NDA Multidisciplinary Review and Evaluation

Application Type	Original NDA
Application Number(s)	NDA 219776
Priority or Standard	Priority
Submit Date(s)	March 12, 2025
Received Date(s)	March 12, 2025
PDUFA Goal Date	December 12, 2025
Division/Office	Division of Pulmonology, Allergy, and Critical Care/Office of Immunology and Inflammation.
Review Completion Date	December 10, 2025
Established/Proper Name	berotralstat
(Proposed) Trade Name	Orladeyo
Pharmacologic Class	Plasma kallikrein inhibitor
Code name	BCX7353
Applicant	BioCryst Pharmaceuticals, Inc.
Dosage form	Oral pellets
Applicant proposed Dosing Regimen	Recommended dosage in patients 2 to <12 years of age is based on weight: 132 mg (≥40 kg), 108 mg (32 to <40 kg), 96 mg (24 to <32 kg), and 78 mg (b) (4) to be taken daily with food.
Applicant Proposed Indication(s)/Population(s)	For prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Unchanged
Recommended Dosing Regimen	Recommended dosage in patients 2 to <12 years of age is based on weight: 132 mg (≥40 kg), 108 mg (32 to <40 kg), 96 mg (24 to <32 kg), and 72 mg (12 to <24 kg) to be taken daily with food.

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Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPV, Division of Pharmacovigilance; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; PM, project manager; RBPM, regulatory business process manager

Signatures

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x

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Glossary

AE	adverse event
AI	acceptable intake
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BW	body weight
C1-INH	C1-esterase inhibitor
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum plasma concentration
CSR	clinical study report
C_{trough}	trough plasma concentration
CYP	cytochrome P450
DAIDS	Division of AIDS
DARRTS	Document Archival, Reporting & Regulatory Tracking System
DPACC	Division of Pulmonology, Allergy, and Critical Care
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GI	gastrointestinal
GLP	good laboratory practice
GMR	geometric mean ratio
HAE	hereditary angioedema
HS9	hamster liver homogenate (s9 fraction)
hprt	hypoxanthine guanine phosphoribosyl transferase
IND	investigational new drug
IRT-CS	Interdisciplinary Review Team for Cardiac Safety
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NCA	noncompartmental analysis
NDA	new drug application
OCP	Office of Clinical Pharmacology
PD	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics

PREA	Pediatric Research Equity Act
QD	once daily
QTc	corrected QT interval
QTcF	fridericia-corrected QT interval
RS	relative survival
RS9	rat liver homogenate (S9 fraction)
SAE	serious adverse event
SMQ	standardized MedDRA query
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
WR	written request

(b) (4)

1 Executive Summary

1.1 Product Introduction

Berotralstat is an oral plasma kallikrein inhibitor. Plasma kallikrein is a protease that generates bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with hereditary angioedema (HAE). Berotralstat decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

BioCryst submitted a new drug application (NDA) 219776 to expand the use of berotralstat (ORLADEYO) to patients aged 2 to less than 12 years of age. The application includes information on a new dosage form of berotralstat as oral pellets to provide an age-appropriate dosage form for patients 2 to less than 12 years of age. Berotralstat was initially approved under NDA 214094 on December 3, 2020, for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years of age and older.

For patients 12 years of age and older, the approved dose is 150 mg daily. A lower dose of 110 mg daily is recommended for patients with moderate to severe hepatic impairment, and persistent gastrointestinal reactions. For patients 2 to less than 12 years of age, the Applicant proposes weight-based dosing:

- 150 mg for patients weighing ≥40 kg,
- 108 mg for patients weighing between 32 kg to <40 kg,
- 96 mg for patients weighing 24 kg to <32 kg, and
- 78 mg for patients who weigh 12 kg to <24 kg.

Berotralstat oral pellets (6 mg/pellet) are manufactured in four unit-dose packet strengths, containing 72 mg, 96 mg, 108 mg, and 132 mg, respectively, to reflect recommended weight-based dosing (as outlined in the review).

1.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for berotralstat to prevent attacks of HAE in children 2 to <12 years of age is provided by extrapolation of efficacy from evidence that supported the approval of berotralstat for the same indication in adults and adolescents 12 years of age and older. Extrapolation is supported by the overlap in the clinical presentation of HAE across adult and pediatric populations, consistency in the therapeutic approach, consistency of the berotralstat mechanism of action, relevance of the clinical endpoints, and similar expected efficacy in children 2 to <12 years of age.

This extrapolation is further supported by pharmacokinetic (PK) analyses demonstrating that

drug exposure in the pediatric population consistently exceeds the levels observed in the adult reference population. Pharmacodynamics (PD) (i.e., kallikrein activity) were not assessed for this NDA given that participants had access to approved medications for treatment and prophylaxis of HAE, which limit the clinical utility of this PD analysis.

The supporting pediatric trial (Trial BCX7353-304, hereafter referred to as Trial 304) is a 48-week, open-label, PK and safety trial with an optional 96-week extension. The trial enrolled 29 pediatric subjects 2 years to <12 years of age with Type I or II HAE. While Trial 304 was not designed to demonstrate efficacy due to its small sample size and uncontrolled design, descriptive efficacy analyses yielded results that aligned with findings from adolescent and adult trials.

The recommended regulatory action for this efficacy supplement is **Approval**.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Substantial evidence of effectiveness for berotralstat to prevent attacks of HAE in children 2 to <12 years of age is provided by extrapolation from evidence of efficacy that supported the approval of berotralstat for the same indication in adults and adolescents 12 years of age and older. PK and safety support relies on Trial 304, a 48-week single-arm, open-label trial, with an optional 96-week extension, that enrolled 29 pediatric patients 2 to <12 years of age and ≥12 kg with Type I or Type II HAE. The trial divided participants into four weight-based daily dosing cohorts: participants ≥40 kg received 150 mg; participants 32 kg to <40 kg received 108 mg; participants 24 kg to <32 kg received 96 mg; participants 12 kg to <24 kg received 78 mg. (b) (4) [redacted] the recommended weight band was modified to 12 to <24 kg to align with the patient population evaluated in Trial 304. The recommend dosage for this weight band was also lowered from the proposed 78-mg dose to 72 mg due to concerns with higher exposure and the threshold known to cause QTc prolongation in adults. Additionally, the recommended dosage for patients ≥40 kg was lowered from the proposed 150-mg dose to 132 mg due to notably higher PK with the 150-mg dose.

The safety profile of berotralstat has been well established since its approval in 2020 and includes a warning and precaution for increased QT prolongation when patients take doses higher than the recommended dose of 150 mg daily. The most common adverse reactions (≥10%) included abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease. The safety profile in children 2 to <12 years of age, as demonstrated Trial 304, did not identify new safety signals compared to that observed in adults and adolescents 12 years of age and older.

In contrast to parenterally or subcutaneously administered options for prophylaxis against HAE attacks, berotralstat offers the advantage of being an oral product. Availability of an oral product for pediatric patients 2 to <12 years of age would add an important treatment option. The only approved oral product for prophylaxis of HAE for this age group is danazol, but safety concerns limit its use in pediatric patients. The overall risk-benefit is favorable for the approval of berotralstat down to age 2 years for prophylaxis to prevent attacks of HAE. Completion of Trial 304 also addresses a Pediatric Written Request.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type I and II HAE are rare conditions caused by autosomal dominant mutations in the SERPING1 gene, resulting in deficiency or dysfunction of C1-esterase inhibitor (C1-INH) protein. • Approximately 85% of patients have Type I HAE, characterized by low production of normal C1-INH protein. The remaining 15% of patients have Type II HAE, characterized by production of dysfunctional C1-INH. Types I and II have the same clinical phenotype and responses to available treatments. • Insufficient quantities of functional C1-INH lead to dysregulation of the kallikrein-kinin system, Factor XII and culminating in the generation of bradykinin. Uncontrolled bradykinin production leads to increased vascular permeability and the cutaneous/submucosal swelling seen in acute HAE attacks. • Acute HAE attacks are sporadic, recurrent, unpredictable and typically self-resolve after 48-72 hours. Attacks often involve the GI/GU tract, extremities (hands/feet), and face/upper airway. Attacks are associated with significant morbidity due to pain, impact on daily functioning, and disfigurement and can be life-threatening in cases of laryngeal edema resulting in airway compromise.	HAE is a rare, genetic, potentially life-threatening disease characterized by unpredictable, recurrent, self-limited cutaneous and submucosal swelling attacks. The pathophysiology of the disease is well characterized. While the disease can be highly variable, patients with severe and/or frequent attacks benefit from prophylactic therapy.
Current Treatment Options	• No cure exists; however, there are several approved therapies for prophylaxis as well as for on-demand treatment of acute attacks. • Therapies for prophylaxis include plasma-derived C1-INH replacement, oral attenuated androgen, plasma kallikrein and pre-kallikrein inhibitors, and a Factor XIIa inhibitor. Available	While there are approved prophylactic therapies for HAE pediatric patients, the availability of additional, convenient oral treatment options is desirable for those who prefer orally administered therapy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment options include oral and injectable (IV and SC) products. • A significant unmet medical need for effective and safe treatment options exists among pediatric subjects with HAE, especially for oral products. A plasma kallikrein inhibitor (lanadelumab) is available for subcutaneous injection for children down to 2 years of age. The only approved oral product for prophylaxis of HAE for this age group is danazol, but safety concerns limit its use in pediatric patients. C1-INH therapies are available for children 6 years of age and older, but these products must be administered intravenously or subcutaneously every 3-4 days.	and/or are unable to tolerate existing treatments or those with suboptimal response to available therapies.
Benefit	• Substantial evidence of effectiveness is provided by extrapolation from evidence that demonstrated substantial evidence of effectiveness from the approval of berotralstat for the same indication in adults and adolescents 12 years of age and older. Extrapolation is reasonable due to the overlap in the clinical presentation of both adult and pediatric HAE, consistency in the therapeutic approach, consistency of the berotralstat mechanism of action, relevance of the clinical endpoints, and similar expected efficacy. Extrapolation is further supported by PK analyses showing consistently higher drug exposure compared to adults. • The supporting pediatric trial (Trial 304) was a 48-week, open-label, PK and safety trial with an optional 96-week extension in 29 pediatric subjects 2 years to 11 years of age with Type I or II HAE. The pediatric trial was not designed to assess efficacy given the	Efficacy was extrapolated for patients 2 to <12 years of age from the adolescent and adult trials based on PK analyses showing consistently higher drug exposure than the one observed in the adult reference population. Berotralstat offers the advantage of being an oral product. Availability of an oral product for pediatric patients 2 to <12 years of age would add an important treatment option. Berotralstat would represent a clinically relevant, beneficial treatment for this

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	small sample size, duration, and uncontrolled design. However, descriptive efficacy analyses were supportive.	difficult to treat patient population.
Risk and Risk Management	• The safety profile of berotralstat is well established since its approval in 2020 and includes a warning and precaution for increased QT prolongation when patients take higher than the recommended dose of 150 mg daily. The most common adverse reactions (≥10%) include abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease. The safety profile in children 2 to <12 years of age was similar to that observed in adults and adolescents 12 years of age and older.	The risk-benefit profile is consistent with that established for the approved indication. Risk can be mitigated through labeling and routine pharmacovigilance.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
X	**Patient-experience-data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	X	Patient-focused drug development or other stakeholder meeting summary reports		Food and Drug Administration (FDA)-

			led Patient-Focused Drug Development Meeting: September 25, 2017
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
	Patient-experience-data was not submitted as part of this application.		

2 Therapeutic Context

2.1 Analysis of Condition

HAE is a rare, autosomal dominant condition, most often caused by pathogenic variants in the SERPING-1 gene that encodes C1-esterase inhibitor (C1-INH), a serine protease-inhibitor involved in the kallikrein-kinin pathway, as well as the classical and lectin complement, contact system/intrinsic coagulation, and fibrinolytic pathways.[1,2] Approximately 85% of patients have Type I HAE, characterized by low production of normal C1-INH protein while the remaining 15% of patients have Type II HAE, characterized by normal production and levels of dysfunctional C1-INH.[3] Absence of functional C1-INH leads to dysregulation of the contact system, a plasma protease cascade initiated by factor XII that activates the proinflammatory kallikrein-kinin system and the procoagulant intrinsic coagulation pathway. Ordinarily, kallikrein activity is regulated by C1-INH, but in HAE patients kallikrein activity goes unchecked, leading to widespread release of bradykinin. In turn, bradykinin increases vascular permeability, which leads to the characteristic swelling of acute HAE attacks.

While the overall prevalence of HAE is estimated to be between 1/30,000 and 1/80,000, limited data are available on the epidemiology of the disease in children.[4] Most studies show that patients with early symptom onset experience a more severe course of disease than those who have first symptoms later in life.[5]

The unpredictable nature of HAE attacks in children results in significant decrements in vocational and school achievement, which poses a considerable burden on patients and their families.[6] Because of the impact that HAE has on quality of life, productivity, anxiety, and absenteeism, prophylactic agents are critical.[7]

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[1] Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020 Mar 19;382(12):1136-1148.

[2] Kyrle PA, Eichinger S. Hereditary angioedema: beyond swelling. Blood. 2024 Jul 25;144(4):354-355.

[3] Ghazi A, Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. Biologics. 2013;7: 103-13.

[4] Christiansen SC, *et al*. The US Hereditary Angioedema Association Scientific Registry: hereditary angioedema demographics, disease severity, and comorbidities. Ann Allergy Asthma Immunol. 2023 Dec;131(6):766-774.e8.

[5] Pagnier A, *et al.* Hereditary angioedema in children: Review and practical perspective for clinical management. Pediatr Allergy Immunol. 2024 Dec;35(12):e14268.

[6] Ameratunga R, Longhurst HJ. New Therapies for Type 1 and Type 2 Hereditary Angioedema. N Engl J Med. 2024 Jul 4;391(1):79-81.

[7] Bork K, *et al*. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. Allergy Asthma Clin Immunol. 2021 Apr 19;17(1):40

2.2 Analysis of Current Treatment Options

In the past decade, several targeted therapies for HAE have been developed with an improved benefit-risk profile and different treatment properties allowing for an individualized treatment approach. Therapeutic approaches for HAE include both acute and prophylactic treatments. The goal of acute treatment is to minimize HAE symptoms during an attack, while prophylaxis aims to reduce the likelihood of swelling during an expected trigger (short-term prophylaxis) or reduce the overall recurrence of angioedema attacks (long-term prophylaxis).[8] Although currently available treatments for routine prophylaxis of acute HAE attacks are effective in reducing the number and frequency of attacks, they do not eliminate all attacks in every individual. In addition to the FDA-approved therapies shown in Table 1, fresh frozen plasma and antifibrinolytics (tranexamic acid, ε-aminocaproic acid) are available for HAE prophylaxis. However, with availability of more effective and targeted FDA-approved therapies, their off-label use in HAE has declined and is no longer recommended.

A significant unmet medical need for effective and safe treatment options exists among pediatric subjects with HAE, especially for oral products. Lanadelumab subcutaneous injection is available for children down to two years of age. The only approved oral product for prophylaxis of HAE for this age group is danazol, but safety concerns limit its use in pediatric patients. C1-INH therapies are available for children 6 years of age and older, but these products must be administered intravenously or subcutaneously every 3 to 4 days.

[8] Ibid.

Table 1. Summary of Prophylaxis Treatment Armamentarium for HAE

Products	Pharmacologic Class	Year Of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Pediatric Indication
Danazol	Androgen	1980	200 mg PO BID-TID	Thromboembolism, hepatic dysfunction, hepatic adenoma, dyslipidemia, myopathy weight gain, acne, hirsutism, menstrual disturbance	No age limit
Cinryze	Plasma derived C1-INH	2008	1000 units IV every 3-4 days.	Thromboembolism, hypersensitivity, transmissible infection	≥6 years
Haegarda	Plasma derived C1-INH	2017	60 IU/kg SC every 3-4 days.	Same as Cinryze	≥6 years
Lanadelumab	Plasma kallikrein inhibitor	2018	300 mg SC every 2 weeks.	Hypersensitivity reactions, injection site reactions, transaminase elevations	≥2 years
Berotralstat	Plasma kallikrein inhibitor	2020	110-150 mg PO once daily.	Abdominal pain, vomiting, diarrhea, back pain, gastroesophageal reflux disease	>12 years
Donidalorsen	Antisense oligonucleotide (ASO) targeting kallikrein B1 (KLKB1) mRNA	2024	80 mg SC every 4 weeks.	Injection site reactions (erythema, swelling, pain), (b) (4) possible hypersensitivity reactions.	≥18 years
Garadacimab	Factor XIIa inhibitor	2025	(b) (4) mg SC loading dose, then (b) (4) mg SC every 4 weeks.	Injection site reactions, (b) (4)	≥12 years

Source: Drugs@fda.gov (Https://www.accessdata.fda.gov/scripts/cder/daf/)
Abbreviations: BID, twice daily; C1-INH, C1 Inhibitor; IU, International Units; IV, Intravenous; PO, oral; PRN, as needed; SC, subcutaneously; TID: three times a day

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Berotralstat (marketed as ORLADEYO) was approved for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older in the United States on December 3, 2020. Currently, berotralstat is approved in over 30 countries globally, including the European Union, with the same age indication. Berotralstat is not approved for patients less than 12 years of age in any country.

3.2 Summary of Presubmission/Submission Regulatory Activity

Berotralstat (ORLADEYO) was developed under investigational new drug (IND) application 135058, which was opened on June 22, 2017. Berotralstat was granted orphan drug designation on November 1, 2017, and fast-track designation on August 2, 2018. Berotralstat was first approved on December 3, 2020, for patients with HAE aged 12 years or older NDA 214094.

In the Type C written responses dated May 8, 2024, the Agency recommended that the Applicant submit a new NDA to expand the indication to include children 2 to <12 years of age, rather than a supplement, as oral pellets constitute a new dosage form. Information regarding this new dosage form, dosage, and results obtained from Trial 304 were incorporated into the existing prescribing information rather than establishing separate labeling for the pediatric population aged 2 to <12 years.

Berotralstat for treatment of HAE is exempt from Pediatric Research Equity Act (PREA) requirements due to the orphan drug designation. A written request (WR) was issued on November 21, 2023, and amended on October 3, 2024. This NDA presents data from a single, phase 3 trial, Trial 304, that was conducted in accordance with the WR Amendment #1.

Relevant pre-submission regulatory interactions between the Agency and Applicant to discuss the clinical development program are summarized in Table 2.

Table 2. Summary of Pre-Submission Regulatory Activity

Interaction	Date	Remarks
Inadequate PPSR Letters	June 25, 2021 and July 20, 2022	PPSR did not include the required GLP-juvenile rat toxicity study.
Written Request Issued	November 21, 2023	A WR was issued after the Sponsor submitted the juvenile rat toxicity study report with the PPSR resubmission.
Type C Written Responses	May 8, 2024	The Agency agreed with the Applicant's proposal to ensure that the interim CSR for Trial 304 included PK data from at least 20 pediatric subjects with a minimum of 15 subjects having completed 48 weeks of berotralstat treatment.

Interaction	Date	Remarks
Pediatric Protocol Review	July 8, 2024	As the trial is fully enrolled at this point, we will recommend to the Sponsor include each subjects' SERPING-1 gene mutation information, where available. Overall, the inclusion and exclusion criteria are acceptable as HAE is a genetic condition and clinical phenotypes are often less severe in the pediatric population.
Pediatric Revised WR	October 3, 2024	FDA suggested to delete pharmacodynamic endpoints: change from baseline in plasma kallikrein activity over the 1-year treatment. The Agency acknowledged that baseline assessment of kallikrein activity may be confounded because subjects had access to approved medications for treatment and prophylaxis of HAE during the ongoing pediatric trial, thereby limiting the clinical significance of this pharmacodynamic analysis.
Type B-Pre NDA Meeting	January 23, 2025	Agency agreed with extrapolation approach for pediatric dose selection using observed Trial 304 data as well as simulated exposure parameters based on population PK analysis. BioCryst acknowledged that it is possible that berotralstat has multiple nitrosamines and planned to submit additional reports to support (b) (4) acceptable intake after the NDA was submitted. FDA noted this was acceptable but could be considered a major amendment and also noted the Nitrosamine Working Group would review the data.

Abbreviations: CSR, clinical study report; GLP, good laboratory practice; HAE, hereditary angioedema; NDA, new drug application; PK, pharmacokinetic; PPSR, Proposed Pediatric Study Request; WR, written request

During the submission, several additional reports were submitted to support (b) (4) nitrosamine acceptable intake limit, including an in vitro cell mutation assay, an in vitro metabolism assay, and additional stability data for the (b) (4) content in the registration and clinical batches of the drug product. A major amendment was issued on June 23, 2025, to provide three additional months for a full review of the submission, extending the goal date from September 12, 2025, to December 12, 2025.

Pediatric exclusivity was granted on August 29, 2025, and the Applicant was notified on September 2, 2025.

An information request was issued to the Applicant on October 7, 2025, acknowledging the justification submitted to support the safety of the proposed 78 mg dosage for patients aged 2 to <12 years. Upon Agency review of data from QT Trial 106, clinically significant QT prolongation was identified following administration of a supratherapeutic dose of 450 mg, which resulted in berotralstat plasma concentrations of approximately 591 ng/mL. Based on (1) the established concentration-dependent relationship between berotralstat exposure and QT prolongation and (2) the proximity of the upper range of predicted pediatric exposure at the

78 mg dosage (i.e., >500 ng/mL) to the threshold associated with QT prolongation in adults, the Agency determined that there was a potential risk for QT prolongation in the lowest body weight patients (12 to <24 kg) receiving this dosage. Consequently, the Agency recommended dose reduction to either 66 mg or 72 mg for pediatric patients weighing 12 to <24 kg. The Applicant has agreed to implement the 72 mg dosage for this patient population.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations

Office of Scientific Investigations inspections were not deemed necessary for this NDA because the berotralstat program was a multicenter trial with each site enrolling a small number of subjects.

4.2 Product Quality

The approved berotralstat capsules under NDA 214094 for the prevention of attacks of HAE in patients 12 years and older, is cross-referenced for the complete drug substance information. During the review process, the chemistry, manufacturing, and control reviewer and Office of Policy for Pharmaceutical Quality labeling reviewed the term used for the dosage form of berotralstat and determined that the dosage form for the drug product should be pellets (mini tablets) instead of granules (irregular particles). This determination reflects the Agency's current practice of following the U.S. Pharmacopeia <1151>pharmaceutical dosage forms guidance, where "oral pellets" is now considered the appropriate dosage form descriptor for drug products such as berotralstat.

Based on these established criteria, the Agency provided labeling comments dated October 27, 2025, requesting the change from dosage form "granules" to "pellets" to align with the recommendations of U.S. Pharmacopeia <1151>. (b) (4)

4.3 Clinical Microbiology

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

A full nonclinical program for berotralstat was reviewed for the approval of NDA 214094. The program consisted of pharmacology (in vitro and in vivo), PK, and toxicology (general toxicology in rats and monkeys, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology) studies. To support the current NDA for the approval in pediatric patients aged 2 years and older, the Applicant submitted a juvenile animal toxicology study in rats. In addition, the Applicant provided study reports to support the safety of a nitrosamine impurity. A summary of these studies is included below.

