dobo, H. A. Iocca, D. Kargl, E. Nagy, S. C. Murray, P. Collis, W. P. Sheridan, M. Maurer and M. A. Riedl (2020). "Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial." J Allergy Clin Immunol. ahead of print.

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

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title:
Non-Interventional Post-Authorization Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting -ApeX-N

EU PAS Register® number: Study is not yet registered
Study reference number (if applicable): BCX7353-401

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☒	☐	Mentioned in section 9.7
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	Not yet registered
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Section Number
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1.1/ 9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.1.1/ 9.3
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.1.1/ 9.3
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.1.1

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3 / 9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3 / 9.4
	9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3 / 9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3 / 9.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.3

Comments:

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

SAP will be written and approved before any analysis

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6/ 9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Zlatko Sisic, MD

Date:19/July/2021

Signature: _____

ENCePP Checklist for Study Protocols (Revision 4) Page 6/6

ANNEX 3. ADDITIONAL INFORMATION

None

DocuSign

Certificate Of Completion

Envelope Id: B42EBFED07324F8780AD1FC203CEA7A5
Status: Completed
Subject: BCX7353-401 Protocol final v3.0_14Dec2023.pdf
Source Envelope:
Document Pages: 55 Signatures: 3
Certificate Pages: 6 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna

Envelope Originator:
Katrin Meub
Am Exerzierplatz 2
Mannheim, Ba-Wü 68167
Katrin.Meub@ams-europe.com
IP Address: 212.144.115.190

Record Tracking

Status: Original
1/11/2024 10:02:35 AM
Holder: Katrin Meub
Katrin.Meub@ams-europe.com
Location: DocuSign

Signer Events	Signature	Timestamp
Eimer Darley edarley@biocryst.com Security Level: Email, Account Authentication (Required), Login with SSO	DocuSigned by: Eimer Darley Signer Name: Eimer Darley Signing Reason: I approve this document Signing Time: 18 January 2024 | 05:11:29 EST 8AA9FC81F200481DB79B029E2FCE8C49 Signature Adoption: Pre-selected Style Signature ID: 8AA9FC81-F200-481D-B79B-029E2FCE8C49 Using IP Address: 37.228.201.62 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/11/2024 10:20:00 AM Viewed: 1/15/2024 11:55:18 AM Signed: 1/18/2024 11:11:33 AM
Electronic Record and Signature Disclosure: Accepted: 1/15/2024 11:55:18 AM ID: 7293b046-e705-4714-b432-1eec6cf3ab88		
Kristin Buske kbuske@biocryst.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Kristin Buske Signer Name: Kristin Buske Signing Reason: I have reviewed this document Signing Time: 11 January 2024 | 07:56:11 EST A3F6FE5E58144B44AEC2F4F35ECD37CE Signature Adoption: Pre-selected Style Signature ID: A3F6FE5E-5814-4B44-AEC2-F4F35ECD37CE Using IP Address: 176.199.210.210 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 1/11/2024 10:19:59 AM Viewed: 1/11/2024 1:55:07 PM Signed: 1/11/2024 1:56:17 PM
Electronic Record and Signature Disclosure: Accepted: 1/11/2024 1:55:07 PM ID: 7fed6425-f165-4f98-935e-591a65c02657		

Signer Events	Signature	Timestamp
Sylvia Dobo sdobo@biocryst.com Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 1/17/2024 8:16:19 PM ID: 7e1b883d-3c2e-4652-ba58-1f36687fea84	 Signature Adoption: Pre-selected Style Signature ID: CF342E18-8D3F-4AC5-8AA2-3782848D98ED Using IP Address: 75.183.205.139 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/11/2024 10:19:59 AM Resent: 1/11/2024 11:22:37 AM Viewed: 1/17/2024 8:16:19 PM Signed: 1/17/2024 8:18:07 PM

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
Hillary Simpson hsimpson@biocryst.com Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 1/11/2024 10:20:02 AM Viewed: 2/2/2024 4:03:19 PM
Rachel Wallace rwallace@biocryst.com Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 1/11/2024 10:20:01 AM

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/11/2024 10:20:02 AM
Envelope Updated	Security Checked	1/11/2024 11:22:36 AM
Envelope Updated	Security Checked	1/15/2024 3:17:44 PM
Envelope Updated	Security Checked	1/15/2024 3:17:44 PM
Envelope Updated	Security Checked	1/15/2024 3:20:50 PM
Certified Delivered	Security Checked	1/17/2024 8:16:19 PM
Signing Complete	Security Checked	1/17/2024 8:18:07 PM
Completed	Security Checked	1/18/2024 11:11:33 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

LEGAL DISCLOSURE

By electronically signing a document provided by AMS through the Docusign electronic signatures system, I expressly consent to the use of the system and confirm that I understand my signature will have the same binding effect as a handwritten signature.

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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
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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:

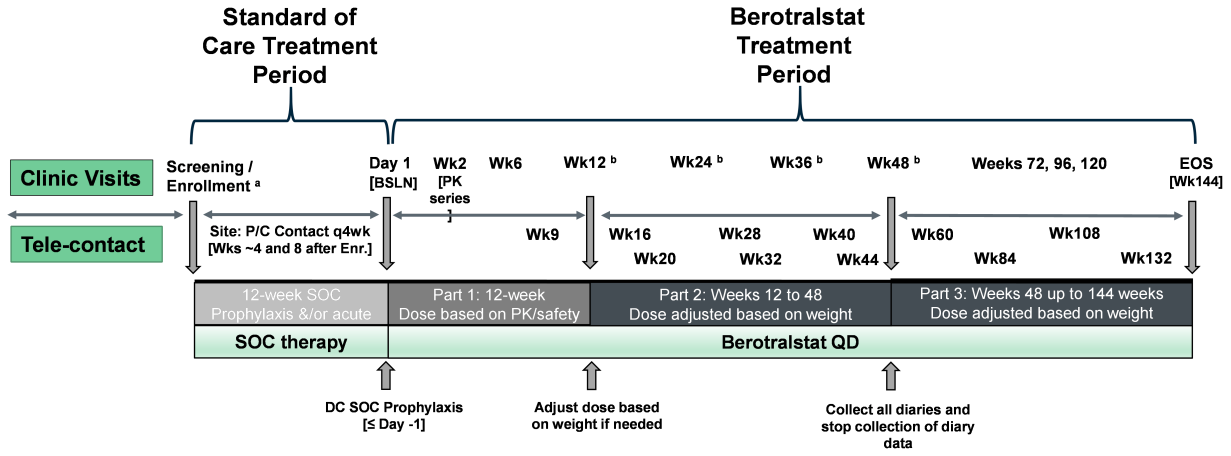
- Age-appropriate questionnaire for palatability/acceptability of berotralstat oral granules as assessed by the site following the first dose

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.

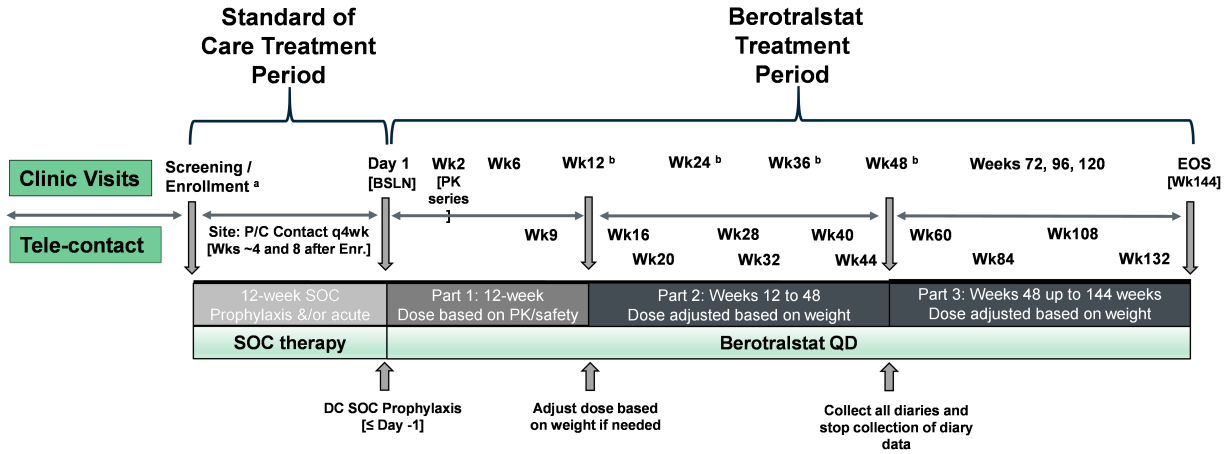
5.2.3. Exploratory Endpoints

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.