5.2 Juvenile Animal Toxicology Study

In a juvenile animal toxicity study in Wistar Han rats, pups (10/sex/dose) were dosed by oral gavage with 0, 5, 20, or 50 mg/kg/day berotralstat (C, LD, MD, and HD, respectively) in water once daily for 49 days. Pups were 21 days old (postnatal day 21) when the dosing started. Additional rats were included to evaluate the lesion recovery and toxicokinetics (10 and 9 rats/sex/dose, respectively). The mean area under the concentration-time curve (AUC) at the end of the treatment period (postnatal day 69) was 764, 5080, and 16800 ng.h/mL in the LD, MD, and HD groups, respectively. The MD and HD groups showed macrophage vacuolation in multiple organs and hepatocellular hypertrophy in the liver. Organs with macrophage vacuolation included the liver, adrenal glands, lymph nodes, small intestine, and spleen. All the findings were fully reversible after a recovery period of 3 weeks. Similar findings were observed in adult rats. The LD group did not show any treatment-related findings. The no-observed-adverse-effect level was 5 mg/kg/day, corresponding to an $AUC_{0\text{-}24}$ of 764 ng.h/mL.

5.3 Studies to Support Safety of the Nitrosamine Impurity

Regulatory History

In the filing review letter dated May 9, 2025, the Applicant was reminded that the complete study reports of the in vitro mammalian cell mutation assay and in vitro metabolism assay with human hepatocytes or microsomes are needed to support the (b) (4) acceptable intake limit of (b) (4) ng/day. In addition, this information may be considered as a major amendment to the NDA. Subsequently, the final reports of the in vitro metabolism assay and in vitro cell mutation assay were submitted to the NDA on May 22, 2025, and June 11, 2025, respectively. The latter submission constituted a major amendment to this application, and this was communicated to the Applicant on June 23, 2025. Therefore, the goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal date is December 12, 2025.

Nitrosamine Safety Assessment

(b) (4)

the Applicant's proposed AI of (b) (4) ng/day (b) (4) is supported by the nonclinical data and is acceptable from the toxicological perspective. The results of these studies were discussed with the CDER Pharmacology and Toxicology Coordinating Committee Nitrosamine Working Group, and the Working Group agreed with this conclusion. *For* a detailed review of these studies refer to Section 14.2.

Table 3. Summary of Nonclinical Studies Conducted to Support the (b) (4) Acceptable Intake Limit of (b) (4) ng/Day

Study	Positive/ Negative/Equivocal	Notes
(b) (4)		

(b) (4)

Study	Positive/	Notes
[redacted]		(b) (4)

6 Clinical Pharmacology

6.1 Executive Summary

Background/Regulatory History

Berotralstat (ORLADEYO) oral capsule was originally approved under NDA 214094 on December 3, 2020, for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years of age and older. The active pharmaceutical ingredient of berotralstat is a plasma kallikrein inhibitor that prevents the proteolytic cleavage of high-molecular-weight kininogen to form bradykinin, which is a known potent vasodilator and a critical mediator leading to the increased vascular permeability, smooth muscle contraction, and tissue swelling that collectively characterize HAE attacks.

On March 12, 2025, the Applicant (BioCryst Pharmaceuticals, Inc.) submitted an original new drug application (NDA 219776) for berotralstat oral pellets, in which they are seeking to expand the currently approved indication to include prophylaxis to prevent attacks of HAE in pediatric patients 2 to <12 years of age. In support of this NDA submission, the Applicant has provided clinical pharmacology data from two trials, including Trial BCX7353-114 (hereafter referred to as Trial 114, phase 1 relative bioavailability [BA] trial between the oral capsule and oral pellet dosage forms) and Trial 304 (phase 3 PK, safety, and efficacy trial in pediatric subjects 2 to <12 years of age with HAE).

Recommended Dosing in Pediatric Patients 2 to <12 Years of Age

The Applicant is developing the novel berotralstat oral pellet dosage form as an age-appropriate formulation to permit additional dosing flexibility for pediatric subjects 2 years of age and older. Berotralstat oral pellets are manufactured in four unit-dose packet strengths, containing 72 mg, 96 mg, 108 mg, and 132 mg, respectively. The recommended dosage for pediatric patients ages 2 to <12 years of age is based on body weight, as outlined below in Table 4.

Table 4. Recommended Weight-Based Dosing of Berotralstat Oral Pellets in Patients 2 to <12 Years of Age With HAE

Weight	Dosage (Oral Pellets)	Administration Instructions
12 to <24 kg	72 mg once daily	Pour directly in mouth and swallow immediately with non-acidic liquid, or, sprinkle over 1 tablespoon (15 mL) of non-acidic soft food and consume immediately. A meal should be consumed just before or after administration.
24 kg to <32 kg	96 mg once daily	
32 kg to <40 kg	108 mg once daily	
≥40 kg	132 mg once daily	

Source. Adapted from Applicant's proposed labeling, dated November 26, 2025 (Highlights of Prescribing Information, pg. 1)
Abbreviations: HAE, hereditary angioedema

Major Clinical Pharmacology Review Findings

The clinical pharmacology review for this NDA focused on analysis of the berotralstat PK data derived from Trials 114 and 304, adequacy of the population PK model which supported the proposed weight-based dosing, and the Applicant's proposed dose adjustments in the pediatric population based on intrinsic/extrinsic factors. The major clinical pharmacology findings for this submission are summarized below:

- In Trial 304, the observed berotralstat systemic exposure (as defined by maximum plasma concentration [C_{max}], trough plasma concentration [C_{trough}], and $AUC_{0\text{-}6h}$) following administration of the weight-based oral pellet dosage regimens for pediatric Cohort 2 (108 mg oral pellet; 32 to <40 kg), Cohort 3 (96 mg oral pellet; 24 to <32 kg), and Cohort 4 (78 mg oral pellet; 12 to <24 kg) was within the 5th to 95th percentile reference range of observed adult values. Berotralstat systemic exposure observed for Cohort 1 (150 mg oral capsule; ≥40 kg) exceeded the adult reference range, indicating the need for a lower to-be-marketed dosage for pediatric subjects weighing ≥40 kg.
- Based on population PK modeling and simulation, the recommended weight-based oral pellet dosing in pediatric patients is predicted to result in a 1% lower to 18% higher median $C_{trough,ss}$, and a 17 to 24% higher median $C_{max,ss}$, relative to adults receiving the approved dosage of berotralstat oral capsule 150 mg once daily (QD). Under the proposed pediatric dosing, less than 6% of children 2 to <12 years of age are predicted to have a $C_{trough,ss}$ below the 5th percentile of adults, while less than 15% are predicted to have a $C_{max,ss}$ exceeding the 95th percentile of adults. Overall, these data support comparable berotralstat systemic exposure between pediatrics and adults at the proposed dosing.
- The proposed dose adjustments based on renal (avoid use in patients with severe renal impairment) and hepatic impairment (avoid use for moderate or severe hepatic impairment) are reasonable to support safety in the target patient population.

Recommendation

The Office of Clinical Pharmacology (OCP), Division of Inflammation and Immune Pharmacology and Division of Pharmacometrics have reviewed the information submitted under NDA 219776. This application is approvable from a clinical pharmacology perspective.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The general clinical pharmacology program for berotralstat oral capsules was previously reviewed following submission under NDA 214094 for the prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older (Refer to the NDA Multidisciplinary Review and Evaluation, dated December 3, 2020 [DARRTS Reference ID: 4711626]).

6.2.2 Individual Trial Reports

In support of the current NDA submission for berotralstat oral pellets for the proposed indication of prophylaxis to prevent attacks of HAE in pediatric patients 2 to <12 years of age, the Applicant submitted clinical pharmacology data derived from two trials:

- Trial 114: Phase 1 relative BA trial to assess berotralstat PK following administration as the oral capsule compared with the oral pellet in healthy adult subjects.
- Trial 304: Phase 3, single-arm, open-label trial to assess berotralstat PK, safety, and efficacy in pediatric subjects 2 to <12 years of age and weighing ≥12 kg with HAE (ongoing at time of NDA submission).

6.2.2.1 Trial 114 (Phase 1 Relative BA Trial)

Trial Design

Trial 114 was designed to evaluate the relative BA of berotralstat when administered as a liquid versus oral pellet (Part 1) and as an oral pellet versus oral capsule (Part 2) in healthy adult subjects. Since the liquid formulation is not a to-be-marketed dosage form, only Part 2 of this trial is considered relevant to this NDA. Therefore, Part 1 will not be discussed further.

Part 2 was a multiple-dose, open-label, randomized, 3-period, crossover trial to assess the safety, tolerability, and relative BA of berotralstat when administered as the approved oral capsule compared with the proposed oral pellet. In Periods 1 and 2, subjects received berotralstat 150 mg QD for 7 days as both the oral capsule (Regimen D) and oral pellet (Regimen E) in a randomized sequence (i.e., D-E or E-D), after which all subjects entered Period 3 to receive berotralstat oral pellet 300 mg QD for 7 days (Regimen F). Each treatment period was separated by a washout period of 21 days. All doses of both the oral capsule and oral pellet

were taken with 240 mL of water following an overnight fast of 10 hours, and participants were instructed not to chew the pellets.

The trial enrolled healthy male and female adult subjects 18 to 55 years of age (inclusive) with body mass index of 18 to 32 kg/m^2 (inclusive). Subjects with creatinine clearance ≤80 mL/min or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) value ≥2 times the upper limit of normal (ULN) were excluded. Additionally, all prescription medications were prohibited within 14 days of Day 1, along with all over-the-counter medications, vitamins, or herbal products within 7 days of Day 1. Participants were permitted to continue to take prescribed contraceptive medications.

Subject Disposition and Demographics

In Part 2, a total of 18 subjects were randomized to berotralstat treatment sequences D-E or E-D in Periods 1 and 2, followed by Period 3. All subjects completed the entire trial and there were no major protocol deviations. There were an equal number of males and females enrolled (N=9 each). Mean (SD) age and body weight were 39.7 (9.6) years and 79.2 (12.7) kg, respectively.

PK Sampling and Analysis

The PK population consisted of subjects who received berotralstat in both Periods 1 and 2 and for whom sufficient concentration data were available for the calculation of PK parameters, which included all 18 enrolled subjects. Mean berotralstat plasma concentration-time profiles were plotted on both linear and semi-logarithmic scales according to treatment regimen. PK parameters were estimated using noncompartmental analysis (NCA) and summarized descriptively according to treatment regimen. Log-transformed berotralstat PK parameters (AUC_{tau} and C_{max}) were analyzed using an analysis of variance model, which included treatment, period, and sequence as fixed effects and subject as a random effect. Results from these analyses were back-transformed to obtain a point estimate with 90% confidence interval (CI) for the geometric mean ratios (GMRs) for comparison of Regimen E to Regimen D for both AUC_{tau} and C_{max}.

The PK sampling scheme for each treatment period was completed as follows:

- PK samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h post-dose on both Days 1 and 7.

All plasma samples for determination of berotralstat concentrations were analyzed using a previously validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay (Report 171354 (b) (4)), which was reviewed and found to be acceptable under NDA 214094 (Refer to the NDA Multidisciplinary Review and Evaluation, dated December 3, 2020 [DARRTS Reference ID: 4711626]). Additionally, the in-study bioanalysis results for Trial 114 met acceptance criteria.

Summary of PK Results

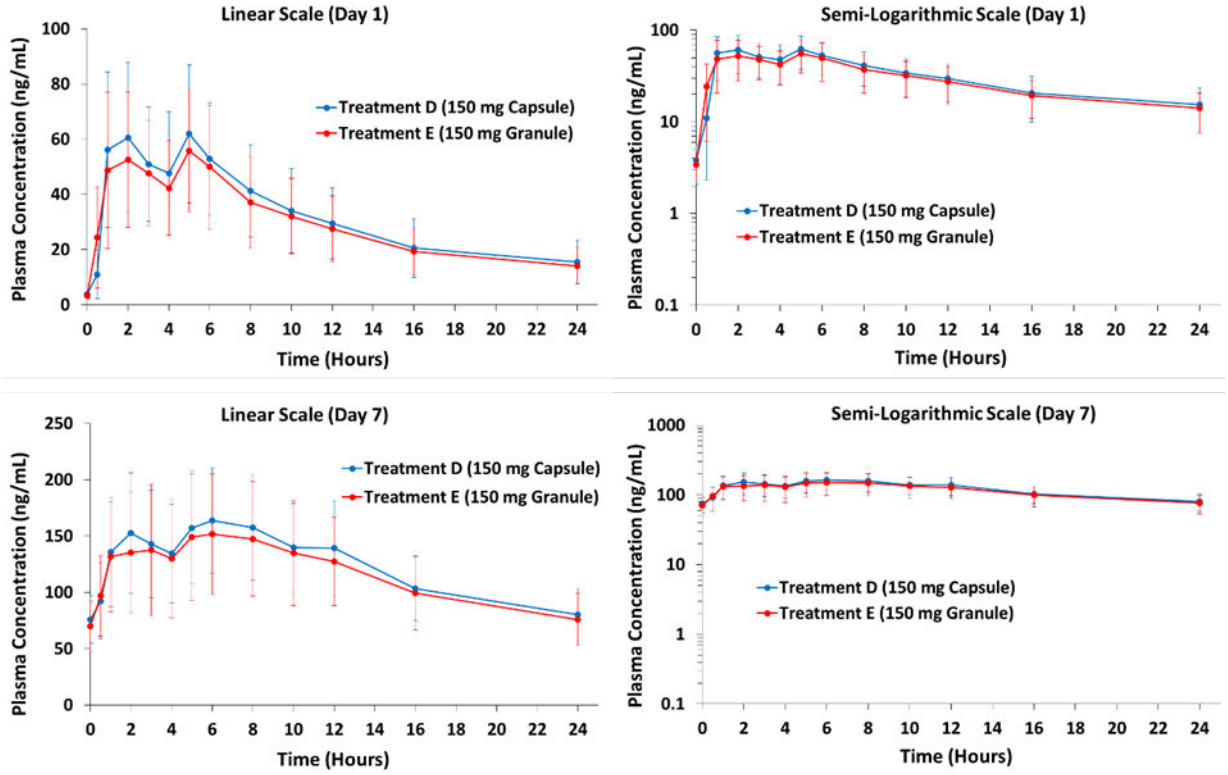
Overall, berotralstat PK parameters were similar between the oral capsule and oral pellet formulations on both Day 1 and Day 7 (Table 5). Berotralstat systemic exposure was slightly lower for the oral pellet relative to the oral capsule, although terminal half-life and apparent clearance were comparable between dosage forms on both Day 1 and Day 7. A greater than dose proportional increase in systemic exposure was observed between Treatments E (150 mg oral pellet) and F (300 mg oral pellet), corresponding to a 2.5- to 3-fold increase in both AUC and C_{max} for this 2-fold dose increase, which is consistent with known berotralstat PK from the currently approved labeling. Arithmetic mean (SD) concentration-time profiles were similar and overlapped at all timepoints, with approximately 2.6- to 4-fold accumulation observed for both formulations following QD dosing for 7 days (Figure 1).

Table 5. Summary of Berotralstat PK Parameters According to Treatment Regimen and Dosage Form on Day 1 and Day 7 (Trial 114; PK Population)

	Treatment Regimen (N=18)			
	Regimen D (150 mg Oral Capsule)		Regimen E (150 mg Oral Pellet)	
PK Parameter[a]	Day 1	Day 7	Day 1	Day 7
AUC_{inf} (ng*h/mL)	954.7 (44.1)	4663.7 (35.0)	858.4 (47.6)	4370.5 (31.9)
AUC_{tau} (ng*h/mL)	717.4 (39.7)	2823.7 (31.8)	656.6 (45.3)	2653.7 (32.5)
C_{max} (ng/mL)	67.2 (41.9)	164.4 (32.4)	57.9 (41.7)	150.7 (36.0)
CL/F (L/h)	209.1 (39.7)	53.1 (31.8)	228.5 (45.3)	56.5 (32.5)
$t_{1/2}$ (h)	11.1 (28.1)	16.2 (21.2)	10.6 (21.7)	16.1 (15.9)
T_{max} (h)	2.0 (1.0, 5.0)	6.0 (1.0, 8.0)	2.0 (0.5, 5.0)	5.0 (1.0, 8.0)
Vz/F (L)	3350 (44.3)	1240 (36.0)	3490 (48.7)	1310 (37.8)

Source. Reviewer's analysis based on adpp.xpt for Trial 114
[a] All PK parameters reported as geometric mean (CV%), except for T_{max}, which is reported as median (min, max)
Abbreviations: AUC_{in}, area under the plasma concentration-time curve from 0 to infinity; AUC_{tau}, AUC from 0 to the end of the dosing interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; Min, minimum; Max, maximum; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time of C_{max}; Vz/F, apparent volume of distribution during the terminal phase

Figure 1. Arithmetic Mean (SD) Berotralstat Plasma Concentration-Time Profile on Day 1/Day 7 (Trial 114; PK Population)



Source. Reviewer's analysis based on adpc.xpt for Trial 114
Abbreviations: SD, standard deviation

Relative BA Assessment (Oral Capsule Versus Oral Pellet)

The statistical analysis of relative BA between dosage forms based on C_{max} and AUC_{tau} in Trial 114 is shown below in Table 6. This reviewer's statistical analysis was conducted using a univariate analysis of variance model to determine the GMRs and associated 90% CIs of C_{max} and AUC_{tau}. The GMRs and 90% CIs for C_{max} and AUC_{tau} when comparing the oral pellet (test) to the oral capsule (reference) were 86.2 (79.2, 93.8) and 91.5 (83.8, 100), respectively, on Day 1, and 91.7 (86.8, 96.9) and 94.0 (90.0, 98.1), respectively, on Day 7. Based on these data, bioequivalence criteria were met between dosage forms for AUC_{tau} at both Day 1 and Day 7, although bioequivalence criteria for C_{max} were only met on Day 7. On Day 1, C_{max} was approximately 14% lower for the oral pellet relative to the oral capsule and the lower bound of the 90% CI of the GMR fell slightly below the no effect boundary of 80 to 125%.

Overall, these data are sufficient to establish a formulation bridge between the proposed oral pellet and approved oral capsule.

Table 6. Relative BA Statistical Analysis of Berotralstat for Oral Pellet vs. Oral Capsule Dosage Forms Following 150 mg QD Dosing (Trial 114; PK Population)

Trial Day PK Parameter	150 mg Oral Capsule (N=18) Geo LS Mean	150 mg Oral Pellet (N=18) Geo LS Mean	Oral Pellet/Oral Capsule GMR	 90% CI of GMR
Day 1				
C_{max} (ng/mL)	67.2	58.0	86.2	(79.2, 93.8)
AUC_{tau} (ng*h/mL)	717.4	656.6	91.5	(83.8, 100.0)
Day 7				
C_{max} (ng/mL)	164.4	150.7	91.7	(86.8, 96.9)
AUC_{tau} (ng*h/mL)	2823.7	2653.7	94.0	(90.0, 98.1)

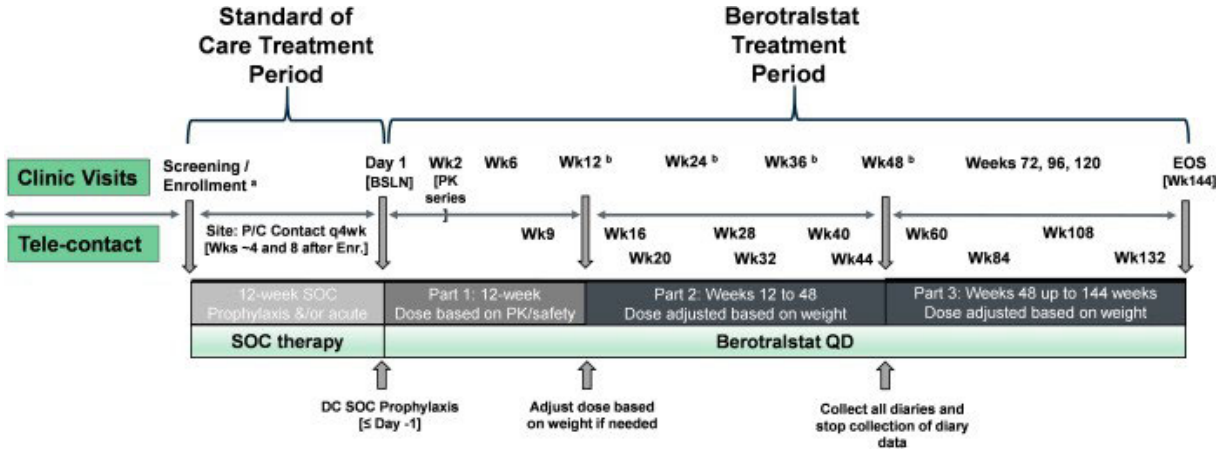
Source. Reviewer's analysis based on adpp.xpt for Trial 114
Abbreviations: AUC_{tau}, area under the plasma concentration-time curve from 0 to the end of the dosing interval; BA, bioavailability; CI, confidence interval; C_{max}, maximum plasma concentration; Geo, geometric; GMR, geometric mean ratio; LS Mean, least-squares mean; N, number of subjects; PK, pharmacokinetic; QD, once daily

6.2.2.2 Trial 304 (Phase 3 Pediatric PK and Safety Trial)

Trial Design

Trial 304 was a phase 3, single-arm, open-label, sequential, 3-part clinical trial in pediatric subjects 2 to <12 years of age and weighing ≥12 kg with HAE. The primary objective was to characterize the PK in pediatric subjects following oral administration of the oral pellet dosage form, with assessments of safety and effectiveness included as secondary objectives. Following a 12-week run-in period during which enrolled participants received standard-of-care (SOC) treatment, subjects received open-label berotralstat treatment for up to a total of 144 weeks in a 3-part treatment period (Figure 2).

Figure 2. Overall Trial Design for Trial 304



Source. CSR for Trial 304 (Figure 1, pg. 27)
Abbreviations: BSLN, baseline; CSR, clinical study report; DC, discontinue; Enr, enrollment; EOS, end of study; P/C, parents and/or caregivers; PK, pharmacokinetic; Q4wk: every 4 weeks; QD, once daily; SOC, standard of care; Wk, week

Participants and primary caregivers were instructed that the pellets were to be swallowed whole and should not be chewed. The pellets were to be either (1) sprinkled on the

participants' tongue and then swallowed with water or milk, or (2) sprinkled over soft non-acidic food in a spoon (up to 15 mL) to aid administration and then consumed immediately. Non-acidic foods permitted for use with the pellets included chocolate pudding, baby food (peas, banana, or carrot), mashed potatoes, or sweet creamed corn. Participants were told to not allow the pellets to sit and/or dissolve in the food and were advised to take each berotralstat dose with food (ideally the largest meal of the day) to help minimize gastrointestinal (GI) effects.

Of note, this trial is currently ongoing. The Agency previously agreed with the Applicant's proposal to ensure that the interim clinical study report (CSR) for Trial 304 included PK data from at least 20 pediatric subjects with a minimum of 15 subjects having completed 48 weeks of berotralstat treatment (Refer to Type C Final Written Response letter under NDA 214094, dated May 8, 2024 [DARRTS Reference ID: 5377575]). These minimum targets have been achieved, as the interim CSR includes PK data for 29 pediatric subjects, of which 17 have completed Part 2 of the trial (i.e., up to 48 weeks of berotralstat treatment).