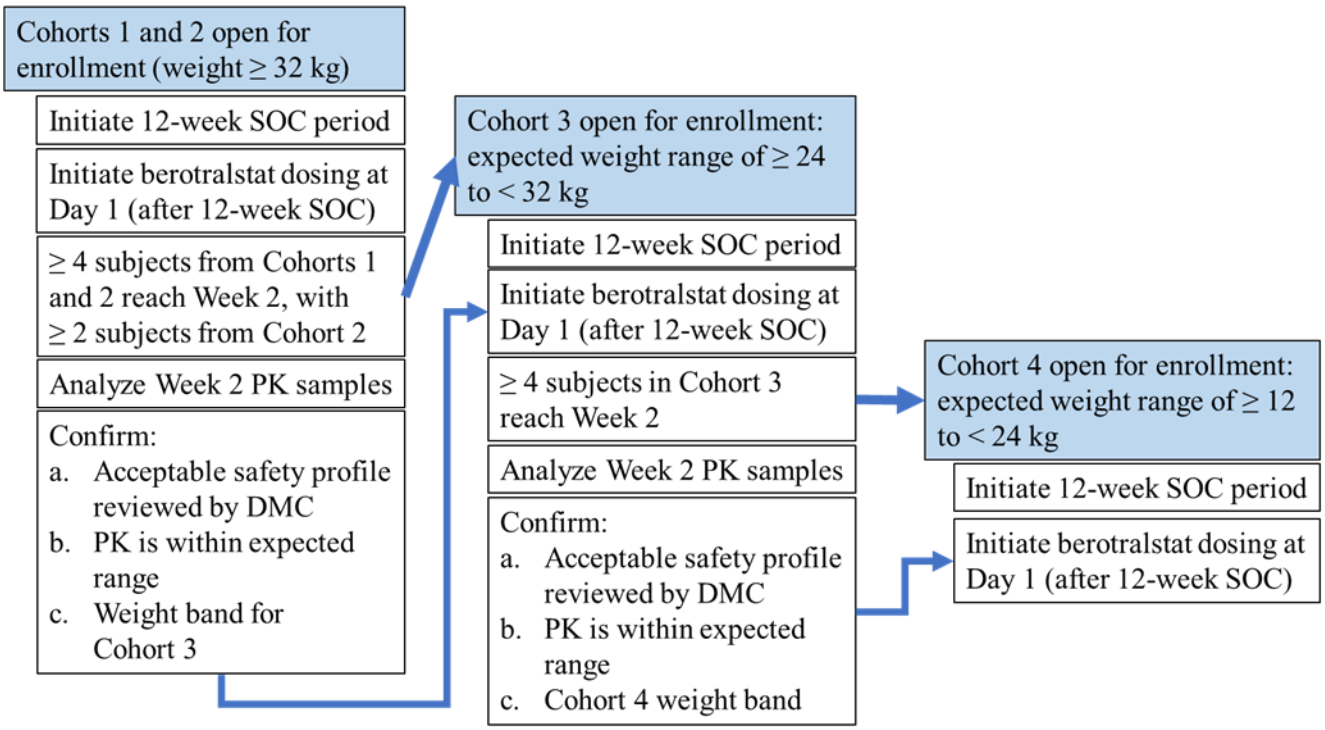
The study will enroll subjects into 4 or more dose cohorts. Subjects will be assigned into each cohort based on subject weight on Day 1/baseline. The subject weight bands for each cohort were determined based on PK modelling and simulation as discussed in Section 4.4.2 and presented in Table 1.

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.