The trial enrolled male and female pediatric subjects 2 to <12 years of age (inclusive) with body weight ≥12 kg and a clinical diagnosis of HAE. Subjects with moderate to severe hepatic impairment (Child-Pugh B or C) and/or severe renal impairment (estimated glomerular filtration rate [eGFR] ≤30 mL/min/1.73 m^2) were excluded. Additionally, subjects were required to abstain from use of breast cancer resistance protein/ P-glycoprotein (P-gp) inhibitors or inducers, angiotensin-converting enzyme inhibitors, and medications with a narrow therapeutic index that are metabolized by cytochrome P450 (CYP) 2D6 and/or CYP3A4 within 7 days of the Day 1 visit. Participants were permitted to remain on their existing long-term prophylaxis regimens during the SOC period.

Pediatric Dose Selection Rationale

On Day 1 of Part 1, enrolled subjects were assigned to one of four dose cohorts according to their baseline body weight, which is known to be a significant covariate affecting berotralstat systemic exposure (Table7).

Table 7. Dose Cohorts and Weight Bands for Pediatric Subjects (Trial 304[a])

Dose Cohort	Number of Subjects	Patient Weight Band	Berotralstat Dosage
1	7	≥40 kg	150 mg oral capsule once daily[b]
2	9	32 to <40 kg	108 mg oral pellet once daily
3	9	24 to <32 kg	96 mg oral pellet once daily
4	4	12 to <24 kg	78 mg oral pellet once daily

Source. Adapted from Summary of Clinical Pharmacology Trials (Table 3, pg. 13)
[a] Interim CSR includes data through the database cutoff date of September 11, 2024
[b] The 150 mg oral capsule is identical to the commercial product (ORLADEYO), which is approved for adult and pediatric patients 12 years of age and older
Abbreviations: CSR, clinical study report

Initial pediatric dose selection and weight bands were derived using a population PK modeling and simulation approach. A population PK model was previously developed based on thirteen

berotralstat clinical trials conducted in 876 adult and adolescent subjects 12 years of age and older under NDA 214094. This model was used to generate steady-state PK profiles of simulated pediatric subjects for the proposed weight groups of 12 to <24 kg, 24 to <32 kg, 32 to <40 kg, and ≥40 kg, after which pediatric doses were selected with the goal of matching steady state berotralstat exposure (C_{max} and C_{trough}) to that found to be safe and efficacious in adults and adolescents at the approved berotralstat oral capsule dosage of 150 mg QD. For the purposes of berotralstat exposure-matching, C_{trough} was the primary PK parameter associated with efficacy, while C_{max} was the primary PK parameter for safety (due to the known risk of concentration-dependent corrected QT interval [QTc] prolongation).

Dose modifications were permitted throughout the trial based on PK/safety findings and/or changes in patient body weight to maintain pediatric exposure within the adult reference range. For additional details regarding the Applicant's population PK modeling and simulation approach to dose selection, refer to Section 14.3.1.

Subject Disposition and Demographics

A total of 29 subjects were enrolled according to their body weight on Part 1/Day 1, including 7 participants in Cohort 1, 9 participants each in Cohorts 2 and 3, and 4 participants in Cohort 4. As of the interim data cutoff date (September 11, 2024), all subjects had completed Part 1 of the trial (through Week 12), 90% (N=26) had completed all visits through Week 24, and 59% (N=17) had completed all visits through Week 48. Across all cohorts, 14% (N=4) of participants had discontinued the trial, including 10% (N=3) due to perceived lack of efficacy and 3% (N=1) due to withdrawal following lack of berotralstat treatment compliance. A total of 86% (N=25) of enrolled subjects were still ongoing, including 10 and 15 subjects in Part 2 and Part 3, respectively. No subjects in Cohort 4 had completed Part 2 of the trial as of the interim data cutoff date.

A summary of baseline demographics across dose cohorts is provided in Table 8. Overall, enrollment of males and females was approximately even across cohorts (52% and 48%, respectively). The age of the trial population ranged from 3 to 11 years, with the youngest patients enrolled in Cohort 4, and baseline body weight ranged from 14.9 to 69.7 kg across cohorts. Body weight distribution within Cohorts 1, 2, and 3 was generally well-balanced across the range of the respective weight bands. However, given the low enrollment in Cohort 4, the body weights of subjects were slightly skewed towards the mid to upper range of the weight band.

Table 8. Summary of Baseline Demographics (Trial 304, Safety Population)

Demographic Statistic	Cohort 1 (≥40 kg; N=7)	Cohort 2 (32 to <40 kg; N=9)	Cohort 3 (24 to <32 kg; N=9)	Cohort 4 (12 to <24 kg; N=4)
Age (years)				
Mean (SD)	9.9 (1.4)	8.9 (1.5)	8.2 (1.4)	4.5 (1.3)
Median (min, max)	10.0 (8, 11)	9.0 (6, 11)	8.0 (6, 11)	4.5 (3, 6)
Sex				
Male, N (%)	4 (57)	3 (33)	4 (44)	4 (100)
Female, N (%)	3 (43)	6 (67)	5 (56)	0 (0)
Body weight (kg)				
Mean (SD)	55.6 (11.4)	35.2 (2.1)	28.8 (1.4)	18.5 (2.5)
Median (min, max)	53.2 (40.2, 69.7)	35.8 (32.1, 37.8)	28.8 (26.2, 30.2)	19.3 (14.9, 20.4)
BMI (kg/m^2)				
Mean (SD)	24.3 (4.5)	18.9 (2.0)	16.6 (1.2)	14.8 (0.7)
Median (min, max)	23.4 (18.9, 30.9)	17.9 (16.5, 22.5)	16.9 (14.7, 18.6)	14.7 (14.2, 15.6)

Source. Adapted from CSR for Trial 304 (Table 10, pg. 75-76)
Abbreviations: BMI, body mass index; CSR, clinical study report; max, maximum; min, minimum; N, number of subjects; SD, standard deviation

PK Sampling and Analysis

A summary of the plasma PK sampling scheme in Trial 304 is outlined below in Table 9. Based on berotralstat plasma concentration data obtained from the PK population, which consisted of all participants in the safety population who had at least one evaluable and quantifiable post-dose PK sample (N=28), PK parameters were derived using NCA and subsequently compared to those observed in the adult reference population. Of note, PK parameters were not calculated for Cohort 4 due to limited PK sampling per protocol. Berotralstat plasma concentration data from pediatric subjects were also incorporated into the Applicant's longitudinal population PK model, from which PK parameters were calculated and summarized to support the proposed pediatric dosing and weight bands.

Table 9. Plasma PK Sampling Scheme (Trial 304)

Trial Part	Timepoint ID	PK Sampling Scheme[a]
Part 1	Week 2 Trial Visit[b]	Cohorts 1 to 3: Collected pre-dose, then post-dose at 1, 2, 4, and 6 h Cohort 4: Collected pre-dose, then post-dose at 1 to 2 h and 4 to 6 h
Part 2	Weeks 12, 24, 36, and 48	Sparse PK sampling; no specified sampling scheme
Part 1/Part 2[c]	2 to 6 Weeks Following Dose Modification	Collected at 20 to 24 h after the previous dose of berotralstat and another sample 2 to 4 h after taking the modified dose at the clinic

Source. Compiled by reviewer from CSR for Trial 304
[a] PK sample collection was discontinued following the interim data cutoff on September 11, 2024
[b] Reduced PK sampling was performed in Cohort 4 to maintain blood sample volumes within acceptable ranges
[c] PK sampling after dose modifications was implemented following Agency recommendation starting with Protocol Version 3.0
Abbreviations: CSR, clinical study report; h, hour; PK, pharmacokinetic

The adult reference population consisted of adult subjects who were dosed to steady state with the approved berotralstat dosage of 150 mg oral capsule QD and who had serial PK sampling sufficient for NCA. Across all prior clinical trials conducted in adults with berotralstat, PK data

meeting these criteria could be derived from two trials: BCX7353-106 (hereafter referred to as Trial 106) and 116, both of which were phase 1 QTc trials. Across both trials, relevant PK data were available from a total of 50 adult subjects. For the purposes of exposure-matching, the reference range was defined as the 5th to 95th percentile of observed steady state adult PK values. Trial 106 was previously submitted and reviewed as part of the original NDA submission for the prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older under NDA 214094 (Refer to the Interdisciplinary Review Team for Cardiac Safety [IRT-CS] review, dated April 16, 2020 [DARRTS Reference ID: 4592746]). Trial 116 was conducted under IND 135058 but has not been formally reviewed under an NDA submission to date. Refer to Section 14.3.2 for additional details pertaining to the overall design and results of this trial which are relevant to the current NDA submission.

There were three major protocol deviations, all of which involved lack of dosing compliance. One subject in Cohort 2 (b) (6) missed 5 doses in the 2 weeks between baseline and Week 2, which resulted in unreliable plasma concentrations at the Week 2 PK visit. Therefore, plasma concentration data from this participant were excluded from the calculation of summary statistics as well as the NCA and population PK analyses. Another subject (b) (6) missed several doses between Weeks 6 and 12, with an overall treatment compliance of 73%. As a result, the Week 12 concentration for this subject was excluded from consideration to be a trough value. For this same subject, dose modification as required per protocol due to weight increase was not implemented at two consecutive visits (Weeks 12 and 24), during which this participant continued taking 108 mg QD rather than 150 mg QD, thereby potentially resulting in lower berotralstat systemic exposure during this time period.

All plasma samples for determination of berotralstat concentrations were analyzed using a previously validated LC-MS/MS assay (Report (b) (4)), which was previously reviewed and found to be acceptable under NDA 214094 (Refer to the NDA Multidisciplinary Review and Evaluation, dated December 3, 2020 [DARRTS Reference ID: 4711626]). Additionally, the in-trial bioanalysis results for Trial 304 met acceptance criteria.

PK Results

A summary of key berotralstat PK parameters derived for pediatric subjects by baseline dose cohort is provided below in Table 10, along with PK parameters for the reference adult population. Additionally, boxplots comparing berotralstat C_{max}, $AUC_{0\text{-}6h}$, and C_{trough} across Trial 304 pediatric dose cohorts and the adult reference population are displayed below in Figure 3.

Table 10. Observed Pediatric Berotralstat PK Parameters Compared to Adult Reference Range

	PK Parameter					
	$C_{max,ss}$ (ng/mL)[b]		$AUC_{0-6h,ss}$ (ng*h/mL)[c]		$C_{trough,ss}$ (ng/mL)[d]	
Dose Cohort[a]	GeoMean (P5 – P95)	Ratio (Ped:Adults)	GeoMean (P5 – P95)	Ratio (Peds:Adults)	GeoMean (P5 – P95)	Ratio (Peds:Adults)
Cohort 1 (N=7)	271.4 (150 – 453)	1.73	1605 (1320 – 2010)	2.09	114.5 (68.8 – 193)	1.25
Cohort 2 (N=9)	181.1 (128 – 266)	1.15	874.3 (630 – 1420)	1.14	105.6 (61.7 – 253)	1.16
Cohort 3 (N=9)	180.4 (128 – 315)	1.15	911.2 (654 – 1560)	1.19	83.3 (54.9 – 160)	0.91
Cohort 4 (N=4)[e]	NC	NC	NC	NC	88.1 (35.8 – 154)	0.96
Adults (N=50)[f]	156.9 (91.3 – 248)	Reference	768.9 (421 – 1250)	Reference	91.4 (53.8 – 162)	Reference

Source: Adapted from Summary of Clinical Pharmacology Trials (Table 4, pg. 17); Corroborated by reviewer's analysis based on adpc.xpt and adpp.xpt for Trials 304, 106, and 116

[a] Trial 304 enrolled subjects into dose cohorts according to baseline weight as follows: Cohort 1, ≥40 kg; Cohort 2, 32 to <40 kg; Cohort 3, 24 to <32 kg; and Cohort 4, 12 to <24 kg. Data are summarized by cohort at baseline, although participants may have had dose modifications from the dose administered at Week 2

[b] Based on N=7 (Cohort 1), N=8 (Cohort 2), and N=9 (Cohort 3)

[c] Based on N=4 (Cohort 1), N=3 (Cohort 2), and N=8 (Cohort 3)

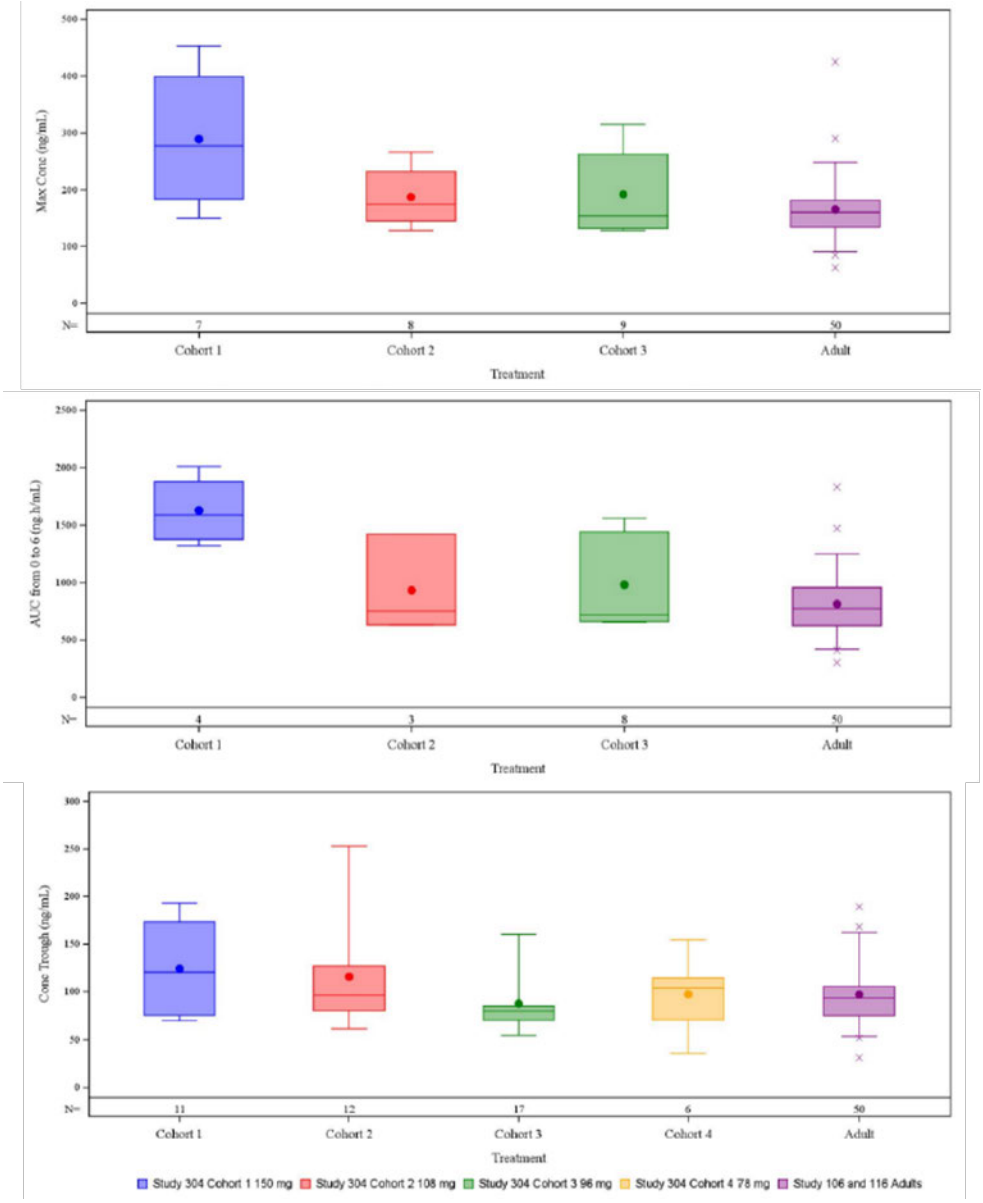
[d] Based on N=11 (Cohort 1), N=12 (Cohort 2), N=17 (Cohort 3), and N=6 (Cohort 4)

[e] Per protocol, reduced PK sampling was performed in Cohort 4, thereby precluding calculation of PK parameters

[f] Adult reference range defined as the 5th to 95th percentiles of observed steady state values derived from Trials 106 and 116 (N=50)

Abbreviations: $AUC_{0-6h,ss}$, area under the plasma concentration-time curve from 0 to 6 hours at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; GeoMean, geometric mean; N, number of subjects; NC, not calculated; P5, 5th percentile; P95, 95th percentile; Peds, pediatrics; PK, pharmacokinetic

Figure 3. Comparison of Observed Berotralstat C_{max} (ng/mL; Top Panel)[a] AUC_{0-6h} (ng*h/mL; Middle Panel)[b], and C_{trough} (ng/mL; Bottom Panel)[c] in Pediatric Patients vs. Adult Reference Population[d,e,f]



Source: Summary of Clinical Pharmacology Trials (Figure 1, pg. 18; Figure 4, pg. 21; Figure 3, pg. 20)
[a] Based on N=7 (Cohort 1), N=8 (Cohort 2), and N=9 (Cohort 3)
[b] Based on N=4 (Cohort 1), N=3 (Cohort 2), and N=8 (Cohort 3)
[c] Based on N=11 (Cohort 1), N=12 (Cohort 2), N=17 (Cohort 3), and N=6 (Cohort 4)
[d] Trial 304 enrolled subjects into dose cohorts according to baseline body weight as follows: Cohort 1, ≥40 kg; Cohort 2, 32 to <40 kg; Cohort 3, 24 to <32 kg; and Cohort 4, 12 to <24 kg; Data are summarized by cohort at baseline, although participants may have had dose modifications from the dose administered at Week 2
[e] Adult reference range defined as the 5th to 95th percentiles of observed steady state values derived from Trials 106 and 116 (N=50)
[f] Boxes represent Q1, median, and Q3 of the distribution. Whiskers represent the 5th and 95th percentile values. The mean is represented by the circle point. Outliers are presented when they exist, and values are higher or lower than the upper and lower whiskers, respectively.
Abbreviations: AUC_{0-6h}, area under the plasma concentration-time curve from 0 to 6 hours; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; N, number of subjects; Q1, Quartile 1; Q3, Quartile 3

Regarding C_{max} and $AUC_{0\text{-}6h}$, observed pediatric values across Cohorts 1, 2, and 3 were consistently higher than those observed in the adult reference population. Most notably, a 73% and 109% higher geometric mean C_{max} and $AUC_{0\text{-}6h}$, respectively, were observed for Cohort 1 relative to the adult population, with the geometric mean pediatric values for both PK parameters falling above the 95th percentile of the adult reference range. Regarding C_{trough}, geometric mean values for Cohorts 1 and 2 were 25% and 16% higher, respectively, than those observed in adults. Conversely, geometric mean C_{trough} values for Cohorts 3 and 4 were 9% and 4% lower, respectively, than those observed in adults. Across all pediatric cohorts, geometric mean C_{trough} fell within the 5th to 95th percentile of the adult reference range.

Dose Modifications

As of the interim data cutoff date, there were a total of twelve dose modifications across eleven subjects. Two subjects in Cohort 1 (b) (6) had a dose reduction from 150 mg to 108 mg due to Week 2 plasma concentrations which were substantially higher than the 95th percentile of adult C_{max} values. There were seven dose increases due to weight gain, including five subjects in Cohort 2 (i.e., 108 mg to 150 mg) and two subjects in Cohort 3 (i.e., 96 mg to 108 mg). One of these subjects (b) (6), whose dose was increased from 108 mg to 150 mg due to weight gain, was subsequently dose reduced back to 108 mg following a treatment-emergent adverse event (TEAE) of Grade 2 affect lability. There were also two dose increases in Cohort 3 (from 96 mg to 108 mg), for which no reason for was recorded for dose modification.

Collection of plasma PK samples following dose modifications was implemented beginning with Protocol Version 3.0. As a result, PK data following dose modification are unavailable for the two subjects in Cohort 1 who received PK-based dose reductions prior to Protocol Version 3.0. Additionally, PK data following dose modifications are unavailable for subject (b) (6) due to a major protocol deviation, and for subjects (b) (6) and (b) (6), as the dose modification PK sampling window for these subjects was after the interim cutoff date of September 11, 2024. Therefore, a summary of berotralstat PK following dose modification for the remaining six subjects, all of whom received dose increases due to weight gain, is provided below in Table 11. Mean berotralstat plasma concentrations following dose modifications were generally comparable to those observed for Cohort 1 at the Week 2 PK visit. This is expected, as most subjects (N=4/6) received the 150 mg capsules after the dose modification.

Table 11. Summary of Plasma Berotralstat Concentrations (ng/mL) Following Dose Modification

		Timepoint (Approximately 2 Weeks Following Dose Modification)	
Cohort	**Statistic**	**20 to 24 h Post-Dose[a]**	**2 to 4 h Post-Dose[b]**
All cohorts	N	6	6
	ArithMean (SD)	135.5 (72.7)	200.0 (100.8)
	GeoMean (CV%)	121.6 (52.3)	179.0 (56.2)

Source. Reviewer's analysis based on adpc.xpt for Trial 304
[a] The 20-to-24-hour post-dose draw was relative to the modified dose taken on the day prior to the clinic visit
[b] The 2-to-4-hour post-dose draw was relative to the dose administered at the clinic visit
Abbreviations: ArithMean, arithmetic mean; CV, coefficient of variation; GeoMean, geometric mean; N, number of subjects; SD, standard deviation

6.2.3 General Dosing and Therapeutic Individualization

General Dosing

The recommended weight-based dosing of berotralstat oral pellet for pediatric subjects 2 to <12 years of age with HAE is outlined below in Table 12.

Table 12. Recommended Weight-Based Dosing of Berotralstat Oral Pellets in Patients 2 to <12 Years of Age With HAE

Weight	Dosage (Oral Pellets)	Administration Instructions
12 to <24 kg	72 mg once daily	Pour directly in mouth and swallow immediately with non-acidic liquid, or sprinkle over 1 tablespoon (15 mL) of non-acidic soft food and consume immediately. A meal should be consumed just before or after administration.
24 kg to <32 kg	96 mg once daily	
32 kg to <40 kg	108 mg once daily	
≥40 kg	132 mg once daily	

Source. Adapted from Applicant's proposed labeling, dated November 26, 2025 (Highlights of Prescribing Information, pg. 1)
Abbreviations: HAE, hereditary angioedema

GI Intolerability

Berotralstat oral pellets should be administered with food, which may help to mitigate GI intolerability associated with oral berotralstat therapy.

Of note, a reduced berotralstat oral capsule dosage of 110 mg QD is currently approved for use in adults and adolescents 12 years of age and older who experience persistent GI adverse events (AEs). However, no dosage adjustment for GI intolerability in pediatric patients 2 to <12 years of age receiving the oral pellet dosage form can be supported based on the totality of available data. Weight-based doses administered to pediatric subjects in Trial 304 aimed to match the exposure achieved in adults who received the 150 mg QD dosage. No dosage adjustments for GI intolerability were evaluated during this trial, so there are no clinical data to suggest that a dosage reduction in these patients would improve any treatment-emergent GI intolerance. Furthermore, since all population PK simulations supporting the proposed pediatric dosing were completed to match the adult 150 mg QD dosage, the available modeling data are inadequate to support that efficacy would be maintained for lower berotralstat oral pellet dosages in children 2 to <12 years of age.