14. REFERENCES

Agostoni, A. and M. Cicardi (1992). "Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients." Medicine (Baltimore) **71**(4): 206-215.

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

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

Christiansen, S. C., D. K. Davis, A. J. Castaldo and B. L. Zuraw (2016). "Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity." Clin Pediatr (Phila) **55**(10): 935-942.

European Medicines Agency (2006). Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. C. f. M. P. f. H. U. (CHMP). London, UK.

European Commission (2008). ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION.

Farkas, H. (2010). "Pediatric hereditary angioedema due to C1-inhibitor deficiency." Allergy Asthma Clin Immunol **6**(1): 18.

FDA (2022). General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, Including Biological Product Guidance for Industry - DRAFT GUIDANCE. C. f. D. E. a. R. (CDER).

Han, E. D., R. C. MacFarlane, A. N. Mulligan, J. Scafidi and A. E. Davis, 3rd (2002). "Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor." J Clin Invest **109**(8): 1057-1063.

ICH (2018). E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population.

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

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

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

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

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

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

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

Table of Contents

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.

Signature Page for VV-CLIN-004817 v5.0

Approval Task	Phil Collis Clinical 05-Nov-2024 17:41:31 GMT+0000

Approval Task	Donald Fong Clinical 05-Nov-2024 21:12:33 GMT+0000

Signature Page for VV-CLIN-004817 v5.0

Exposure during Pregnancy & Breastfeeding Report Form

IN CONFIDENCE

Please complete this form in confidence and return to PM_Safety@biocryst.com.

AWARENESS DATE:

Person filling out form (i.e., BioCryst staff or vendor who collected AE data):	
Reporter name (i.e., provided event info - HCP, patient, family, office staff etc.)	
Address (include country):	
Country of occurrence	
E-mail:	
Telephone number:	
If healthcare professional, state profession and area of specialty below:	
Profession:	
Area of specialty:	
If BioCryst vendor, or performing outsourced activity on behalf of BioCryst, state vendor name and project/ activity name:	
Vendor:	
Project / Activity Name:	

SECTION B: PRODUCT DETAILS

Who was exposed to the company product? Mother ☐ Father ☐
(Please tick one box only)

Route of exposure (i.e., womb, sperm, breast milk):

BioCryst drug(s)[1]	Dose & Frequency (e.g.,50 mg BID; 150 mg QD)	Route	Batch no.	Therapy Start date:	Therapy Stop date:

Reason/ indication for treatment (BioCryst drug):

Action Taken with drug:

SECTION C: DETAILS OF MOTHER AND PREGNANCY

Patient initials/ Patient number:	Age: or DOB (month/year): Height: Weight:	Country:

Pregnancy History: Overall number: Normal deliveries[2]: Spontaneous miscarriage:

Others (i.e., foetal abnormalities, voluntary termination): Specify:

[1] Please use brand names where possible

[2] A normal delivery is defined as spontaneous in onset, low risk at the start of labour and remaining so throughout labour and delivery. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth mother and infant are in good condition. [Care in Normal Birth: a practical guide. World Health Organization]

Exposure during Pregnancy & Breastfeeding Report Form

Current Pregnancy:

Date of Last menstrual period: Estimated due date:

Date of Positive pregnancy test: Estimated conception date:

Was the patient and or partner using contraception at the time of conception? Yes ☐ No ☐

If yes, what type of contraception (tick all that apply)?

☐ Barrier ☐ Implant ☐ IUD ☐ Birth control pill, include name:

☐ Other, specify:

SECTION D: OUTCOME OF PREGNANCY

☐ Unknown / Lost to follow-up

☐ Full Term (39+ wks.)

☐ Early Term (37 to 38 wks., 6 days)

☐ Premature Birth (< 37 wks.)