Therapeutic Individualization

The following dose adjustments are recommended based on intrinsic/extrinsic factors:

- Intrinsic Factors
  - Age: No dose adjustment recommended
  - Body Weight: Recommended pediatric dosing is based on body weight; See Section 6.3
  - Renal Impairment: Avoid use in pediatric patients 2 to <12 years of age with severe renal impairment
  - Hepatic Impairment: Use is not recommended for pediatric patients 2 to <12 years of age with moderate or severe hepatic impairment
- Extrinsic Factors
  - Refer to current United States Prescribing Information (USPI) for berotralstat oral capsules

Additional Review Considerations

Bioanalytical Site Inspection by the Office of Study Integrity and Surveillance

A request for a biopharmaceutical inspection of the analytical site for Trial 304 was submitted to the Office of Study Integrity and Surveillance. No objectionable conditions were observed following completion of a remote regulatory assessment. Therefore, the Office of Study Integrity and Surveillance concluded that there are no identified concerns regarding the reliability of data derived from Trial 304 for the consideration of the review division (Refer to Bioequivalence Establishment Inspection Report Review Memorandum, dated July 3, 2025 [DARRTS Reference ID: 5619287]).

Considerations For and Against Weight-Based Dosing in Adolescents 12 to <18 Years of Age

Based on the significant covariate effect of body weight on berotralstat PK, the known concentration-dependent risk for QTc prolongation, and the recommended oral pellet dosage of 132 mg for children 2 to <12 years of age weighing ≥40 kg, the review team considered the suitability of implementing a weight-based dosing paradigm for lower body weight adolescents, particularly those weighing <40 kg. Based on the weight-for-age growth charts from the Centers for Disease Control and Prevention (CDC), a considerable number of U.S. adolescents 12 to <15 years of age are expected to have body weights which are lower than or near 40 kg.[10] However,

[10] US Pediatric Weight-for-Age Growth Charts for Ages 2 to 20; Developed by the National Center for Health Statistics (NCHS) in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) at the CDC (2000); http://www.cdc.gov/growthcharts

following internal discussion across review disciplines, it was ultimately concluded that the currently approved dosing recommendations for adolescents 12 to <18 years of age are most appropriate based on several factors.

First, there was unexplained inter-individual variability in berotralstat PK based on observed PK data derived from Cohort 1 in Trial 304. Specifically, two pediatric subjects received dose reductions from 150 mg oral capsule to 108 mg oral pellets due to substantially higher Week 2 exposures compared to the adult reference range, including the following participants:

- Subject (b) (6) (body weight [BW] of 64.6 kg) had an observed C_{max} of 453 ng/mL, which was the highest concentration observed across all subjects in Trial 304
- Subject (b) (6) (BW of 49.8 kg) had a C_{max} of 399 ng/mL, which was the second-highest C_{max} observed across all subjects in Trial 304

Conversely, Subject (b) (6) (BW of 40.2 kg) had a C_{max} of 150 ng/mL at Week 2. Although this subject had the lowest body weight among those receiving the 150 mg oral capsule, the resulting C_{max} value fell within the adult reference range and was notably lower compared to those observed for subjects (b) (6) and (b) (6). The population PK analyses submitted with the current application clearly demonstrate that body weight is a significant covariate affecting berotralstat exposure and are supportive of the proposed weight-based dosing paradigm for children 2 to <12 years of age based on an exposure-matching approach. However, the observed PK data in Trial 304 suggest that (1) body weight may not adequately explain all of the variability in drug exposure in any given patient, and (2) a subject having lower body weight does not guarantee a higher exposure compared to a subject with higher body weight.

Additionally, in the original NDA submission for berotralstat oral capsules (NDA 214094), population PK analyses included PK data from 16 adolescents from Trials 302 and 204 with body weights ranging from 40.1 to 88.5 kg, which supported the recommendation for no body weight-based dosage adjustment for adolescents 12 to <18 years of age.

Therefore, while is it acknowledged that berotralstat PK is significantly affected by a patient's body weight, there are insufficient PK data available to make a clear recommendation for weight-based dosing in adolescent subjects, especially considering the established safety and efficacy profile of berotralstat 150 mg oral capsule in adolescents based on both observed clinical data and prior population PK analyses under NDA 214094. As a result, no modification of the recommended dosing regimen for pediatric patients 12 years of age and older is recommended.

6.3 Comprehensive Clinical Pharmacology Review

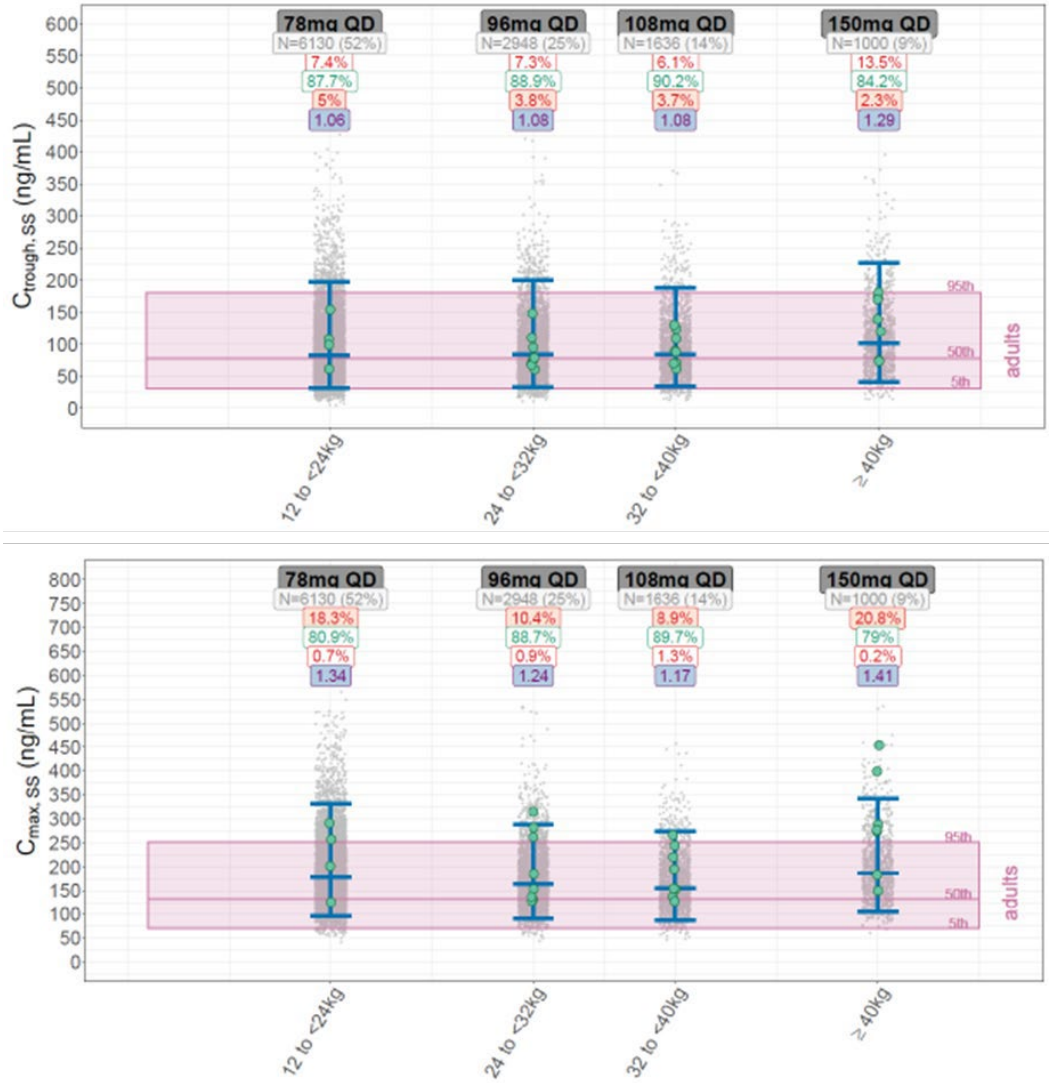
6.3.1 Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Assessment of Initial Dose Selection for Trial 304

Initial pediatric doses for Trial 304 were derived based on an exposure-matching approach using simulations of predicted pediatric berotralstat exposure generated from the Applicant's previously developed population PK model for adults and adolescents. The reference population consisted of adults who received the approved dosage regimen of berotralstat oral capsule 150 mg QD. Briefly, in Trial 304, the observed geometric mean $C_{max,ss}$ for pediatric subjects in Cohorts 1, 2, and 3 exceeded that of the adult population. However, while geometric mean $C_{max,ss}$ for Cohorts 2 and 3 fell within the adult reference range (5^{th} to 95^{th} percentile), geometric mean $C_{max,ss}$ for Cohort 1 exceeded the 95^{th} percentile of the adult population. Regarding $C_{trough,ss}$, observed geometric means for all pediatric cohorts fell within the adult reference range (Refer to Section 6.2.2.2 for detailed discussion of Trial 304 results). After finalizing the population PK model by incorporating the observed pediatric PK data derived from Trial 304, updated simulations were conducted to predict pediatric berotralstat exposure ($C_{trough,ss}$ and $C_{max,ss}$) at the doses administered in Trial 304 (Figure 4).

Figure 4. Final Population PK Model-Predicted Berotralstat $C_{trough,ss}$ (Top Panel) and $C_{max,ss}$ (Bottom Panel) at Dosing Administered in Trial 304



Source: Summary of Clinical Pharmacology Trials (Figure 6, pg. 32)
Note: Red horizontal lines correspond to 5th, 50th, and 95th percentiles of the simulated $C_{trough,ss}$ and $C_{max,ss}$ for adults following steady-state dosing with 150 mg commercial capsule; Grey points correspond to simulated $C_{trough,ss}$ and $C_{max,ss}$ for pediatric patients following the dose levels specified in the grey boxes above each group, which are summarized with 5th, 50th, and 95th percentiles presented in blue; Grey shaded rectangles at the top represent the dosing regimen (oral pellets formulation) for each weight bands; Light grey rectangles summarize the number and percent of simulated values for each weight band; Top red rectangle represents the percent of simulated pediatric values >95th percentile of adults; Green rectangle represents the percent of simulated pediatric values within 5th and 95th percentiles of adults; Lower red rectangle represents the percent of simulated pediatric values <5th percentile of adults; Bottom purple rectangle represents the ratio of 50th percentile of pediatric values to 50th percentile of adults; Green circle symbols represent the observed pre-dose plasma concentrations (i.e., C_{trough}) at Week 2 or the observed C_{max} at Week 2.
Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; N, number of subjects; PK, pharmacokinetic; QD, once daily

Based on the final model, berotralstat systemic exposure for the 96 mg QD and 108 mg QD oral pellet dosages for children weighing 24 to <32 kg and 32 to <40 kg, respectively, align well with the adult reference range. For both weight bands, median $C_{trough,ss}$ is predicted to be

approximately 8% higher in pediatrics compared to adults, with nearly 17% and 24% higher median predicted $C_{max,ss}$ for the 24 to <32 kg and 32 to <40 kg pediatric weight bands, respectively, relative to adults. The 78 mg QD oral pellet dosage showed a 34% higher median predicted $C_{max,ss}$ for pediatrics compared to adults. For Cohorts 2, 3, and 4, all individual observed pediatric $C_{trough,ss}$ values fell within the 5th to 95th percentile of those for the reference adult population. Additionally, no more than 5% of pediatric subjects are predicted to have a $C_{trough,ss}$ below the 95th percentile of adults, supporting maintenance of efficacy at all three dosages/weight bands.

For pediatric subjects weighing ≥40 kg who received berotralstat oral capsule 150 mg QD, median predicted exposure was notably higher than the adult reference range based on both $C_{trough,ss}$ (29%) and $C_{max,ss}$ (41%). Additionally, more than 20% of pediatric subjects at Cohort 1 dosing were predicted to have a $C_{max,ss}$ exceeding the adult 95th percentile. Observed PK data from Trial 304 aligned with these population PK model predictions. Four pediatric subjects in Cohort 1 had $C_{max,ss}$ values exceeding the adult reference range, two of which also exceeded the 95th percentile of observed pediatric values and required PK-based dose reductions. Refer to Section 14.3.1 for details pertaining to the adequacy of the Applicant's population PK model.

This topic was discussed during the pre-NDA meeting held under IND 135058, during which the Applicant sought the Agency's feedback regarding their pediatric dose selection strategy and proposed dosing based on the interim PK data from Trial 304. FDA generally agreed with the Applicant's overall approach for dose selection. Additionally, given that berotralstat carries a risk of concentration-dependent QTc prolongation, the Agency also acknowledged that a lower dose was warranted for subjects with body weight ≥40 kg based on the observed PK data for subjects in Cohort 1 (Refer to the Type B Pre-NDA Meeting Minutes, dated February 13, 2025 [DARRTS Reference ID: 5531320]).

Applicant's Final Pediatric Dose Selection

Based on data derived from Trial 304, the Applicant proposed a weight-based dosing paradigm for berotralstat oral pellets for pediatric subjects 2 to <12 years of age. As with the initial dose selection for Trial 304, the Applicant's final pediatric dose selection was also based on an exposure-matching approach with the adult reference population, for which $C_{trough,ss}$ and $C_{max,ss}$ were the primary PK parameters of interest for efficacy and safety, respectively. Additionally, to permit reliance on observed safety data, the Applicant aimed to ensure that the proposed final dosing was comparable to that administered in Trial 304.

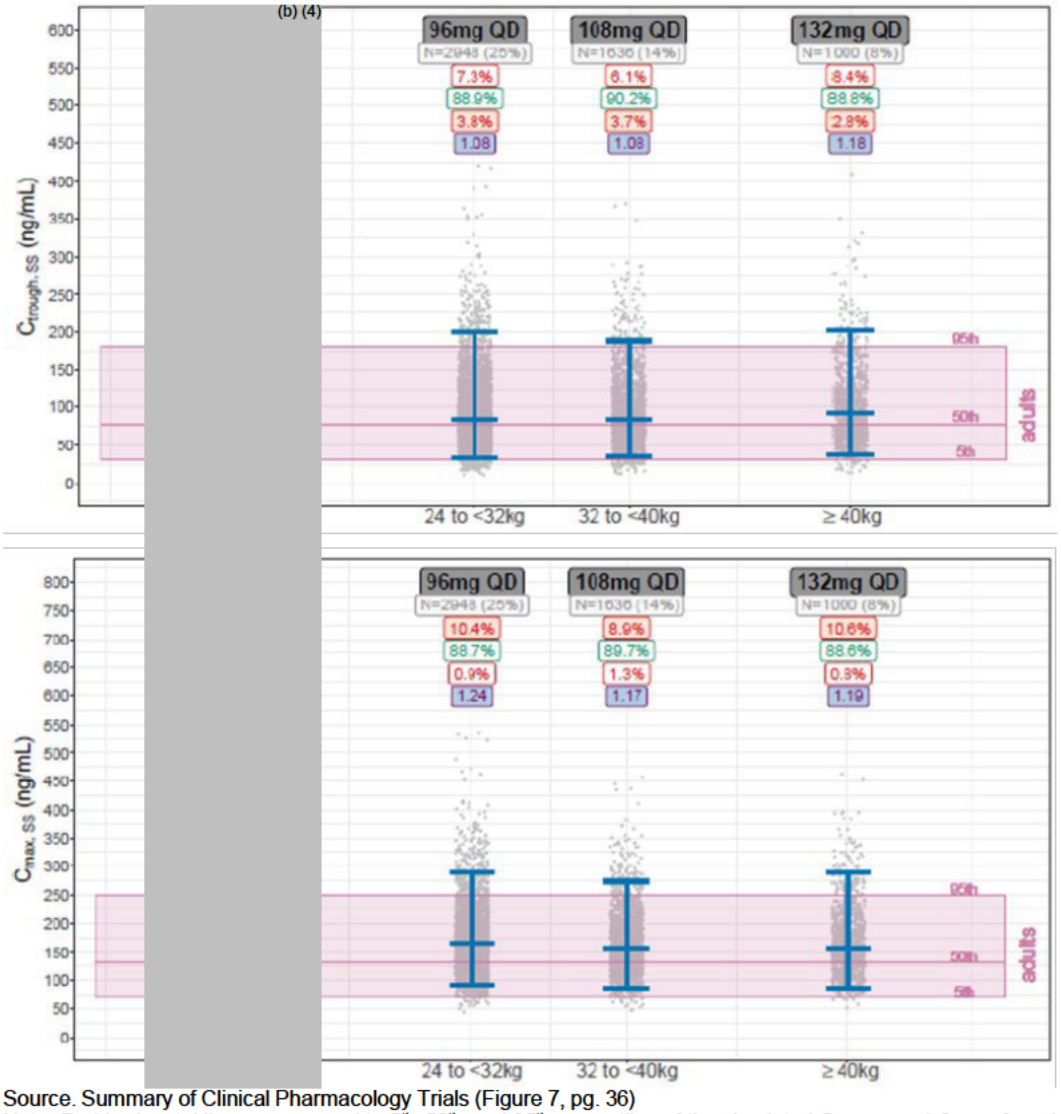
There were two main differences between the Applicant's proposed dosing and that administered in Trial 304:

(1) Berotralstat dose for the highest weight band (≥40 kg) reduced from 150 mg (oral capsule) to 132 mg (oral pellets)

(2) [redacted] (b) (4)

Following incorporation of these changes to the highest and lowest weight bands, the Applicant conducted additional simulations of berotralstat $C_{trough,ss}$ and $C_{max,ss}$ in pediatric subjects using the final population PK model (Figure 5).

Figure 5. Final Population PK Model-Predicted Berotralstat $C_{trough,ss}$ (Top Panel) and $C_{max,ss}$ (Bottom Panel) at Applicant's Proposed Dosing at Time of NDA Submission



Source. Summary of Clinical Pharmacology Trials (Figure 7, pg. 36)
Note: Red horizontal lines correspond to 5th, 50th, and 95th percentiles of the simulated $C_{trough,ss}$ and $C_{max,ss}$ for adults following steady-state dosing with 150 mg commercial capsule; Grey points correspond to simulated $C_{trough,ss}$ and $C_{max,ss}$ for pediatric patients following the dose levels specified in the grey boxes above each group, which are summarized with 5th, 50th, and 95th percentiles presented in blue; Grey shaded rectangles at the top represent the dosing regimen (oral pellets formulation) for each weight bands; Light grey rectangles summarize the number and percent of simulated values for each weight band; Top red rectangle represents the percent of simulated pediatric values >95th percentile of adults; Green rectangle represents the percent of simulated pediatric values within 5th and 95th percentiles of adults; Lower red rectangle represents the percent of simulated pediatric values <5th percentile of adults; Bottom purple rectangle represents the ratio of 50th percentile of pediatric values to 50th percentile of adults
Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; N, number of subjects; NDA, new drug application; PK, pharmacokinetic; QD, once daily

96 mg QD (24 to <32 kg) and 108 mg QD (32 to <40 kg) Dose Levels

Given the general PK alignment with the adult reference range for the 96 mg QD and 108 mg QD berotralstat oral pellet dosage regimens for pediatric subjects weighing 24 to <32 kg and 32 to <40 kg, respectively, these doses and weight bands have remained unchanged from Trial 304 and are reasonable from a clinical pharmacology perspective.

132 mg QD (≥40 kg) Dose Level

For pediatric subjects weighing ≥40 kg, median predicted $C_{trough,ss}$ and $C_{max,ss}$ at the proposed dosage of 132 mg oral pellet QD are approximately 18% and 19% higher, respectively, than the adult reference range. For both PK parameters, approximately 89% of pediatric values are predicted to fall within the adult reference range, representing a largely improved PK alignment relative to the 150 mg oral capsule QD dosage regimen administered in Trial 304. Additionally, less than 3% of children 2 to <12 years of age are predicted to have a $C_{trough,ss}$ below the 5th percentile of adults, thereby providing support that efficacy is maintained at the lower dose of 132 mg oral pellet.

78 mg QD (b) (4) Dose Level

(b) (4)

Furthermore, based on previous Agency review of data derived from the QTc Trial 106, clear QTc prolongation was observed following QD administration of a supratherapeutic berotralstat dose of 450 mg for 14 days, which resulted in a mean plasma C_{max} of ~591 ng/mL (Refer to the IRT-CS review, dated April 16, 2020 [DARRTS Reference ID: 4592746]). Given both (1) the concentration-dependency of QTc prolongation associated with berotralstat treatment and (2) the proximity of the upper range of predicted exposure in pediatric patients weighing 12 to <24 kg and receiving the 78 mg QD dosage (i.e., >500 ng/mL) to the threshold known to cause QTc prolongation in adults, the Agency remained concerned about potential safety risks in this

patient population due to elevated berotralstat exposures, particularly in subjects with body weights falling in the lower range of the weight band. A comprehensive review of the simulated dosing scenarios investigated by the Applicant for various body weight bands and berotralstat dosages, as discussed in the Applicant's Modeling and Simulation Report (BCX7353-MS-002), was completed to identify potential appropriate alternative dosing regimens for these subjects.

A summary of the berotralstat dosages and weight bands which were considered throughout the review cycle, along with the corresponding model-predicted simulated exposures, is provided below in Table 13.

Table 13. Comparison of Simulated Berotralstat Exposures Across Dosing Scenarios Considered for Children 2 to <12 Years of Age and Weighing (b) (4), Using the Final Population PK Model

		PK Parameter					
		$C_{trough,ss}$ (ng/mL)			$C_{max,ss}$ (ng/mL)		
Berotralstat Dose[a]	BW (kg)	Median (P5 – P95)	Ratio (Peds:Adults)	% < Adult P5	Median (P5 – P95)	Ratio (Peds:Adults)	% > Adult P95
150 mg QD	Adults[b]	78 (31 – 180)	Reference	Reference	133 (70 – 251)	Reference	Reference
							(b) (4)
78 mg QD	12 to <24	83 (31 – 198)	1.06	5.0	178 (96 – 331)	1.34	18.3
	15 to <24	80 (31 – 188)	1.02	5.5	168 (93 – 304)	1.26	13.0
72 mg QD	12 to <24	77 (29 – 182)	0.99	6.1	164 (88 – 306)	1.23	13.3
66 mg QD	12 to <24	70 (27 – 167)	0.90	7.9	150 (81 – 280)	1.13	8.5

Source: Compiled by reviewer based on Summary of Clinical Pharmacology Trials (Table 9, pg. 35), Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 22, pg. 237), and Applicant's response to Agency request for information, dated October 14, 2025 (Table 1, pg. 4)
[a] 150 mg QD given as commercial oral capsule dosage form; All other doses (78 mg, 72 mg, and 66 mg QD) represent administration as the oral pellet dosage form
[b] Adult reference range defined as the 5th to 95th percentiles of observed steady state values derived from Trials 106 and 116 (N=50)
Abbreviations: BW, body weight; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; N, number of subjects; P5, 5th percentile; P95, 95th percentile; PK, pharmacokinetic; QD, once daily

For pediatric patients weighing 12 to <24 kg and receiving the lower 72 mg QD and 66 mg QD oral pellet doses, 13.3% and 8.5% of subjects would have predicted $C_{max,ss}$ exceeding the adult reference range, respectively, compared with more than 18% for 78 mg QD. Similarly, the median predicted $C_{max,ss}$ would be up to 23% and 13% higher at these respective doses, compared to up to 34% higher for the Applicant's proposed dose of 78 mg QD. Regarding efficacy considerations, although median predicted $C_{trough,ss}$ is slightly lower for the 72 and 66-mg doses (0.99- and 0.9-fold lower compared to adult reference range, with 6.1 and 7.9% falling below the adult 5th to 95th percentile, respectively), maintenance of efficacy is justifiable given that a lower dosage of 110 mg QD was approved for use in adults experiencing persistent GI intolerability. Given these considerations, the Agency strongly recommended that the Applicant consider a lower berotralstat dosage of either 66 mg QD or 72 mg QD for pediatric

patients weighing 12 to <24 kg (Refer to the Advice/Information Request, dated October 7, 2025 [DARRTS Reference ID: 5672778].

(b) (4)

(b) (4) Therefore, the Agency recommended maintaining the 12 to <24 kg weight band with a reduction of the recommended oral pellet dosage to 72 mg QD.

Final Recommended Dosing of Berotralstat Oral Pellets in Children 2 to <12 Years of Age

The predicted berotralstat exposure in children 2 to <12 years of age at the final proposed dosing compared to the adult reference range is summarized below in Table 14. Overall, median predicted $C_{max,ss}$ is predicted to be up to 24% higher for pediatric subjects weighing 24 to <32 kg and receiving the 96 mg QD oral pellet dosage compared to adults, although this increased exposure is justifiable based on the totality of available data.

Per the current USPI, a 47% increase in berotralstat C_{max} was observed in adults with severe renal impairment, which was not considered clinically meaningful.[11] Furthermore, based on population PK modeling and simulation, adolescents (weighing 40 to 71 kg) were predicted to have approximately 38% and 29% higher C_{max} and AUC, respectively, compared to normal-weight adults (weighing 80 to 100 kg) at the approved berotralstat oral capsule dosage of 150 mg QD (Refer to the NDA Multidisciplinary Review and Evaluation dated December 3, 2020 [DARRTS Reference ID: 4711626]). In both cases, no dose adjustment was recommended, suggesting that the potential increase in C_{max} of up to 24% in pediatric subjects is within acceptable safety margins. This is further supported by the absence of any observed QTc prolongation or other cardiac abnormalities across all dose cohorts in Trial 304.

[11] Refer to the United States Prescribing Information (USPI) for ORLADEYO (berotralstat) oral capsules, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/214094s003lbl.pdf

Table 14. Simulated Berotralstat $C_{trough,ss}$ and $C_{max,ss}$ for Pediatric Subjects 2 to <12 Years of Age Relative to Adult Reference Range Using the Final Population PK Model (Final Proposed Dosing)

		PK Parameter					
		$C_{trough,ss}$ (ng/mL)			$C_{max,ss}$ (ng/mL)		
Berotralstat Dose[a]	BW (kg)	Median (P5 – P95)	Ratio (Peds:Adults)	% < Adult P5	Median (P5 – P95)	Ratio (Peds:Adults)	% > Adult P95
150 mg QD	Adults[b]	78 (31 – 180)	Reference	Reference	133 (70 – 251)	Reference	Reference
132 mg QD	≥40	92 (38 – 202)	1.18	2.8	158 (87 – 290)	1.19	10.6
108 mg QD	32 to <40	84 (35 – 188)	1.08	3.7	156 (87 – 274)	1.17	8.9
96 mg QD	24 to <32	84 (33 – 200)	1.08	3.8	165 (91 – 289)	1.24	10.4
72 mg QD	12 to <24	77 (29 – 182)	0.99	6.1	164 (88 – 306)	1.23	13.3

Source. Compiled by reviewer based on Applicant's response to Agency request for information, dated October 14, 2025 (Table 1, pg. 4)
[a] 150 mg QD given as commercial oral capsule dosage form; All other doses (132, 108, 96, and 72 mg QD) given as oral pellet dosage form
[b] Adult reference range defined as the 5th to 95th percentiles of observed steady state values derived from Trials 106 and 116 (N=50)
Abbreviations: BW, body weight; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; N, number of subjects; P5, 5th percentile; P95, 95th percentile; PK, pharmacokinetic; QD, once daily

Additionally, regarding the lowest weight band of 12 to <24 kg, according to the weight-for-age growth charts from the CDC, the 3rd to 97th percentiles of expected body weight for 2-year-olds in the United States are approximately 10.4 to 15.7 kg and 10.0 to 15.1 kg for boys and girls, respectively.[10] Based on these data, the majority of the youngest U.S. children are expected to have a body weight within 5 kg of the lowest body weight pediatric subject enrolled in Trial 304, supporting the applicability of the observed data to the expected real-world patient population.

Given these considerations, the final proposed dosing for children 2 to <12 years of age is acceptable from a clinical pharmacology perspective. Refer to Section 8.3 for additional discussion of the supportive pediatric safety data available from Trial 304. Refer to Section 14.3.1 for details pertaining to the adequacy of the Applicant's population PK model.

Are the proposed dose adjustments based on intrinsic/extrinsic factors reasonable?

Age/Body Weight

Based on population PK analyses, age was not identified as a significant covariate affecting berotralstat PK. All differences in observed berotralstat exposure between the adult/adolescent and pediatric populations are explained by differences in body weight, which was identified as a statistically significant modifier of berotralstat PK.

- Therefore, no dose adjustment is recommended based on age and the Applicant has proposed a weight-based dosing paradigm for pediatric subjects 2 to <12 years of age with HAE receiving berotralstat oral pellets (Table 12; Section 6.2.3).

Renal Impairment

Berotralstat has not been evaluated in pediatric subjects 2 to <12 years of age with any degree of renal impairment. In adults with severe renal impairment, berotralstat C_{max} was increased by 47% compared to those with normal renal function, which was not considered clinically meaningful and for which no dose adjustment was recommended.[11] However, given that pediatric subjects are predicted to have up to a 24% higher C_{max} compared to adults at the proposed berotralstat oral pellet dosing, the clinical relevance of the potential additional increase in berotralstat systemic exposure in the setting of severe renal impairment is unknown. Therefore, it is recommended to avoid use of berotralstat in pediatric patients 2 to <12 years of age with severe renal impairment.

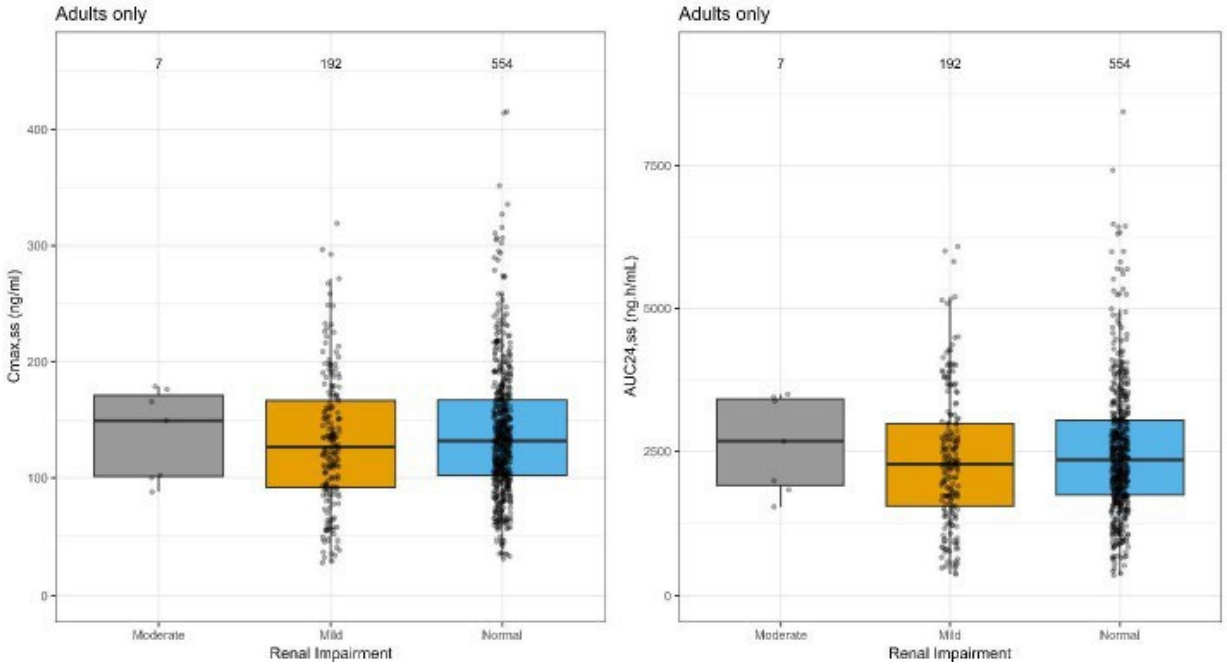
The impact of mild and moderate renal impairment on berotralstat PK was not studied in adults, although a total of 23 and 2 adult HAE patients with mild and moderate renal impairment, respectively, were enrolled across two long-term prophylactic trials (Trials 204 and 302). The safety profile in these 25 subjects was similar to that of the overall trial population (Refer to the NDA Multidisciplinary Review and Evaluation, dated December 3, 2020 [DARRTS Reference ID: 4711626]).

The potential impact of renal impairment on berotralstat systemic exposure was also assessed using population PK modeling, which included a total of 199 subjects with renal impairment, comprising 192 adults with mild renal impairment (eGFR 61 to 89 mL/min/1.73m^2) and 7 adults with moderate renal impairment (eGFR 49 to 59 mL/min/1.73m^2). According to the final model, baseline eGFR was not identified as a statistically significant covariate affecting apparent clearance of berotralstat. As shown below in Figure 6 and Table 15, there is large degree of overlap in predicted $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ between mild renal impairment, moderate renal impairment, and normal renal function subjects. Specifically, for mild renal impairment, the predicted geometric mean $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ were 7% and 9% lower, respectively, relative to normal renal function. For moderate renal impairment, the predicted geometric mean $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ were 3% and 10% higher, respectively, compared to normal renal function.

Furthermore, per the current USPI, urinary excretion of berotralstat following oral dosing is low (approximately 9%), providing additional support that impaired renal function is unlikely to result in a clinically significant increase in systemic exposure.[11]

Therefore, based on the totality of available data, the Applicant's proposal to permit dosing in pediatric subjects with mild to moderate renal impairment is considered acceptable.

Figure 6. Boxplots of Estimated $C_{max,ss}$ (Left Panel) and $AUC_{0\text{-}24h,ss}$ (Right Panel) Based on Individual PK Parameters Derived From the Final Population PK Model, Stratified by Renal Impairment Category[a]



Source. Applicant's response to Agency request for information, dated May 22, 2025 (Figure 2, pg. 8)
[a] Estimated PK parameters assuming administration of the approved berotralstat oral capsule dosage of 150 mg QD
Abbreviations: $AUC_{0\text{-}24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours; $C_{max,ss}$, maximum plasma concentration at steady state; PK, pharmacokinetic; QD, once daily

Table 15. Summary of Estimated $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ Based on Individual PK Parameters Derived From the Final Population PK Model, Stratified by Renal Impairment Category[a]

		Renal Function Group		
Parameter		**Normal Renal Function**	**Mild Renal Impairment**	**Moderate Renal Impairment**
N		554	192	7
Range of baseline eGFR (mL/min/1.73m^2)		90 – 177	61 – 89	49 – 59
$C_{max,ss}$ (ng/mL)[b]		128 (42.7)	119 (51.3)	132 (30.9)
$AUC_{0\text{-}24h,ss}$ (ng*h/mL)[b]		2260 (49.9)	2060 (62.3)	2500 (35.3)
GMR	$C_{max,ss}$	Reference	0.93	1.03
	$AUC_{0\text{-}24h,ss}$	Reference	0.91	1.10

Source. Adapted from Applicant's response to Agency request for information, dated May 22, 2025 (Table 2, pg. 7)
[a] Estimated PK parameters assuming administration of the approved berotralstat oral capsule dosage of 150 mg QD
[b] Reported as geometric mean (CV%)
Abbreviations: $AUC_{0\text{-}24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours; $C_{max,ss}$, maximum plasma concentration at steady state; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; GMR, geometric mean ratio; N, number of subjects; PK, pharmacokinetic; QD, once daily

Hepatic Impairment

Berotralstat has not been evaluated in pediatric subjects 2 to <12 years of age with any degree of hepatic impairment. In adults with mild hepatic impairment, berotralstat PK was unchanged compared to those with normal hepatic function. In adults with moderate hepatic impairment,

C_{max} and AUC_{inf} were 77% and 78% higher, respectively, whereas in subjects with severe impairment, C_{max} was increased by 27%, while AUC_{last} was decreased by 5%.[11] Given that pediatric subjects are predicted to have up to a 24% higher C_{max} compared to adults at the proposed berotralstat oral pellet dosing, the clinical relevance of the potential additional increase in berotralstat systemic exposure in the setting of moderate to severe hepatic impairment is unknown.

- Therefore, use of berotralstat is not recommended for pediatric patients 2 to <12 years of age with moderate or severe hepatic impairment.

The proposed dosage adjustments based on intrinsic/extrinsic factors are reasonable from a clinical pharmacology perspective.

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Trials

The sources of the clinical data used in this review are summarized in Table 16.

Table 16. Listing of Clinical Trials Relevant to this NDA

Trial Identifier	Trial Design	Treatment Regimen (Weight)	Trial Endpoints	No. of Subjects	Trial Population	No. of Centers/Countries
Phase 3 Trial to Support Efficacy and Safety						
Trial BCX7353-304 NCT # 05453968	Open label, single arm	• 150 mg capsule daily (≥40 kg) • 108 mg oral pellets (32 to <40 kg) • 96 mg oral pellets (24 to <32 kg) • 78 mg oral pellets (12 to <24 kg)	Safety, PK, # HAE attacks Efficacy (descriptive)	29	2 to <12 years of age	11/Austria, Canada, France, Germany, Israel, Italy, Poland, Spain, and the United Kingdom

Source: CSR table 2, pg. 15
Abbreviations: CSR, clinical study report; NCT, national clinical trial number; NDA, new drug application; HAE, hereditary angioedema; PK, pharmacokinetics

The Applicant also submitted the results (b) (4) (b) (4) (b) (4) The Division did not review this trial as it was not directly applicable to this pediatric efficacy supplement.

7.2 FDA Review Strategy

This NDA contains one clinical trial (Trial 304) evaluating PK and safety, with descriptive efficacy and exploratory palatability assessments in subjects 2 to <12 years of age. Palatability outcomes were not reviewed, other than if they pertained to safety/compliance. The clinical review was conducted by one primary clinical reviewer and one statistical reviewer. Trial 304 was designed to provide PK to support pediatric efficacy extrapolation and safety to support partial extrapolation of safety from adults. Trial 304 was not designed to assess efficacy in the pediatric population 2 to <12 years of age; however, descriptive effectiveness was summarized as a secondary objective and included measures similar to those measured in the adult population.

For the evaluation of safety, FDA medical officer Dr. Diana Nichols-Vinueza analyzed data from Trial 304 using JMP, JMP Clinical, and Analysis Studio. The safety results presented in Section 8.3 represent the medical office reviewer's own analyses.

8 Clinical and Statistical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Trial 304

8.1.1.1 Administrative Information

- Trial 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.
- Trial Dates: First participant screened: October 4, 2022; database lock for interim analysis: October 1, 2024.
- Trial Sites: Austria, Canada, France, Germany, Italy, Israel, Poland, Spain, and the United Kingdom.
- Trial Report Date: January 27, 2025

8.1.1.2 Objectives

Primary Objective

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

Exploratory Objective

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

8.1.1.3 Trial Design

This was a sequential, 3-part, open-label, uncontrolled, multicenter trial to evaluate the PK, safety, and effectiveness of berotralstat in participants with HAE who were 2 to <12 years of age at enrollment. Participation in this trial was expected to be a minimum of 12 weeks in the SOC period, 12 weeks on berotralstat in Part 1 of the trial, and up to an additional 132 weeks in Parts 2 (Week 13-48) and 3 (Week 40 up to 144 weeks). The trial design is outlined in Figure 2, and the schematic of trial visits is shown in Table 17.

Table 17. Schedule of Assessments (Trial 304)

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]	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 ± 1Wk	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/ coagulation[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				
HAE therapy														
• SOC	X	X												
• Berotralstat				X	X	X	X	X[x]	X	X	X	X	X	
Acceptability/palatability assessment[y]				X										
AEs	X	X		X	X	X	X	X	X	X	X	X	X	X[z]
Concomitant medications	X			X	X	X	X	X	X	X	X	X	X	X

Source: Trial Report Body: Table 3 (pg. 30-31)

[a] Participants who discontinued berotralstat either at the Week 144 visit or earlier were required to attend an EOS follow-up visit 3 weeks (±3 days) after trial intervention discontinuation. Participants who discontinued the trial but continued to receive berotralstat via another mechanism had EOS assessments performed at their last regularly scheduled visit.

[b] Screening assessments were conducted at the screening visit although, if necessary, the assessments may have taken place over a screening period not to exceed 14 days without prior consent of the sponsor. Participants were considered enrolled into the trial as of the date of the screening visit if all available results satisfied the inclusion and exclusion criteria as of that date. If, after the screening visit, screening results were returned that indicated the participant no longer met the inclusion and exclusion criteria, the participant was considered a screen failure.

[c] The Day 1 visit occurred 12 weeks ±4 days after enrollment. If extenuating circumstances prevailed, this timeframe may have been extended with medical monitor approval (see Section 9.3.1 of the Protocol, Appendix 16.1.1).

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

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

The SOC period served as a control for safety assessments and provided additional data regarding baseline attack rates in the patient population to inform descriptive efficacy assessment. During the SOC period, patients received their SOC, which could include short or long-term prophylaxis therapy. Open-label oral QD berotralstat was initiated after the SOC period and continued for up to 144 weeks. Specific administration instructions were included (see Section 6.2.2.2). The dose remained static for the first 12 weeks (Part 1) and could be adjusted based on weight changes thereafter. Symptom diaries were collected through Week 48 (end of Part 2). On-demand acute treatment was available throughout the trial.

Participants were assigned into weight-based dosing cohorts (Table 7). Cohorts 1 and 2 were enrolled in parallel. After 4 participants from either Cohort 1 and/or 2 completed the Week 2 visit, population PK modeling was used to verify doses for subsequent cohorts. Cohort 3 enrollment began after at least 4 participants from the first two cohorts (including at least 2 participants from Cohort 2) had completed 2 weeks of treatment. Cohort 4 was opened for enrollment and the 12-week SOC phase was initiated after at least 4 participants in Cohort 3 had reached Week 2. PK modeling from all available PK data to confirm the dose and weight band for the cohort, and safety assessments, were reviewed by the Applicant and Data Monitoring Committee prior to dosing participants in Cohorts 3 and 4 with berotralstat.

An interim analysis was planned after at least 15 participants completed 48 weeks of treatment (through Part 2). The Applicant submitted an interim CSR using interim locked data (database cutoff date: September 11, 2024) to support the regulatory filing of berotralstat for prophylaxis to prevent attacks of HAE in patients 2 to <12 years of age. Effectiveness data were not collected after Week 48.

8.1.1.4 Trial Population

The trial population included pediatric subjects aged 2 to <12 years of age with a confirmed clinical diagnosis of HAE and a minimum baseline attack rate of ≥2 HAE attacks in the 6 months prior to enrollment for participants who were not receiving prophylaxis for HAE. For patients receiving prophylaxis for HAE, no minimum baseline attack rate was required for enrollment.

Key Inclusion Criteria

- Children (male or female) 2 to <12 years of age at screening.
- HAE diagnosis based on:
  - 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 C4 level below the LLN reference range.
  - For participants 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 1 or 2, as assessed during the screening period OR a repeat C1-INH functional level <50% was considered acceptable for enrollment.
  - Historical or new laboratory documentation of a SERPING-1 mutation.
  - For participants who currently used 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.

Key Exclusion Criteria

- Concurrent diagnosis of any other type of recurrent angioedema.
- Significant cardiac disease or known family history of sudden cardiac death at a young age (<40 years of age).
- Moderate to severe hepatic impairment (Child-Pugh B or C).
- History of severe hypersensitivity to multiple medicinal products or severe hypersensitivity/anaphylaxis with unclear etiology.

Key Subject Discontinuation Criteria

A subject was discontinued from the trial drug for any of the following reasons, which was recorded in the source documents and the electronic case report form:

- Emergence of any laboratory abnormality or AE that in the judgment of the investigator compromised the ability of the subject to continue trial-specific procedures or altered the subject's benefit-risk profile such that it was considered not to be in the subject’s best interest to continue.
- Confirmed ALT or AST elevation as follows: greater than eight-fold the ULN; greater than five-fold the ULN for >2 weeks; greater than three-fold the ULN and a total bilirubin level greater than two-fold the ULN; and greater than three-fold the ULN if accompanied by

fatigue, nausea, vomiting, right upper quadrant pain and tenderness, fever, rash and/or eosinophilia (>5%).

- Subject noncompliance with the trial drug or the trial protocol.
- A Fridericia-corrected QT interval (QTcF) of >500 ms (confirmed on repeat electrocardiogram [ECG] testing).

The proposed inclusion, exclusion, and subject discontinuation criteria are considered acceptable and align with established criteria utilized in previous clinical trials of approved HAE therapeutic products and the pivotal adult berotralstat Trial 302.

The specified minimum attack frequency threshold in the eligibility criteria appropriately identifies a target patient population with clinically significant disease burden that would warrant consideration for prophylactic therapeutic intervention.

8.1.1.5 Treatment

Participants remained on their SOC regimen for the first 12 weeks of the trial (SOC period). All SOC medications taken during the trial were recorded on the case report form.

Beginning on Day 1, participants were to take open-label berotralstat orally daily for 12 weeks in Part 1, for 36 weeks in Part 2 (Weeks 13 to 48), and for up to an additional 96 weeks in Part 3 (i.e., through Week 144).

Berotralstat was supplied as either 150 mg capsules (identical to commercial product) or pellets (78, 96, or 108 mg) for oral administration. Dosage schedule is provided in Table 12. Dose modifications were allowed throughout the trial for safety and/or PK reasons and in Parts 2 and 3 based on increased weight.

Concomitant medications:

- Allowed: therapies for co-existing conditions, treatment for acute HAE attacks (including C1-INH for acute attack therapy, but not for long term prophylaxis), treatment for short-term HAE prophylaxis, therapies to treat any AEs.
- Prohibited:
  - Angiotensin-converting enzyme inhibitors within 7 days of the baseline visit or planned initiation during the trial.
  - Another investigational drug within 30 days of the screening visit or initiation during the trial.
  - Daily use of concomitant medications with a narrow therapeutic index that are metabolized by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine,

fentanyl) within 7 days of the baseline visit or planned initiation of such medications during the trial.

- Chronic administration of P-gp or breast cancer resistance protein inhibitors (e.g., cyclosporine).
- Any use of P-gp inducers (e.g., rifampin, St. John's wort)

8.1.1.6 Trial Endpoints

Primary Endpoints

- Characterization of the PK profile of berotralstat in participants aged 2 to <12 years.

Secondary Endpoints

- Safety: The frequency and severity of AEs and serious adverse events (SAEs), laboratory analyses (clinical chemistry, hematology, coagulation), height, weight, vital signs, ECGs, and findings from physical examinations.
- Efficacy
  - The frequency (number and rate) of HAE attacks
  - Duration of symptoms
  - Anatomical location
  - Number and proportion of attacks requiring on-demand treatment
  - Number and proportion of days with angioedema symptoms
  - Assessment of attack severity
  - Discontinuation due to lack of efficacy
  - Number of hospitalizations and clinic visits from Week 1 through Weeks 12 and 48

Secondary efficacy endpoints utilized investigator-confirmed attacks and adjusted attacks as the primary assessment criteria, rather than patient-reported attacks. This methodology aligns with established practices in other HAE clinical development programs and ensures that only verified swelling episodes are classified as distinct HAE attacks, thereby excluding prodromal symptoms or instances of pre-emptive rescue medication administration.