☐ Spontaneous Miscarriage (< 20 wks.): If so, date: **report as an SAE*

☐ Elective Termination: If so, date:

If elective termination: ☐ Non-Medical Reason ☐ Medical Reason **report as an SAE*

Please specify medical reason for termination and report as SAE if applicable:

SECTION E: DETAILS OF BIRTH / DELIVERY

Date of Birth:

Gestational age in weeks: Apgar at 1 min: Apgar at 5 min:

Weight: Units: ☐ lbs ☐ kgs Gender: Male ☐ Female ☐

Length: Units: ☐ in ☐ cm

☐ Healthy Baby ☐ Multiple Births – Number infants:

☐ Sick Baby (e.g. birth trauma, infection, etc.) (complete details of other infants in additional details section F)

☐ Stillbirth (20+ weeks) **report as an SAE*

☐ Congenital Anomaly / Birth Defect **report as an SAE*

Describe defect:

SECTION F: ADDITIONAL DETAILS

Provide any additional information regarding outcome of birth, delivery, or multiple infants. Include any complications or other relevant details:

Exposure during Pregnancy & Breastfeeding Report Form

SECTION F: PERMISSION TO FOLLOW-UP	
Permission to follow-up with reporter: Yes ☐ No ☐	If you are not the patient's obstetrician, do you provide BioCryst permission to follow-up with patient's applicable healthcare provider: Yes ☐ No ☐ If yes, please enter healthcare provider name, email, and contact detail:

Please report within 1 business day of awareness of Pregnancy and update as pregnancy progresses, and additional information is received throughout pregnancy.

Thank you for taking the time to complete this form.
Please email to PM_Safety@biocryst.com

***NOTE:** **This form is governed by applicable laws on personal identity protection. The information collected may be transferred and processed internationally. BioCryst requests that you do not provide identifiable details such as full name, address, phone number, or government-issued ID—only the specific information required by this form should be provided.**

ORLADEYO Associated Arrhythmia Follow-up Questionnaire

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

[date pulled]

Dear [primary reporter – Sal. First name Last name, Suffix],

You are receiving this questionnaire because an Adverse Reaction was reported for your patient after taking Orladeyo (berotralstat). The reported adverse event of [verbatim term] that occurred on [event onset date] requires further information to assess the causality between Orladeyo and [verbatim term].

We request your help in investigating the event and determining if there may have been other underlying causes. This questionnaire is focused on QT-prolongation, Torsade de pointes, and other conditions that can lead to a ventricular arrythmia.

Please help us by answering as many questions as you can, focusing on the period when the event occurred (1-2 weeks before event and during treatment phase). BioCryst personnel has prefilled some fields based on the information received in the initial report. Any information you provide will be useful and by providing this information, you are actively participating in safety monitoring of Orladeyo (berotralstat) use. There is no expectation to perform additional follow-up with the patient to complete the questionnaire.

Please do not hesitate to reach out with any questions:

- E-mail: *PM_Safety@biocryst.com*

Thank you very much for your help and support.

Sincerely,
BioCryst Global Drug Safety and Pharmacovigilance
PM_Safety@biocryst.com

P.S. If you are a patient who has received this letter and questionnaire, please provide it to the physician treating this event for completion.

ORLADEYO Associated Arrhythmia Follow-up Questionnaire

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

Patient initials _____

Age at time of event _____

Orladeyo ☐		
Dose	**Frequency**	**Route**

1. Final diagnosis if known:

2. Clinical signs and symptoms, if present (if none please state):

3. Event start date *(dd/mm/yyyy)*: _____ **Event stop date *(dd/mm/yyyy)*:** _____

4. Please provide outcome for arrhythmia/reported event?

☐ Recovered ☐ Not recovered ☐ Unknown ☐ Death

☐Specify, if other _____

5. Did patient take more than one dose of Orladeyo in any day? ☐ Yes ☐ No

If yes, provide details such as how many capsules per day and on how many occasions:

6. Does the patient have a relevant cardiac/arrhythmia history/risk factors?

Please check applicable history:	**YES**	**NO**
Personal history/congenital or family history of long QT syndrome	☐	☐
Prior history of drug-induced QT prolongation		
Electrolyte abnormalities (especially potassium, magnesium or calcium)	☐	☐
Alcoholism	☐	☐
Liver disease or failure	☐	☐
Kidney failure	☐	☐
Cardiac risk factors such as heart failure, left ventricular hypertrophy, bradycardia (heart rate <60), IHD, myocarditis, MI	☐	☐
Syncope	☐	☐
Hypothyroidism	☐	☐
Family History of Sudden Cardiac Death or Syncope	☐	☐
Other (e.g. Romano-Ward Syndrome, Jervell and Lange-Nielsen Syndrome, sinus node dysfunction, AV block)	☐	☐

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

7. Please provide information about:

- Prescribed drugs with potential to prolong QTc interval. This includes antiarrhythmics, antibiotics, antidepressants, antipsychotics and antiemetics.
- Drugs that may lead to increase toxicity, e.g. due to patient's metabolizer status, drug interaction or accidental or intentional overdose. Include medications stopped within 30 days of the event *(use separate sheet if necessary)*

Medication	**Indication**	**Start date** ***(dd/mm/yyyy)***	**End date** ***(dd/mm/yyyy)***	**Dose/Route/ Frequency**

8. If available, please provide the results/copy of electrocardiogram (ECG) done prior to patient starting Orladeyo along with completed Follow-up questionnaire.

If any relevant, please specify type of ECG abnormality:		
Was an ECG done during evaluation and diagnosis of the associated event	☐ Yes ☐ No ☐ Unknown	
If no to the above, are there any ECGs available since the patient started taking Orladeyo®? If yes, please provide the diagnosis and copy of ECG:		

9. Please provide the available results of the diagnostic workup including lab results such as serum potassium, magnesium, calcium, thyroid function tests and cardiac evaluations such as Holter monitoring, imaging and angiograms. – use separate sheet if necessary)

Laboratory Testing	**Results available?**	**If yes, please list result values**	**Date**
Serum Potassium	☐ Yes ☐ No ☐ Unknown		
Serum Mg	☐ Yes ☐ No ☐ Unknown		
Calcium	☐ Yes ☐ No ☐ Unknown		
Thyroid function tests	☐ Yes ☐ No ☐ Unknown		
Other relevant, please list	☐ Yes ☐ No ☐ Unknown		

10. **Please provide the suspected *etiology of the event***

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

11. Please provide specific treatments and interventions received for the reported event:

12. Please provide causality assessment for reported event and Orladeyo:

☐ Related ☐ Not related ☐ Unknown

HEALTHCARE PROVIDER/REPORTER:

Printed Name: _____ **Date:** _____
(dd/mm/yyyy)

Signature: _____

Credentials / Job Title: _____

Phone No: _____

Email: _____

Please return the completed form along with any supporting documentation to

Email: PM_Safety@biocryst.com

***NOTE: This form is governed by applicable laws on personal identity protection. The information collected may be transferred and processed internationally. BioCryst requests that you do not provide identifiable details such as full name, address, phone number, or government-issued ID—only the specific information required by this form should be provided.**

ORLADEYO Pediatric Follow-up Questionnaire

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

[date pulled]

Dear [primary reporter – Sal. First name Last name, Suffix],

You are receiving this questionnaire because an Adverse Reaction was reported for your patient after taking Orladeyo (berotralstat). The reported adverse event of [verbatim term] that occurred on [event onset date] requires further information to assess the causality between Orladeyo and [verbatim term].

We request your help in investigating the event and determining if there may have been other underlying causes.

The questionnaire is already prefilled with all the available information collected at the time of the initial report, only additional information should be filled in. By providing as detailed information as possible, you can make a useful contribution to the safety of "Orladeyo"

Please do not hesitate to reach out with any questions:

- E-mail: *PM_Safety@biocryst.com*

Thank you very much for your help and support.

Sincerely,
BioCryst Global Drug Safety and Pharmacovigilance
PM_Safety@biocryst.com

P.S.: If you are a patient who has received this letter and questionnaire, please provide it to the physician treating this event for completion.