Exploratory Endpoints

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

8.1.1.7 Safety Assessments

Safety monitoring included recording frequency and severity of AEs and SAEs, physical exams, vital signs (temperature, heart rate, blood pressure, respiratory rate), clinical laboratory tests (hematology, chemistry, liver function tests, coagulation, urinalysis, pregnancy) and 12-lead ECG according to the schedule in Table 17.

8.1.1.8 Statistical Analysis Plan

Sample Size

No formal sample size calculation was performed. The trial was 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 was considered adequate to evaluate PK and to describe safety and tolerability. The sample size was selected based on feasibility considerations, however, with 30 subjects enrolled in the trial, there was approximately a 96% chance of observing at least 1 TEAE that occurred 10% of the time. Formal inferential testing of effectiveness and safety endpoints was not planned.

Analysis Populations

All clinical outcome analyses were based on the safety population, which was defined as all subjects who received any dose of berotralstat. The safety population included all subjects who received at least 1 dose of berotralstat. This population was used for all analyses of accountability, demographics, berotralstat drug dosing, effectiveness, compliance, and safety.

Effectiveness Endpoints

- Frequency (number and rate) of HAE attacks
- Duration of symptoms
- Anatomical location
- Number and proportion of attacks requiring on-demand treatment
- Number and proportion of days with angioedema symptoms
- Assessment of attack severity
- Discontinuation due to lack of efficacy
- Number of hospitalizations and clinic visits from Week 1 through Weeks 12 and 48

Interim Analyses

Data summaries were provided to the Data Monitoring Committee. Interim analyses of PK, safety and effectiveness data were conducted after at least 15 subjects completed 48 weeks of

treatment (through Part 2) using interim locked data. Effectiveness data were not collected after the Week 48 visit. Safety and dosing tables for the end of 48-week analysis only included data through the Week 48 visit.

8.1.1.9 Compliance With Good Clinical Practices

A statement of compliance with Good Clinical Practice is in the CSR.

8.1.1.10 Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators as recommended in the guidance for industry "Financial Disclosure by Clinical Investigators" (see Section 14.1).

8.2 Trial Results

8.2.1 Protocol Amendments

Trial 304 was initiated at non-U.S. sites in October 2022 and was fully enrolled outside the United States and prior to FDA protocol review as of January 2024. The protocol underwent 5 global amendments and 4 country-specific amendments (Canada, Germany, UK and Italy) during the trial. The Sponsor submitted 3 versions of the protocol to the Agency: version 5 (June 24, 2024), 6 (September 4, 2024) and 7 (November 12, 2024).

The Agency reviewed Trial 304 protocol version 5 in a Type C Written Responses Only meeting (issued May 8, 2024; full protocol review, dated July 8, 2024). The Agency issued an Advice/Information Request letter on the protocol on July 9, 2024, requesting to include the SERPING-1 mutation information for each subject where available given that all patients were already enrolled. The clinical team reviewed all versions of the protocol, including the final version (7.0) submitted on November 12, 2024. The Sponsor adequately addressed the Division's recommendations, and the Division agreed with the pediatric protocol. The study was fully enrolled with patients outside the United States prior to FDA review. Modifications to the protocol based on FDA feedback were non-substantial and did not impact the trial interpretation.

8.2.2 Protocol Deviations

Protocol deviations were collected at both the site and subject level. After Applicant review of the major deviations, 5 important protocol deviations were identified in 4 participants (14%):

- One participant missed 5 doses in the 2 weeks between baseline and week 2, resulting in trial intervention compliance of 64%.
- Another participant had 73% dose compliance during the Weeks 6 through 12 trial period. Dose modification required by protocol due to weight increase was not enacted at 2 consecutive visits (Weeks 12 and 24).
- In two participants, the parent-guardian inform consent form was signed by only 1 parent prior to screening.

A minor protocol deviation occurred in which the activated partial thromboplastin time was not measure for any sample received by the central laboratory prior May 8, 2024.

8.2.3 Efficacy

8.2.3.1 Patient Disposition

A total of 32 participants were screened, of which 29 participants were enrolled at 11 sites located in 9 countries: 19 participants were enrolled in the EU (Austria, France, Germany, Italy, Poland, and Spain), 5 participants in the UK, 3 participants in Canada, and 2 participants in Israel. Of the 32 screened participants, 3 participants failed screening; 2 participants withdrew consent prior to the Day 1 visit, and 1 participant did not meet weight requirements for the available open cohort. None of the participants failed screening due to an inability to meet the inclusion/exclusion criteria.

All 29 enrolled participants received berotralstat. At the time of the interim data cutoff date, all 29 enrolled participants (100%) completed Part 1 of the trial (through Week 12), 26 participants completed all visits through Week 24, and 17 participants (59%) completed Part 2 of the trial (through Week 48). A total of 25 participants (86%) were still ongoing in the trial, including 10 participants in Part 2 and 15 participants in Part 3. Across all cohorts, 4 participants (14%) had discontinued the trial, including 3 participants (10%) due to perceived lack of efficacy and 1 participant (3%) due to withdrawal by participant on Day 195 following lack of compliance with prescribed dosing. Of the 3 participants who discontinued due to perceived lack of efficacy, 2 participants discontinued after Week 48. No Cohort 4 participants have yet completed Part 2 of the trial (through Week 48). See Table 18 for additional details.

Table 18. Trial Disposition by Treatment Group (Trial 304)

Parameter	Cohort 1[a]: (150 mg Capsules) (N=7)	Cohort 2[a]: (108 mg Pellets) (N=9)	Cohort 3[a]: (96 mg Pellets) (N=9)	Cohort 4[a]: (78 mg Pellets) (N=4)	Total[b] (N=29)
Participants screened (%)	-	-	-	-	32 (100)
Participants screen failed (%)	-	-	-	-	3 (9)
Did not meet Inclusion Criteria/met Exclusion Criteria (%)	-	-	-	-	0
Participant's consent withdrawn (%)	-	-	-	-	8 (25)
Other (%)	-	-	-	-	1 (3)
Intent-to-treat population (%)	7 (100)	9 (100)	9 (100)	4 (100)	29 (100)
Safety population (%)	7 (100)	9 (100)	9 (100)	4 (100)	29 (100)
Week 12 (Part 1) completer population (%)	7 (100)	9 (100)	9 (100)	4 (100)	29 (100)
Part 2 ongoing (%)	0	1 (11)	5 (56)	4 (100)	10 (35)
Week 48 (Part 2) completer population (%)	7 (100)	6 (67)	4 (44)	0	17 (59)
Participants discontinued after Week 48 (%)	1 (14)	1 (11)	0	0	2 (7)
Part 3 ongoing (%)	6 (86)	5 (56)	4 (44)	0	15 (52)
Participants ongoing (%)	6 (86)	6 (67)	9 (100)	4 (100)	25 (86)
Participants completed trial (%)	0	0	0	0	0
Participants with early discontinuation (%)	1 (14)	3 (33)	0	0	4 (14)
Withdrawn due to AE (%)	0	0	0	0	0
Withdrawal by participant (%)	0	1 (11)	0	0	1 (3)
Perceived lack of efficacy (%)	1 (14)	2 (22)	0	0	3 (10)

Source: Trial report body, table 9, pg. 70-71
Note: "All Participants" included those participants for whom informed written consent was provided by the parent/caregiver and assent was provided (where appropriate), whether the participant was allocated to trial treatment or not.
[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] Percentages for reasons for screening failures were based on the number of participants screened. The remaining percentages were based on the number of participants enrolled.
Abbreviations: AE, adverse event; N, number of subjects

8.2.3.2 Demographics

Enrollment was similar between males and females (52% males and 48% females). The proportion of females was higher in the berotralstat 108 mg pellets group (67%) than any other group. Relatively small proportions of the subjects were in the lower weight group (Cohort 4) where all the participants were male. The majority of subjects (76% across treatment arms) were white. The mean age at onset of HAE symptoms was 3 years of age. Historical SERPING-1 genetic results were available for 4 participants (not shown). Family history of Type I or Type II HAE was reported in 90% of patients. Approximately half of the participants (52%) required a median of 3 emergency room visits in the past year due to HAE symptoms. The demographics are summarized in Table 19.

Table 19. Subject Demographics (Trial 304, Safety Population)

Demographic	Cohort 1: (150 mg Capsules) (N=7)	Cohort 2: (108 mg Pellets) (N=9)	Cohort 3: (96 mg Pellets) (N=9)	Cohort 4: (78 mg Pellets) (N=4)	Total (N=29)
Age (%)					
2-5	0	0	0	3 (75)	3 (10)
6-11	7 (100)	9 (100)	9 (100)	1 (25)	26 (90)
Sex (%)					
F	3 (43)	6 (67)	5 (56)	0	14 (48)
M	4 (57)	3 (33)	4 (44)	4 (100)	15 (52)
Race (%)					
Unknown	1 (14)	1 (11)	3 (33)	2 (50)	7 (24)
White	6 (86)	8 (89)	6 (67)	2 (50)	22 (76)
Weight (%)					
≥40 kg	7 (100)	0	0	0	7
32 to <40 kg	0	9 (100)	0	0	9
24 to <32 kg	0	0	9 (100)	0	9
12 to <24 kg	0	0	0	4 (100)	4
Median weight kg (min, max)	53 (40, 70)	36 (32, 38)	29 (26, 30)	19 (15, 20)	32 (15, 70)
Age at onset of first symptoms					
Mean (SD)	4 (2)	3 (3)	3 (3)	2 (1)	3 (2)
Median (min, max)	4 (1, 7)	2 (1, 8)	2 (0.3, 7)	1 (1, 3)	2 (0.3, 8)
Family history of Type 1 or 2 HAE (%)					
No	2 (29)	1 (11)	0	0	3 (10)
Yes	5 (71)	8 (89)	9 (100)	4 (100)	26 (90)

Demographic	Cohort 1: (150 mg Capsules) (N=7)	Cohort 2: (108 mg Pellets) (N=9)	Cohort 3: (96 mg Pellets) (N=9)	Cohort 4: (78 mg Pellets) (N=4)	Total (N=29)
Days of education missed in the past					
Year Mean (SD)	14 (13)	28 (30)	15 (16)	8 (8)	18 (20)
Median (min, max)	12 (0, 30)	17 (5, 90)	10 (0, 50)	5 (3, 20)	10 (0, 90)
Number of ER visits due to HAE symptoms in the past year					
N	3 (43)	3 (33)	7 (78)	2 (50)	15 (52)
Mean (SD)	3 (2)	2 (0.6)	14 (15)	1 (0)	8 (11)
Median (min, max)	3 (1, 5)	2 (2, 3)	8 (2, 43)	1 (1, 1)	3 (1, 43)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Age - Dataset: Demographics; Filter: None.
Sex - Dataset: Demographics; Filter: None.
Race - Dataset: Demographics; Filter: None.
Weight - Dataset: Demographics; Filter: None.
Age at Onset of First Symptoms - Dataset: Demographics; Filter: None.
Family History of Diagnosed Type 1 or 2 HAE - Dataset: Demographics; Filter: None.
Days of Education Missed in the Past Year - Dataset: Demographics; Filter: None.
Number of ER Visits in the Past Year - Dataset: Demographics; Filter: None.
Abbreviations: ER, emergency room; F, female; HAE, hereditary angioedema; M, male; SD, standard deviation

All ethnicities and races are affected by types I and II HAE; however, most of the extant epidemiologic and genetic data are derived from European populations. The interaction between race and disease expression is poorly understood.

8.2.3.3 Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Medications)

The most common anatomic region where swelling occurred was the stomach/abdomen (90%), and correspondingly the most common symptoms of an HAE attack were abdominal pain (79%), vomiting (69%), and nausea (62%). Pre-trial laryngeal attacks were reported less frequently but still occurred in 4 participants (14%). The majority of the reported attacks were moderate in severity. Treatment compliance was high in this group and was not affected by palatability. All patients received at least one dose of berotralstat. Table 20 summarizes the past prophylactic treatments taken by the participants in the safety population.

Table 20. Past Prophylactic Medications for HAE (Trial 304, Safety Population)

	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)
Any past prophylactic treatment for HAE[b]	3 (42.9%)	3 (33.3%)	4 (44.4%)	1 (25.0%)	11 (37.9%)
Androgens	0	0	0	0	0
Cinryze®	1 (14.3%)	0	0	0	1 (3.4%)
Berinert®	1 (14.3%)	2 (22.2%)	4 (44.4%)	0	7 (24.1%)
Tranexamic acid	2 (28.6%)	1 (11.1%)	2 (22.2%)	1 (25.0%)	6 (20.7%)
Haegarda®	0	0	0	0	0
Takhzyro®	0	1 (11.1%)	0	0	1 (3.4%)
Other	0	0	0	0	0
Any C1-INH[c]	2 (28.6%)	2 (22.2%)	4 (44.4%)	0	8 (27.6%)

Source: CSR Table 14.1.3.3.1 tables and figures. Pg 48.
[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] Responses for individual drugs may not be mutually exclusive. Percentages were based on the number of responses per category and may not sum to 100%.
[c] The summary of any C1-INH includes plasma-derived C1-INH replacement (brand names = Cinryze, Berinert, Haegarda), recombinant C1-INH replacement (brand name = Ruconest®), and fresh frozen plasma.
Abbreviations: C1-INH, C1 esterase inhibitor; CSR, clinical study report; HAE, hereditary angioedema; WHO, World Health Organization

Lanadelumab (Takhzyro) was not approved for pediatric patients 2 years of age and older until February 2023, during the middle of Trial 304 enrollment, which may have contributed to the low number participants using this medication in the trial population.

During the SOC period, four subjects were treated with tranexamic acid and one subject with lanadelumab. Three subjects had access to Berinert for short-term prophylaxis as needed.

8.2.3.4 Primary Endpoint

The primary endpoint of Trial 304 was to describe the PK parameters of berotralstat administered orally to pediatric participants 2 to <12 years of age with HAE. The PK results were discussed in the Clinical pharmacology Section 6. Safety endpoints are reviewed in Section 8.3.

8.2.3.5 Secondary Endpoints

Safety and efficacy were the secondary endpoints. Safety endpoints are reviewed in Section 8.3.

Effectiveness endpoints included 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. Effectiveness endpoints were analyzed based on the actual treatment received. Trial 304 was not designed to assess efficacy given the small sample size, and uncontrolled design. However, exploratory efficacy analysis demonstrated results consistent with the adolescent and adult trials (See Table 21).

Table 21. Comparison of Efficacy Measures Trial 304, 2 to <12 Years of Age vs. Trial 302≥12 Years of Age

	Berotralstat (ORLADEYO)						
	Trial 304 (2 to <12yo)				Trial 302 (≥12yo)		
Criteria	Cohort 1 (150 mg Capsule) N=7	Cohort 2 (108 mg Pellets) N=9	Cohort 3 (96 mg Pellets) N=9	Cohort 4 (78 mg Pellets) N=4	BCX7353 (110 mg Capsule) N=41	BCX7353 (150 mg Capsule) N=40	Placebo N=39
Adjusted attack rate reduction from baseline mean (SD)	0.68 (0.65)*	1 (1.61)*	1.29 (1.41)*	0.77 (0.6)*	1.5 (1.44)	1.78 (1.5)	0.66 (1.35)
% Adjusted attack rate reduction from baseline mean (SD)	56.06 (27.43)	-12.67 (175.83)	58.28 (55.75)	75.67 (17.05)	47.95 (38.34)	58.59 (35.12)	24.5 (41.17)
Number of attack free subjects n (%)	1 (14.29)	0 (0)	3 (33.33)	1 (25)	1 (2.44)	4 (10)	1 (2.56)
Proportion of days with symptoms mean (SD)	0.04 (0.03)	0.05 (0.04)	0.04 (0.06)	0.02 (0.02)	0.13(0.13)	0.12 (0.13)	0.19 (0.15)

Source: Statistical reviewer using adeff.xpt datasets from NDA 219776 (with subjects <12 year) and NDA 214094 (with subjects >12 years).
* Mean and SD values were calculated after excluding individuals with baseline HAE rates of zero, which would result in undefined percent change values.
Abbreviations: N, total number; SD, standard deviation; yo, years old

For Trial 304, Cohort 2 had a % adjusted attacks rate reduction from baseline of −12.67. One subjects in this cohort reported a substantially higher attack rate during the Parts 1 and 2 compared with the baseline rate, which could explain the negative value in this cohort. The subject was on lanadelumab prophylaxis during the SOC baseline period. This subject discontinued due to lack of perceived efficacy.

Overall, the mean (±SEM) adjusted attack rates decreased from 1.51 (±0.24) attacks/month during the SOC period to 0.52 (±0.17) attacks/month at Month 1 on treatment and remained lower than the SOC period through Parts 1 and 2 (up to Week 48).

8.2.3.6 Assessment of Efficacy

Substantial evidence of effectiveness for berotralstat to prevent attacks of HAE in children 2 to <12 years of age is provided by extrapolation from evidence that supported the approval of berotralstat for the same indication in adults and adolescents 12 years of age and older. Extrapolation is supported by the overlap in the clinical presentation of HAE across adult and pediatric populations, consistency in the therapeutic approach, consistency of the berotralstat mechanism of action, relevance of the clinical endpoints, and similar expected efficacy in children 2 to <12 years of age.

This extrapolation is further supported by PK analyses demonstrating that drug exposure in the pediatric population consistently exceeds the levels observed in the adult reference population.

PD (i.e., kallikrein activity) was not assessed for this NDA given that participants had access to approved medications for treatment and prophylaxis of HAE, which limit the clinical utility of this PD analysis.

The supporting pediatric trial (Trial 304) is a 48-week, open-label, PK and safety trial with an optional 96-week extension. The trial enrolled 29 pediatric subjects 2 years to <12 years of age with Type I or II HAE. While Trial 304 was not designed to demonstrate efficacy due to its small sample size and uncontrolled design, descriptive efficacy analyses yielded results that aligned with findings from adolescent and adult trials.

8.3 Review of Safety

8.3.1 FDA Approach to the Safety Review

For the evaluation of safety, FDA medical officer Dr. Diana Nichols-Vinueza analyzed data from Trial 304 using JMP, JMP Clinical, and Analysis Studio. The safety results presented in Section 8.3 represent the medical office reviewer's own analyses. All safety analyses were conducted in the safety population, which consisted of any subject who received at least one dose of berotralstat.

8.3.2 Review of the Safety Database

Overall Exposure

At the time of data cutoff for Trial 304 interim CSR (September 11, 2024), 29 subjects were enrolled and exposed to at least 1 dose of berotralstat. A total of 29 subjects were enrolled in the ongoing single pediatric trial (Trial 304) to support safety in pediatric subjects aged 2 to <12 years of age. At the time of the interim data cutoff date, all 29 enrolled participants completed 12 weeks of treatment, 26 (90%) participants completed 24 weeks, and 17 (59%) participants completed through Week 48. A total of 25 participants (86%) were still ongoing in the trial.

Mean (SD) overall duration of exposure was 43 (18) weeks for all 29 subjects, and median overall duration of exposure was 48 weeks (range: 12 to 73 weeks).

Adequacy of the Safety Database

Overall, the safety database is of sufficient size and duration to assess the safety of the proposed pediatric dose given the previous safety database for the approved adolescent and adult HAE indication

8.3.3 Adequacy of Applicant' Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this NDA were identified.

Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious events in the protocols. AEs were captured from signing of informed consent through the final follow-up visit or until the AE was resolved or the subjects is in a clinically stable condition with regard to the AE. This included events occurring during the SOC therapy phase, regardless of whether the investigational product had been administered. For this protocol, no events of special interest were identified. All AEs and SAEs were 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 (published date July 2017[12]). Any AEs not covered by the DAIDS table were assessed and classified into 1 of 5 clearly defined categories as follows: mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death (Grade 5). AEs were classified into system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA).

[12] DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

TEAEs were defined as AEs that occurred on or after the first dose of berotralstat through 30 days post discontinuation of trial treatment. All AEs that occurred prior to the initiation of berotralstat or those recorded with an onset 30 days after the last dose of berotralstat were excluded from the tables but were included in the listings.

No adverse events of special interest were formally designated in the Trial 304 Protocol; however, the Applicant included a summary of the following AEs: hypersensitivity reactions, anaphylactic reactions, severe cutaneous adverse reactions, and Torsade de pointes/QT prolongation standardized MedDRA queries (SMQs) and monitor all AEs until symptom resolution or until clinical stabilization. The Applicant's methodology for coding verbatim adverse event terms to MedDRA preferred terms was deemed acceptable.

8.3.4 Safety Results

Deaths

There were no deaths reported during the trial.

Serious Adverse Events

Only one participant in Cohort 1 experienced two SAEs of Grade 3: accident (skateboarding accident) and elbow fracture during Part 2 of the Trial. Both SAEs were determined to be unrelated to the trial intervention. No other SAEs were reported during the trial.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no trial discontinuations or dropouts due to AEs during Trial 304. Palatability was not a cause of treatment interruption or discontinuation.

Treatment Emergent Adverse Events and Adverse Reactions

Given the absence of a placebo control group in Trial 304, causality assessment of adverse events relative to trial drug administration is limited. A review of all AEs in Trial 304 did not reveal any new safety concerns. Common AEs (occurring in ≥2 subjects by system organ class) reported are summarized in Table 22. The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache, cough, gastroenteritis, and vomiting. Overall, the common adverse events for pediatric patients are similar to those observed in patients aged 12 years and older which included nasopharyngitis, upper respiratory tract infections, abdominal pain, and headache.

Table 22. Summary of Treatment Emergent Adverse Events by System Organ Class Preferred Term, and Treatment Group (Trial 304, Safety Set)

System Organ Class Preferred Term	Berotralstat N=29	
	n	%
Any AE	25	(86.2)
Infections and infestations	**18**	**(62.1)**
Nasopharyngitis	8	(27.6)
Upper respiratory tract infection	7	(24.1)
Gastroenteritis	3	(10.3)
Viral upper respiratory tract infection	3	(10.3)
Bronchitis	2	(6.9)
Ear infection	2	(6.9)
Gastrointestinal infection	2	(6.9)
Influenza	2	(6.9)
Otitis media acute	2	(6.9)
Respiratory, thoracic and Mediastinal Disorders	**7**	**(24.1)**
Cough	3	(10.3)
Oropharyngeal pain	2	(6.9)
Gastrointestinal disorders	6	(20.7)
Vomiting	3	(10.3)
Abdominal pain	2	(6.9)
Nausea	2	(6.9)
Musculoskeletal and connective tissue disorders	**6**	**(20.7)**
Arthralgia	1	(3.4)
Back pain	1	(3.4)
Groin pain	1	(3.4)
Mobility decreased	1	(3.4)
Myalgia	1	(3.4)
Pain in extremity	1	(3.4)
Ear and labyrinth disorders	**4**	**(13.8)**
Ear pain	2	(6.9)
Excessive cerumen production	2	(6.9)
Injury, poisoning and procedural complications	**4**	**(13.8)**
Accident	1	(3.4)
Contusion	1	(3.4)
Eye contusion	1	(3.4)
Head injury	1	(3.4)
Upper limb fracture	1	(3.4)
Nervous system disorders	**4**	**(13.8)**
Headache	4	(13.8)
General disorders and administration site conditions	**3**	**(10.3)**
Influenza like illness	1	(3.4)
Pyrexia	2	(6.9)
Psychiatric disorders	**3**	**(10.3)**
Affect lability	2	(6.9)
Aggression	1	(3.4)
Immune system disorders	**2**	**(6.9)**
Hypersensitivity	1	(3.4)
Seasonal allergy	1	(3.4)
Investigations	**2**	**(6.9)**
Aspartate aminotransferase increased	1	(3.4)
Crystal urine present	1	(3.4)

System Organ Class Preferred Term	Berotralstat N=29 n	 %
Gamma-glutamyl transferase increased	1	(3.4)
Renal and urinary disorders	**2**	**(6.9)**
Albuminuria	1	(3.4)
Pyelocaliectasis	1	(3.4)
Skin and subcutaneous tissue disorders	**2**	**(6.9)**
Pruritus	1	(3.4)
Rash	1	(3.4)
Rash maculo-papular	1	(3.4)
Urticaria	1	(3.4)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "BCX7353 150 mg" or "BCX7353 108 mg" or "BCX7353 96 mg" or "BCX7353 78 mg" and SAFFL = Y (Berotralstat); TRTEMFL = "Y" (Adverse Events).
Abbreviations: AE, adverse event

Laboratory Findings

Laboratory assessments (hematology, chemistry, and urinalysis) were conducted periodically during the trial. All chemistry results were compared with baseline. The majority of subjects had values for clinical chemistry within the normal range. The safety program in patients aged 12 years and older identified a potential risk of elevated liver enzymes. One participant had elevated AST and gamma-glutamyl transferase due to acute hepatitis. Although the observed AST and gamma-glutamyl transferase elevations met the criteria for consideration of treatment discontinuation according to the drug-induced liver injury guidance (ALT or AST >3 × ULN and total bilirubin >2 × ULN), this participant was not discontinued, as fluctuations of liver function tests were not consistent with a drug effect, liver enzymes began improving while berotralstat dosing continued, and the final diagnosis was acute hepatitis due to a viral origin. However, no clinically relevant elevations in liver function tests were observed, and no participant had a post-baseline elevation in AST, ALT, or total bilirubin >1.5 × ULN.

Vital Signs

Routine vital signs (pulse rate, respiratory rate, blood pressure, and temperature) were performed periodically during the trial. The mean changes from baseline in all parameters were small and there was no treatment effects detected.

Immunogenicity

Immunogenicity trials were not required or performed as part of this trial.

8.3.5 Analysis of Submission-Specific Safety Issues

Adverse Events in the Hypersensitivity, Anaphylactic Reaction, or Severe Cutaneous Adverse Reaction SMQs

Although this protocol did not include the evaluation of adverse events of special interest, these were monitored and were among the reported AEs. Four participants (14%) experienced five TEAEs in the Hypersensitivity SMQ (refer to Table 23) classified as mild or moderate. Hypersensitivity events were primarily localized and limited to skin symptoms. No TEAEs were reported under the severe cutaneous reaction SMQ. No cases of anaphylaxis were identified in the program.

Table 23. Subjects Reporting Treatment-Emergent Adverse Events in the Hypersensitivity SMQ (Trial 304, Safety Population)

	150 mg Capsules		108 mg Oral Pellets		96 mg Oral Pellets		78 mg Oral Pellets		Total
Group Term	N=7		N=9		N=9		N=4		N=29
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n (%)
Hypersensitivity	0	(0.0)	2	(22.2)	2	(22.2)	0	(0.0)	4 (13.8)
Allergic eosinophilia	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	1 (3.4)
Hypersensitivity	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	1 (3.4)
Rash	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	1 (3.4)
Rash maculo-papular	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	1 (3.4)
Urticaria	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	1 (3.4)

Source: OCS Analysis Studio, Safety Explorer.
Filters: ACTARM = "BCX7353 150 mg" and SAFFL = Y (150); ACTARM = "BCX7353 108 mg" and SAFFL = Y (108); ACTARM = "BCX7353 96 mg" and SAFFL = Y (96); ACTARM = "BCX7353 78 mg" and SAFFL = Y (78); TRTEMFL = "Y" (Adverse Events).
Abbreviations: SMQ, standardized MedDRA query

Adverse Events in the Torsade de pointes/QT Prolongation SMQ

QTc prolongation emerged as a potential safety signal based on the adult berotralstat trial (Trial 302). Patients aged 12 years and older who received higher dose of berotralstat tablets of 450 mg daily for 14 days had exposures ~3-fold higher than achieved at the recommended 150-mg dose, had a significant increase in the mean QTc increased. Therefore, cardiac parameters were monitored closely for safety in Trial 304. No cardiac TEAEs were reported, and no participant experienced clinically meaningful cardiac observations, including no clinically significant increases in QTcF, PR interval, or QRS duration. No QTcF >450 msec was observed, and no participants had a QTcF change from baseline >60 msec. There were no TEAEs for Torsades de pointes.

In the adult program (Trial 302) GI reactions, including abdominal pain, vomiting, and diarrhea occurred more frequently in patients receiving berotralstat 150 mg versus berotralstat 110 mg or placebo. For Trial 304, GI reactions were reported in six patients (21%), four participants (14%) had Grade 1 TEAEs, and two participants (7%) had Grade 2 TEAEs by highest severity. Dose modification (from 150 mg to 110 mg) was recommended for adolescents and adults with

persistent GI symptoms, but no dose modification is recommended for children 2 to <12 years of age.

8.3.6 Safety Analysis by Demographic Subgroups

Safety analysis by demographic subgroup was not conducted due to the small trial size.

8.3.7 Safety in the Postmarket Setting

The Sponsor submitted a Periodic Benefit-Risk Evaluation Report for berotralstat which included an analysis of the safety and efficacy profile collected for the period from December 3, 2023, to December 2, 2024, as well as safety data on cumulative adverse drug reactions (ADRs) since the first worldwide approval of berotralstat (International Birth Date: December 3, 2020, in the United States) and safety data on cumulative Serious Adverse Events from clinical trials based on the development international birth date. The report, prepared by BioCryst Pharmaceuticals, represents the sixth Periodic Benefit-Risk Evaluation Report for this medication. During the reporting period, the company updated their safety information to include nausea as a non-serious adverse drug reaction based on post marketing data, (b) (4) The safety profile remains consistent with no important identified risks, while six important potential risks continue to be monitored: hepatotoxicity, hypersensitivity, QT prolongation, drug-drug interactions with narrow therapeutic index drugs, carcinogenicity, and phospholipidosis.

The Sponsor submitted a 90-day safety report for Trial 304 with a data cutoff date of March 24, 2025. A total of 27 participants completed Week 48. The remaining two participants discontinued prior to Week 48. During this reporting period two SAEs were reported.

- One participant in Cohort 1 (150 mg capsules) experienced a temporary dose interruption for the management of acute hepatitis. The event was assessed as unrelated to trial drug (attributed to acute infection (rhinovirus and enterovirus)) and the drug was restarted without increased in liver function tests assessed 6 days after resuming berotralstat.
- One patient experienced an SAE of hemiparesis but had a pre-existing diagnosis of hemiparesis.

The global cumulative post-marketing patient exposure to berotralstat since launch is estimated to be approximately (b) (4) patient-years.

During this reporting interval, no new safety or efficacy concerns have been identified.

8.3.8 Integrated Assessment of Safety

A total of 29 subjects were enrolled in the ongoing single pediatric trial (Trial 304) to support safety in pediatric subjects aged 2 to <12 years of age. At the time of the interim data cutoff

date, all 29 enrolled participants completed 12 weeks of treatment, 26 (90%) participants completed 24 weeks, and 17 (59%) participants completed through Week 48. A total of 25 participants (86%) were still ongoing in the trial. The mean overall duration of exposure was 43 weeks.

The frequency and type of AEs were consistent with previous trials in adults and adolescents. No deaths or AEs leading to discontinuation were reported. One participant experienced two SAEs, determined unrelated to berotralstat (skateboarding accident with elbow fracture). The most common AEs were nasopharyngitis and upper respiratory tract infection. Most TEAEs were mild or moderate in severity. The 90-day safety update encompassed 27 subjects who completed Week 48 (with 2 subjects discontinuing before Week 48) and demonstrated consistency with the safety profile reported in the interim trial data analysis. No new safety signals were identified compared to previous controlled trials conducted in adults and adolescents ≥12 years of age.

The pediatric safety assessment is subject to limitations due to the small trial size (N=29), which may limit the ability to detect less common adverse events, therefore safety of berotralstat for pediatric patients 2 to <12 years of age relies on partial extrapolation of safety from the adult and adolescent trials.

The observed berotralstat systemic exposure was within the 5^{th} to 95^{th} percentile reference range of observed adult values, except for Cohort 1 (150 mg oral capsule: ≥40 kg) which exceeded the adult reference range. A lower dose of 132 mg is recommended for Cohort 1. The Applicant's proposed dose for Cohort 4 (78 mg oral pellet; 12 to <24 kg) raised Agency concerns regarding increased systemic exposure and potential risk for QT interval prolongation. The Agency acknowledges that Trial 304 did not demonstrate QT prolongation or identify safety signals in Cohort 4; however, the limited sample size in this population precluded definitive safety conclusions regarding the proposed 78-mg dose. Based on these safety considerations, the Agency recommended that the Applicant reduce the dose to 72 mg for pediatric patients 12 to <24 kg.

The totality of safety data from Trial 304 supports the favorable risk-benefit profile of berotralstat for prophylactic treatment of HAE in pediatric patients aged 2 to <12 years, with appropriate labeling to ensure safe use in this population.

9 Advisory Committee Meeting and Other External Consultations

As berotralstat is approved for the same indication in adolescents and adults and there were no safety or efficacy concerns identified for this pediatric program, no advisory committee meeting was required.

10 Pediatrics

Berotralstat was granted Orphan Designation for treatment of angioedema on November 1, 2017, for the treatment of angioedema which exempts berotralstat for HAE from PREA. A WR was issued November 21, 2023, and amended on October 3, 2024. The single trial that supports this NDA (Trial 304) was conducted to fulfil WR Amendment #1. At the Pediatric Exclusivity Board on June 11, 2025, it was determined that the Applicant fulfilled all requirements (including and that Applicant submitted the trial before the June 30, 2025, deadline). Exclusivity was granted on August 29, 2025, (See Pediatric Exclusivity Determination Checklist submitted to NDA 219776 on August 29, 2025) and the Applicant was notified on September 2, 2025. On October 14, 2025, The Pediatric Review Committee was informed of the Pediatric Exclusivity Board's decision for this product.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Table 24. Prescription Drug Labeling

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE	Indication was expanded to include patients 2 years to <12 years of age with the following indication statement: *ORLADEYO® is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 2 years of age and older.*
2 DOSAGE AND ADMINISTRATION	A new subsection for Recommended Dosage in Pediatric Patients 2 Years to Less Than 12 Years of Age was added to provide the recommended dosage based on weight (in a table) for the newly added patient population. The Applicant did not have information for dosage modification in pediatric patients 2 years to less than 12 years of age with persistent GI adverse reactions. Therefore, the language was revised to advise healthcare providers to weigh the risks and benefits for treatment with ORLADEYO among these patients. Administration instructions were added for oral pellets.
6 ADVERSE REACTIONS	Added a heading for Adverse Reactions in Pediatric Patients 2 to Less than 12 Years of Age in the *Clinical Trials Experience* subsection that included a summary of the trial that evaluated safety in this patient population; for which no new safety signals were observed.
7 DRUG INTERACTIONS	The section was updated to current labeling practices.

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.4 Pediatric Use subsection was updated with a summary of the trials that support safety and effectiveness of ORLADEYO use in the new pediatric population (2 years to less than 12 years of age). 8.5 Geriatric Use subsection was revised consistent with Geriatric Information in Human Prescription Drug and Biological Product Labeling. 8.6 Renal Impairment subsection was updated to include a recommendation to avoid use for patients 2 to <12 years of age with severe renal impairment 8.7 Hepatic Impairment subsection was updated to include a recommendation to avoid use in patients 2 to <12 years of age with moderate or severe hepatic impairment.
12 CLINICAL PHARMACOLOGY	Added PK results for patients 2 to <12 years of age. Updated for consistency with best labeling practices for Clinical Pharmacology sections.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	The product quality section of the PI was updated with the information that provides for the new dosage form of oral pellets. The Applicant proposed the new dosage form as oral granules but based on USP <1151>Pharmaceutical Dosage Forms, the new dosage form was considered oral pellets, and the PI reflects the appropriate dosage form.

12 Risk Evaluation and Mitigation Strategies

Given the favorable safety profile of berotralstat for 2 to <12 years old, there are no additional risk management strategies required.

13 Division Director (DPACC) Comments

This NDA seeks to expand the approved indication for berotralstat (ORLADEYO) to include pediatric patients aged 2 to less than 12 years for prophylaxis to prevent attacks of HAE. The submission includes a new age-appropriate dosage form consisting of oral pellets (6 mg/pellet) in four proposed weight-based unit-dose packets ((b) (4) mg, 96 mg, 108 mg, and 132 mg) to facilitate administration in younger patients who cannot swallow capsules.

In support of this NDA submission, the Applicant provides clinical pharmacology data from two trials, including Trial 114 (Phase 1 relative BA trial between the oral capsule and oral pellet dosage forms) and Trial 304 (Phase 3 PK, safety, and descriptive efficacy trial in pediatric subjects 2 to <12 years of age with HAE). This data supports efficacy extrapolation from the efficacy determination previously made in adult and pediatric patients ≥12 years of age.

Office of Product Quality

The Office of Product Quality review identified no deficiencies and recommended that drug substance, drug product, manufacturing, and biopharmaceutics were all adequate to support approval.

Nonclinical

A comprehensive nonclinical program for berotralstat (NDA 214094) included pharmacology, pharmacokinetics, and toxicology studies, with additional juvenile animal toxicology and nitrosamine impurity safety studies to support pediatric approval for patients aged 2 years and older. The juvenile toxicology study in Wistar Han rats (21-day-old pups dosed for 49 days) established a no-observed-adverse-effect level of 5 mg/kg/day, with higher doses causing reversible macrophage vacuolation in multiple organs and hepatocellular hypertrophy. For the nitrosamine impurity [redacted] (b) (4), the Applicant conducted enhanced Ames assays, in vitro mammalian cell mutation assays, and metabolism studies to support an acceptable intake limit of [redacted] (b) (4) ng/day, [redacted] (b) (4) was deemed acceptable based on negative mutagenicity results and lack of bioactivation potential, with approval from the CDER Pharmacology and Toxicology Coordinating Committee Nitrosamine Working Group.

The Pharmacology-Toxicology Team recommended approval of this application from the nonclinical perspective.

Clinical Pharmacology

The clinical pharmacology review focused on analyzing berotralstat pharmacokinetic data from Trials 114 and 304, evaluating the population PK model supporting weight-based dosing, and assessing proposed dose adjustments for intrinsic/extrinsic factors. Trial 304 demonstrated that systemic exposure (C_{max}, C_{trough}, and $AUC_{0\text{-}6h}$) for pediatric cohorts receiving weight-based oral pellets (78-108 mg) fell within the 5th to 95th percentile reference range of adult values, while Cohort 1 (150 mg capsule; ≥40 kg) exceeded this range, necessitating a lower marketed dose (132 mg) for pediatric patients ≥40 kg. Similarly, the proposed dose of 78 mg for patients 12 to < 24 kg was decreased to 72 mg due to safety concerns related to elevated berotralstat exposure. The population pharmacokinetic modeling predicted that approximately 20% of pediatric subjects receiving 78 mg would have C_{max} exceeding the 95th percentile of adult values, with some predicted exposures approaching levels known to cause QTc prolongation in adults (>500 ng/mL).

The proposed dose adjustments for renal and hepatic impairment (avoiding use in severe renal impairment and moderate-to-severe hepatic impairment) were deemed reasonable.

The Office of Clinical Pharmacology determined this application approvable from a clinical pharmacology perspective.

Clinical

The regulatory approach for this pediatric extension relies primarily on extrapolation of efficacy from the established adult and adolescent data, supported by pharmacokinetic analyses from Trial 304, a 48-week open-label safety and PK trial in 29 pediatric subjects. This extrapolation strategy is scientifically sound given the consistent pathophysiology of HAE across age groups, the well-characterized mechanism of action of berotralstat as a plasma kallikrein inhibitor, and the demonstration that pediatric patients achieve drug exposures that consistently exceed those observed in the adult reference population. While Trial 304 was not designed to assess effectiveness due to its small sample size and uncontrolled design, exploratory efficacy analyses yielded results consistent with findings from the pivotal adult trials.

The safety profile in the pediatric population mirrors that established in adults and adolescents, with no new safety signals identified.

Importantly, the dosing recommendations have been refined based on PK data to mitigate potential QTc prolongation risks, with weight-based dosing ranging from 72 mg daily for patients weighing 12to < 24 kg to 132 mg daily for those weighing ≥40 kg.

Pediatrics

Berotralstat was granted Orphan Designation for treatment of hereditary angioedema on November 1, 2017, and as a result, was exempted from PREA requirements. A WR was issued November 21, 2023, and amended on October 3, 2024. Trial 304, as submitted with this NDA, was conducted to fulfil WR Amendment #1. The Pediatric Exclusivity Board determined on June 11, 2025, that the Applicant fulfilled all requirements of the WR, including submission of the trial results before the June 30, 2025, deadline. Exclusivity was granted on August 29, 2025 (See Pediatric Exclusivity Determination Checklist submitted to NDA 219776 on August 29, 2025) and the Applicant was notified on September 2, 2025.

Conclusion

The benefit-risk assessment is favorable, and I concur with the review team's recommendation for **approval** of this NDA, as labeled, at doses of:

- 132 mg for patients weighing ≥40 kg
- 108 mg for patients weighing between 32 kg to <40 kg
- 96 mg for patients weighing 24 kg to <32 kg,
- 72 mg for patients who weigh 12 kg to <24 kg

This approval of berotralstat for children ≥2 years of age provides an additional option in the treatment armamentarium for the prophylaxis of HAE attacks in this age group. Availability of

an oral kallikrein inhibitor for this indication provides patients with an important option for preventing HAE attacks to be considered in shared decision-making with their providers.

14 Appendices

14.1 Financial Disclosure

The financial disclosure checklist for the clinical trial submitted to this NDA is provided below.

Covered Clinical Trial (Name and/or Number): 304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 15 principal investigators (PI) and 21 Sub-investigators (SI)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the trial where the value could be influenced by the outcome of the trial: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered trial: 0		
Is an attachment provided with details	Yes ☒	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2 Nonclinical Pharmacology/Toxicology

(b) (4)

[redacted]

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14.3 OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.3.1 Pharmacometrics Review

In this application, the Applicant submitted a population PK report (BCX7353-MS-002) entitled "*Population Pharmacokinetic Modeling and Simulation of Berotralstat Exposures for Pediatric Participants with Hereditary Angioedema Who Are 2 to <12 Years of Age*." The objectives of these population PK analyses were to characterize berotralstat PK in pediatrics and to support dose recommendations for pediatric patients 2 to less 12 years of age with HAE.

Notably, the Applicant previously developed a population PK model using data obtained from 876 adults and adolescents across thirteen clinical trials, which was deemed adequate following review under NDA 214094 (Refer to the NDA Multidisciplinary Review and Evaluation, dated December 3, 2020 [DARRTS Reference ID: 4711626]). The previous model was utilized for Monte-Carlo simulation of berotralstat exposures in pediatric patients 2 to <12 years of age under different dosing scenarios to determine initial dose selection for Trial 304. Additionally, this previous model informed the model structure and initial estimates for the updated population PK model, which included pediatric subjects 2 to <12 years of age with HAE.

Development of the updated pediatric population PK model occurred in two stages. First, an initial model was developed based on intensive PK data to reassess the previous model structure and perform covariate search. The final model was established following incorporation of sparse PK data to the dataset, which was subsequently validated using bootstrap analysis and prediction-corrected visual predictive check. The final dataset consisted of 12,394 berotralstat plasma samples measured from 786 healthy subjects and HAE patients enrolled across eleven clinical trials. Forest plots were generated to assess the impact of statistically significant covariates on relevant berotralstat PK parameters, including $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0\text{-}24h,ss}$, and $C_{ave,ss}$. The impact of body weight on berotralstat exposure was further characterized using Monte-Carlo simulations of various dosing scenarios, which ultimately supported the Applicant's final proposed pediatric doses and weight bands.

The population PK analyses conducted by the Applicant are summarized below in Table 26. In general, the Applicant's population PK model is considered acceptable for the stated objectives.

Table 26. Applicant's Population PK Analysis of Berotralstat in Subjects 2 to Less than 12 Years of Age With HAE

Parameter	Details
General Information	
Objectives of population PK analysis	To characterize berotralstat PK in pediatric patients with HAE that are 2 to less than 12 years of age To support dose recommendation for pediatric patients with HAE that are 2 to less than 12 years of age
Clinical trials included (11)	BCX7353-101 (including treatment arms ranging from 87 to 871 mg), −103, −106, −113, −114 (all treatment arms that administered (b) (4) capsule and oral pellets; not including liquid formulation), −116, −203, −204, −301, −302, and −304 (up to the interim data cut to support regulatory submissions)
Selection criteria for clinical trials	Inclusion Criteria • PK trials in healthy subjects or subjects with HAE, where berotralstat was administered either as a (b) (4) capsule or as an oral pellets formulation either in fasted or fed conditions • Treatment arms with relevant doses (i.e., doses in adult and pediatric participants 12 years of age and older ranging from 55 mg to 871 mg [free base]) • PK samples were collected from at least five participants in a trial Exclusion Criteria • Trials and/or treatment arms that administered berotralstat as a liquid • Hepatic impairment, renal impairment, and DDI trials • Doses of 8.7 mg and 26 mg (free base) in adults, as they fell outside of the therapeutically relevant dose range • ADME trials (since berotralstat was administered as an oral solution)
Population baseline characteristics	A summary of continuous and categorical baseline characteristics of the subjects included in the population PK dataset is provided below in Table 27 and Table 28, respectively.