ORLADEYO Pediatric Follow-up Questionnaire

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

Patient initials _____

Age at time of event _____

Orladeyo ☐		
Dose	**Frequency**	**Route**

1. **Final diagnosis if known:**

2. **Clinical signs and symptoms, if present (if none please state):**

3. **Event start date *(dd/mm/yyyy)*:** _____ **Event stop date *(dd/mm/yyyy)*:** _____

4. **Please provide outcome for the reported event?**

☐ Recovered ☐ Not recovered ☐ Unknown ☐ Death

☐Specify, if other _____

5. **Did patient take more than one dose of Orladeyo in any day**? ☐ Yes ☐ No

If yes, provide details such as how many capsules per day and on how many occasions:

6. **Does the patient have relevant growth and development risk factors?**

Please check applicable growth and development risk factors:	**YES**	**NO**
Genetic predisposition, sex, race and nationality	☐	☐
Prenatal factors, such as maternal malnutrition, maternal infection, maternal substance abuse, maternal illness, hormones	☐	☐
Postnatal factors, such as growth potential nutrition, childhood illness, physical and psychological environment, social economic status hormonal influence	☐	☐
Maternal substance abuse	☐	☐

7. **Please provide information about maternal substance abuse (e.g drugs with potential impact on growth and development of the child, such as cocaine and methamphetamine).**

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

Please provide information about concomitant drugs received by the child that may lead to increase toxicity, e.g. due to patient's metabolizer status, drug interaction or accidental or intentional overdose. Include medications stopped within 30 days of the event *(use separate sheet if necessary)*

Medication	Indication	Start date *(dd/mm/yyyy)*	End date *(dd/mm/yyyy)*	Dose/Route/ Frequency

8. If available, please provide the results of child's measures outcome

Measures		
Was the child Preterm as < 37 weeks of gestation at delivery	☐ Yes ☐ No ☐ Unknown	
Was the child physical growth during the newborn period affected (please tick the below):		
• Low birth weight (LBW) as birth weight < 2,500 g	☐ Yes ☐ No ☐ Unknown	
• Small for gestational age (SGA) as birth weight < 10th percentile for gestational age of the same sex in local population.	☐ Yes ☐ No ☐ Unknown	
Was the child physical growth during the childhood period affected (please tick the below):		
• Childhood growth problem defines as falling off 2 or more centiles from the growth curve of the same sex and age in local population.	☐ Yes ☐ No ☐ Unknown	
Was the child affected by significant congenital malformations affecting organ function.	☐ Yes ☐ No ☐ Unknown	
Was the child affected by the following (please tick the below):		
• Developmental delay by clinical assessment with reference to the developmental milestones	☐ Yes ☐ No ☐ Unknown	
• Specific learning disorder, e.g., dyslexia	☐ Yes ☐ No ☐ Unknown	
• Psychological and behavioral outcomes: attention-deficit hyperactive disorder (ADHD), autistic spectrum disorder (ASD), and non-specific behavioral disorders, emotional disorders.	☐ Yes ☐ No ☐ Unknown	

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

9. Please provide the laboratory tests for children's growth and development, if available.

Laboratory Testing	Results available?	If yes, please list result values	Date
Growth hormone (GH)	☐ Yes ☐ No ☐ Unknown		
Insulin-like growth factor-I (IGF-I)	☐ Yes ☐ No ☐ Unknown		
Binding protein-3 (IGFBP03) tests	☐ Yes ☐ No ☐ Unknown		
Thyroid function tests	☐ Yes ☐ No ☐ Unknown		
Other relevant, please list	☐ Yes ☐ No ☐ Unknown		

10. Please provide child's weight, height, head circumference and body mass index (BMI)

11. Please provide specific treatments and interventions received for the reported event:

12. Please provide a causality assessment for the reported event and Orladeyo:

☐ Related ☐ Not related ☐ Unknown

HEALTHCARE PROVIDER/REPORTER:

Printed Name: _____ **Date:** _____ *(dd/mm/yyyy)*

Signature: _____

Credentials / Job Title: _____

Phone No: _____

Email: _____

ORLADEYO Pediatric Follow-up Questionnaire

Date of the Report (dd/mm/yyyy):	Case MCN: [case number]

Please return the completed form along with any supporting documentation to

Email: PM_Safety@biocryst.com

***NOTE**: **This form is governed by applicable laws on personal identity protection. The information collected may be transferred and processed internationally. BioCryst requests that you do not provide identifiable details such as full name, address, phone number, or government-issued ID—only the specific information required by this form should be provided.**