Table 27. Summary of Continuous Baseline Characteristics of Final Population PK Dataset (All Trials) by Population

	Population					
Parameter Statistic	2 to <6 Years With HAE (N=3)	6 to <12 Years With HAE (N=25)	12 to <18 Years With HAE (N=33)	Adults With HAE (N=454)	Healthy Adults (N=271)	Overall (N=786)
Body Weight (kg)						
Mean (SD)	17.8 (2.56)	37.9 (13.1)	65.5 (16.5)	81.4 (21.2)	74.9 (12.1)	76.8 (20.1)
Median (min, max)	19.0 [14.9, 19.6]	34.0 [20.4, 69.7]	62.7 [40.1, 102]	76.6 [44.4, 175]	74.2 [45.6, 112]	74.5 [14.9, 175]
Height (cm)						
Mean (SD)	109 (5.77)	138 (10.6)	164 (9.25)	169 (9.03)	172 (9.10)	169 (11.5)
Median (min, max)	112 [102, 112]	138 [120, 162]	163 [147, 190]	168 [149, 198]	173 [147, 203]	169 [102, 203]
Missing	0 (0%)	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)	3 (0.4%)

Parameter	Details						
	IBW (kg)						
	Mean (SD)	19.5 (2.02)	32.4 (5.86)	50.7 (8.11)	62.7 (9.71)	66.7 (9.76)	62.4 (11.8)
	Median (min, max)	20.7 [17.2, 20.7]	31.7 [23.8, 50.6]	50.0 [35.5, 72.2]	61.2 [42.8, 91.0]	68.9 [41.0, 95.9]	62.6 [17.2, 95.9]
	Missing	0 (0%)	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)	3 (0.4%)
	BMI (kg/m^2)						
	Mean (SD)	15.0 (0.656)	19.4 (4.27)	24.3 (5.50)	28.2 (6.43)	25.2 (3.18)	26.7 (5.80)
	Median (min, max)	15.1 [14.3, 15.6]	17.8 [14.2, 30.9]	23.1 [14.6, 35.8]	27.2 [18.0, 54.1]	24.8 [18.5, 32.4]	26.1 [14.2, 54.1]
	Missing	0 (0%)	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)	3 (0.4%)
	Age (year)						
	Mean (SD)	4.00 (1.00)	8.84 (1.60)	14.2 (1.79)	42.3 (13.5)	33.5 (9.91)	36.9 (14.5)
	Median (min, max)	4.00 [3.00, 5.00]	9.00 [6.00, 11.0]	14.0 [12.0, 17.0]	42.0 [18.0, 74.0]	32.0 [18.0, 55.0]	37.0 [3.00, 74.0]
	Albumin (g/dL)						
	Mean (SD)	4.47 (0.153)	4.59 (0.211)	4.48 (0.260)	4.36 (0.296)	4.54 (0.290)	4.43 (0.301)
	Median (min, max)	4.50 [4.30, 4.60]	4.60 [4.20, 5.10]	4.50 [3.80, 4.90]	4.40 [3.60, 5.40]	4.50 [3.50, 5.50]	4.40 [3.50, 5.50]
	Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	37 (13.7%)	37 (4.7%)
	ALT (U/L)						
	Mean (SD)	13.3 (3.51)	16.1 (5.61)	13.9 (7.35)	25.1 (28.6)	20.8 (11.2)	22.8 (23.0)
	Median (min, max)	13.0 [10.0, 17.0]	15.0 [10.0, 37.0]	13.0 [7.00, 48.0]	19.0 [4.00, 476]	17.0 [5.00, 72.0]	18.0 [4.00, 476]
	AST (U/L)						
	Mean (SD)	32.3 (6.11)	26.3 (7.70)	16.5 (5.95)	20.1 (11.7)	18.8 (4.68)	19.7 (9.63)
	Median (min, max)	31.0 [27.0, 39.0]	25.0 [17.0, 49.0]	15.0 [9.00, 41.0]	18.0 [7.00, 164]	18.0 [9.00, 34.0]	18.0 [7.00, 164]
	Total Bilirubin (mg/dL)						
	Mean (SD)	0.153 (0.0115)	0.295 (0.159)	0.496 (0.357)	0.543 (0.246)	0.612 (0.310)	0.555 (0.280)
	Median (min, max)	0.160 [0.140, 0.160]	0.250 [0.140, 0.770]	0.420 [0.240, 2.20]	0.480 [0.160, 1.87]	0.526 [0.117, 1.90]	0.497 [0.117, 2.20]
	eGFR ($mL/min/1.73\ m^2$)						
	Mean (SD)	230 (2.31)	162 (41.3)	139 (16.8)	102 (16.9)	96.6 (18.0)	104 (24.0)
	Median (min, max)	231 [227, 231]	151 [107, 287]	137 [97.0, 165]	103 [49.0, 141]	95.0 [64.0, 177]	102 [49.0, 287]

Source. Adapted from Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 5, pg. 51-53)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HAE, hereditary angioedema; IBW, ideal body weight; Min, minimum; Max, maximum; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Parameter	Details

Table 28. Summary of Categorical Baseline Characteristics of Final Population PK Dataset (All Trials) by Population

	Population					
Parameter (N, %)	2 to <6 Years With HAE (N=3)	6 to <12 Years With HAE (N=25)	12 to <18 Years With HAE (N=33)	Adults With HAE (N=454)	Healthy Adults (N=271)	Overall (N=786)
Sex						
Male	0 (0%)	13 (52.0%)	19 (57.6%)	287 (63.2%)	88 (32.5%)	407 (51.8%)
Female	3 (100%)	12 (48.0%)	14 (42.4%)	167 (36.8%)	183 (67.5%)	379 (48.2%)
Ethnicity						
Hispanic/Latino	0 (0%)	0 (0%)	4 (12.1%)	11 (2.4%)	56 (20.7%)	71 (9.0%)
Not Hispanic/Latino	3 (100%)	21 (84.0%)	28 (84.8%)	421 (92.7%)	215 (79.3%)	688 (87.5%)
Not Reported	0 (0%)	4 (16.0%)	1 (3.0%)	22 (4.8%)	0 (0%)	27 (3.4%)
Region						
Japan	0 (0%)	0 (0%)	0 (0%)	17 (3.7%)	22 (8.1%)	39 (5.0%)
Not Japan	3 (100%)	25 (100%)	33 (100%)	437 (96.3%)	249 (91.9%)	747 (95.0%)
Race						
Asian	0 (0%)	0 (0%)	0 (0%)	41 (9.0%)	27 (10.0%)	68 (8.7%)
Black/African American	0 (0%)	0 (0%)	3 (9.1%)	8 (1.8%)	40 (14.8%)	51 (6.5%)
White	2 (66.7%)	19 (76.0%)	26 (78.8%)	390 (85.9%)	198 (73.1%)	635 (80.8%)
American Indian or Alaska Native	0 (0%)	0 (0%)	1 (3.0%)	1 (0.2%)	2 (0.7%)	4 (0.5%)
Native Hawaiian/Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.4%)	2 (0.3%)
Multiple or Other	0 (0%)	0 (0%)	3 (9.1%)	13 (2.9%)	3 (1.1%)	19 (2.4%)
Unknown	1 (33.3%)	6 (24.0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.9%)

Source. Adapted from Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 5, pg. 52)
Abbreviations: HAE, hereditary angioedema; N, number of subjects; PK, pharmacokinetic

Number of subjects, PK samples, and BLQ	The source PK dataset included 14,292 PK records from 866 trial participants in eleven clinical trials (six Phase 1 trials, two Phase 2 trials, and three Phase 3 trials). • A total of 1,898 PK samples collected from 80 subjects were excluded from the analysis based on inclusion/exclusion criteria stated above (1,110 PK samples) or because they were BLQ (788 PK samples). After exclusions, the final population PK dataset consisted of 12,394 PK samples collected from 786 subjects.
Covariates evaluated	A summary of covariates investigated during construction of the final model are outlined below in Table 29.

Parameter	Details

Table 29. Covariate-PK Parameter Relationships Evaluated in the Population PK Analyses

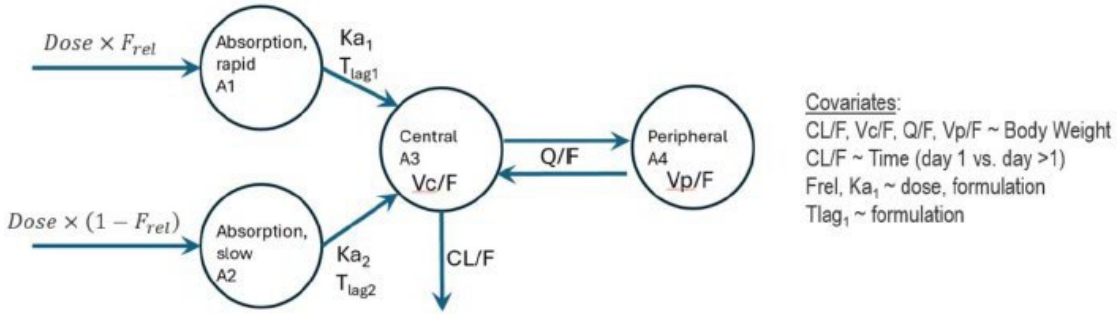
Category	Covariate	PK Parameter	Rationale
Population	HAE vs healthy adult; pediatric vs. adult	CL/F	Clinical interest
Dose	Berotralstat dose (mg)	CL/F, Vc/F, F_{rel}, K_a	Clinical interest, prior knowledge of dose effect; assessed as part of structural model development
Food Status	Food (fasted/with food)	F_{rel}, K_a, T_{lag}	Clinical interest; assessed as part of structural model development
Formulation	Formulation (b) (4) capsule, (b) (4) capsule, oral pellets)	F_{rel}, K_a, T_{lag}	Clinical interest, prior knowledge of formulation effect; assessed as part of structural model development
Demographic	Baseline and time-varying body weight and other body size metrics (IBW, BMI)	CL/F, Vc/F, Q/F, Vp/F	Clinical interest, prior knowledge of body weight effect; assessed as part of structural model development
	Baseline age, sex, race, ethnicity	CL/F, Vc/F	Clinical interest
Region	Japan vs. non-Japan	CL/F, Vc/F	Clinical interest
Hepatic Function	Baseline albumin, ALT, AST, and total bilirubin	CL/F	Clinical interest
Renal Function	Baseline eGFR	CL/F	Clinical interest

Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 2, pg. 38)
Abbreviations: ALT, alanine aminotransferase; API, active pharmaceutical ingredient; AST, aspartate aminotransferase; BMI, body mass index; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; F_{rel}, relative bioavailability; HAE, hereditary angioedema; IBW, ideal body weight; K_a, absorption rate constant; PK, pharmacokinetic; Q/F, apparent intercompartmental clearance; T_{lag}, lag time in absorption; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment

Final Model	*Summary*
Software and version	Exploratory data analysis, plotting, simulations, and table generation to support population PK analysis were performed using R version 4.3.3 and RStudio version 2023.12.1 (Build 402). Population PK modeling was conducted using NONMEM software version 7.5.1. The first-order conditional estimation method with eta-epsilon interaction (FOCEI) was used for parameter estimation during model development. Perl-speaks-NONMEM (PsN) version 4.9.0 was used for post-modeling analysis, including prediction-corrected VPCs and bootstrap procedures. The mrgsolve package in R was used for simulations.

Parameter	Details
Model structure	The final model was a two-compartment model with dual lagged parallel first-order absorption processes (rapid and slow) and linear elimination from the central compartment, which included parameters for apparent clearance from the central compartment (CL/F) and between compartments (Q/F), as well as for apparent volume of distribution in both the central and peripheral compartments (Vc/F, Vp/F; Figure 8). Following covariate investigation, the Applicant retained the following covariates in the final population PK model: • Time-varying body weight on all apparent clearances and volumes of distribution (CL/F, Q/F, Vc/F, Vp/F) • Formulation on the rate of absorption, lag-time, and relative bioavailability • Dose on the rate of absorption and relative bioavailability for patients 12 years of age and older

Figure 8. Schematic of Final Population PK Model for Berotralstat



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 5, pg. 59)
Abbreviations: CL/F, apparent clearance; F_{rel}, relative bioavailability; Ka_{1-2}, absorption rate constants; PK, pharmacokinetic; Q/F, apparent intercompartmental clearance; T_{lag1-2}, lag time in absorption; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment

Model parameter estimates	Model parameter estimates from the final model are shown below in Table 30.

Table 30. Model Parameter Estimates for the Final Population PK Model for Berotralstat

Parameter	Unit	Estimate	Variability (%)[a]	RSE (%)	Shrinkage (%)
Fixed parameters (θ)					
Apparent (oral) clearance (CL/F)	L/h	134	-	2.53	-
Apparent volume of the central compartment (Vc/F)	L	177	-	7.65	-
Apparent intercompartmental clearance (Q/F)	L/h	189	-	3.58	-
Apparent volume of the peripheral compartment (Vp/F)	L	5040	-	3.56	-
Fractional decrease in CL/F after 24 hr	-	0.437	-	2.78	-
Exponent of body weight on CL/F	-	0.582	-	11.11	-
Exponent of body weight on Vc/F	-	0.649	-	40.58	-

Parameter	Details					
	Exponent of body weight on Q/F	-	1.142	-	9.99	-
	Exponent of body weight on Vp/F	-	0.712	-	12.71	-
	Dose on F_{rel}, (b) (4)-capsule in adults	-	0.351	-	4.39	-
	Dose on F_{rel}, (b) (4)-capsule in adults	-	0.301	-	3.06	-
	Dose on F_{rel}, Oral pellets in adults	-	0.361	-	1.69	-
	Rapid absorption compartment					
	$Tlag_1$, (b) (4)-capsule & (b) (4)-capsule	h	0.457	-	0.38	-
	$Tlag_1$, oral pellets	h	0.371	-	1.49	-
	Ka_1, Dose >450 mg, (b) (4)-capsule	h^{-1}	0.160	-	19.80	-
	Ka_1, Dose ≤450 mg, (b) (4)-capsule	h^{-1}	0.129	-	3.11	-
	Ka_1, Dose >450 mg, (b) (4)capsule	h^{-1}	0.122	-	6.43	-
	Ka_1, Dose ≤450 mg, (b) (4)-capsule	h^{-1}	0.140	-	3.02	-
	Ka_1, Dose >450 mg, Oral pellets	h^{-1}	0.118	-	9.50	-
	Ka_1, Dose ≤450 mg, Oral pellets	h^{-1}	0.117	-	3.97	-
	Logit of fraction of dose to rapid absorption compartment	-	2.440	-	3.04	-
	Fraction of dose to rapid absorption compartment	-	0.920	-	-	-
	Slow absorption compartment					
	$Tlag_2$	h	4.020	-	FIXED	-
	Ka_2	h^{-1}	0.460	-	9.14	-
	Inter-individual variability (η)					
	CL/F	-	0.0986	31.4	10.13	26.5
	Vc/F	-	0.4429	66.6	24.17	58.3
	Q/F	-	0.1427	37.8	14.33	44.6
	Vp/F	-	0.1533	39.2	11.96	52.0
	Ka[b]	-	0.0409	20.2	22.27	59.6
	Inter-occasion variability (ξ)					
	CL/F	-	0.0745	27.3	11.46	56.4/40.4[c]
	Vc/F	-	0.8008	89.5	12.91	54.4/54.2[c]
	Residual error (σ)					7.5
	Additive error	ng/mL	4.291	-	0.12	-
	Proportional error, Phase 1	-	0.175	17.5	0.44	-
	Proportional error, Phase 2/3 serial	-	0.174	17.4	2.13	-
	Proportional error, Phase 2/3 sparse	-	0.294	29.4	0.97	-

Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 6, pg. 61-62)
[a] Variability is expressed as a percent coefficient of variation
[b] There was a single inter-individual variability term for both Ka_1 and Ka_2
[c] Shrinkage on inter-occasion variability is shown for each of the two occasions
Abbreviations: API, active pharmaceutical ingredient; CL/F, apparent clearance; F_{rel}, relative bioavailability; Ka_2, slow absorption rate constant; PK, pharmacokinetic; Q/F, apparent intercompartmental clearance; RSE, relative standard deviation; $Tlag_1$, lag time in absorption for rapid absorption compartment; Ka_1, rapid absorption rate constant; $Tlag_2$, lag time in absorption for slow absorption compartment; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment

Parameter	Details
Bootstrap analysis	A nonparametric bootstrap was performed, for which the population PK dataset was resampled with replacement (N=200 samples) with individual subjects as the sampling term and stratified by age group (i.e., pediatric [2 to <12 years of age] and all others [≥12 years of age]). All parameter estimates for the final model were contained within the 95% prediction intervals calculated across the bootstrap replicates (Table 31).

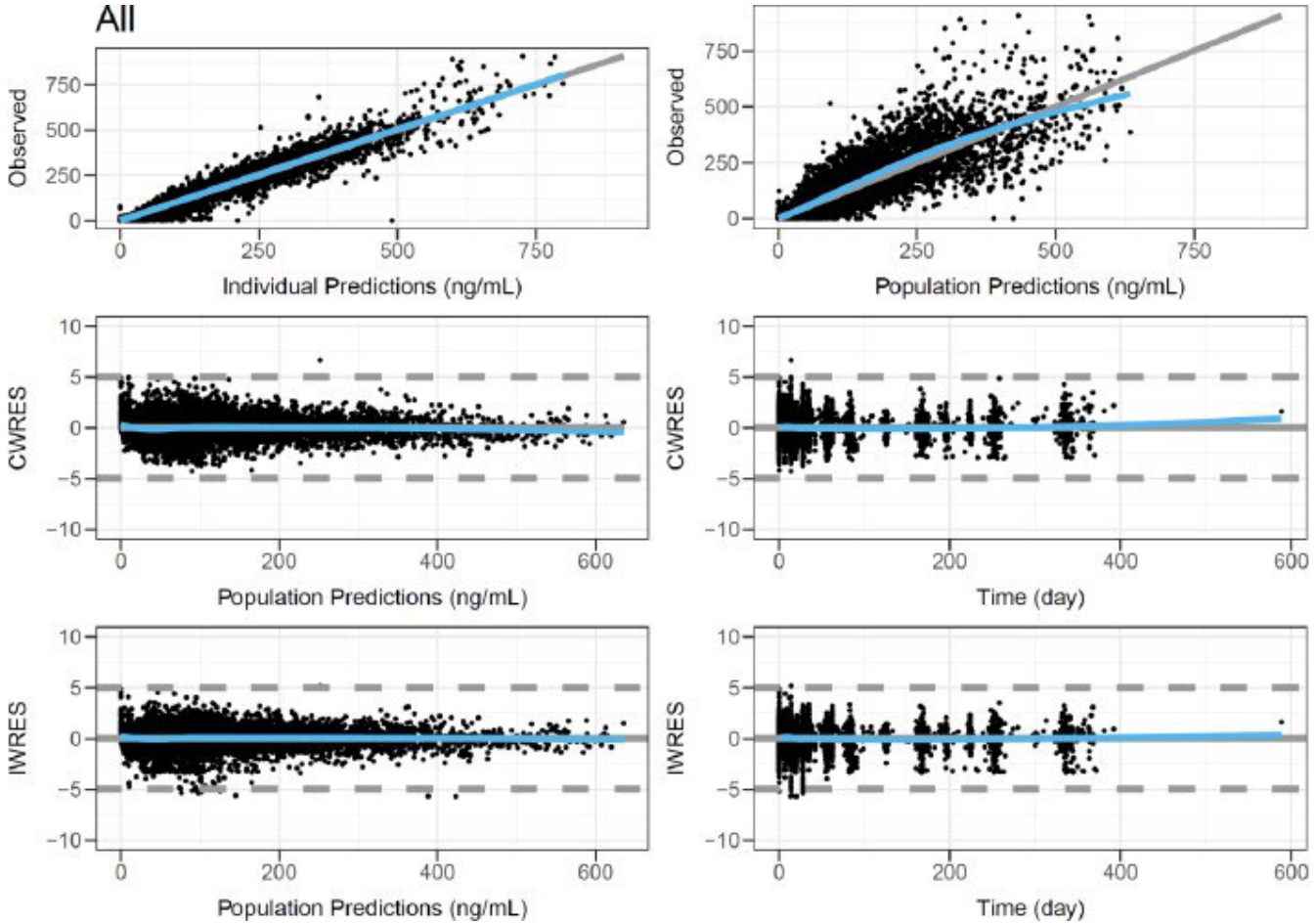
Table 31. Bootstrap Estimates for the Final Population PK Model[a]

Parameter	Estimates	Bootstrap Estimates 5%	50%	95%
Fixed parameters (θ)				
Apparent (oral) clearance (CL/F)	134	124	133	141
Apparent volume of the central compartment (Vc/F)	177	154	175	199
Apparent intercompartmental clearance (Q/F)	189	174	191	209
Apparent volume of the peripheral compartment (Vp/F)	5040	4617	5060	5739
Fractional decrease in CL/F after 24 hr	0.437	0.416	0.437	0.472
Exponent of body weight on CL/F	0.582	0.489	0.582	0.667
Exponent of body weight on Vc/F	0.649	0.325	0.656	0.975
Exponent of body weight on Q/F	1.142	0.951	1.150	1.312
Exponent of body weight on Vp/F	0.712	0.420	0.727	1.046
Dose on F_{rel}, [(b) (4)]-capsule in adults	0.351	0.290	0.352	0.432
Dose on F_{rel}, [(b) (4)]-capsule in adults	0.301	0.259	0.309	0.352
Dose on F_{rel}, Oral pellets in adults	0.361	0.282	0.369	0.458
Rapid absorption compartment				
$Tlag_1$, [(b) (4)]-capsule & [(b) (4)]-capsule	0.457	0.449	0.459	0.466
$Tlag_1$, oral pellets	0.371	0.346	0.371	0.405
Ka_1, Dose >450 mg, [(b) (4)]-capsule	0.160	0.102	0.159	0.212
Ka_1, Dose ≤450 mg, [(b) (4)]-capsule	0.129	0.120	0.129	0.141
Ka_1, Dose >450 mg, [(b) (4)]-capsule	0.122	0.106	0.121	0.148
Ka_1, Dose ≤450 mg, [(b) (4)]-capsule	0.140	0.128	0.141	0.158
Ka_1, Dose >450 mg, oral pellets	0.118	0.093	0.114	0.147
Ka_1, Dose ≤450 mg, oral pellets	0.117	0.103	0.118	0.131
Logit of fraction of dose to rapid absorption compartment	2.440	2.126	2.441	2.674
Slow absorption compartment				
$Tlag_2$	4.020	4.020	4.020	4.180
Ka_2	0.460	0.337	0.473	0.580
Inter-individual variability (η)				
CL/F	0.0986	0.0742	0.0975	0.1233

Parameter	Details				
	Vc/F	0.4429	0.2660	0.4426	0.6905
	Q/F	0.1427	0.1072	0.1422	0.1854
	Vp/F	0.1533	0.0918	0.1509	0.1978
	Ka[b]	0.0409	0.0253	0.0409	0.0584
	Inter-occasion variability (ξ)				
	CL/F	0.0745	0.0610	0.0738	0.0923
	Vc/F	0.8008	0.6284	0.8150	1.0145
	Residual error (σ)				
	Additive error	4.291	2.125	4.248	6.007
	Proportional error, Phase 1	0.175	0.160	0.175	0.193
	Proportional error, Phase 2/3 serial	0.174	0.147	0.172	0.203
	Proportional error, Phase 2/3 sparse	0.294	0.278	0.294	0.315
	Source. Adapted from Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 20, pg. 185) [a] Data was stratified by pediatric (2 to <12 years of age) and all others (≥12 years of age) [b] There was a single inter-individual variability term for both Ka_1 and Ka_2 Abbreviations: API, active pharmaceutical ingredient; CL/F, apparent clearance; F_{rel}, relative bioavailability; Ka_1, rapid absorption rate constant; Ka_2, slow absorption rate constant; PK, pharmacokinetic; Q/F, apparent intercompartmental clearance; $Tlag_1$, lag time in absorption for rapid absorption compartment; $Tlag_2$, lag time in absorption for slow absorption compartment; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment				
Goodness-of-Fit, VPC	Goodness-of-fit (GoF) plots are provided below for all trials and stratified by Trial 304 cohort (intensive and sparse PK sampling) in Figure 9 and Figure 10, respectively. Overall, good agreement was demonstrated between observed and predicted berotralstat concentrations.				

Parameter	Details

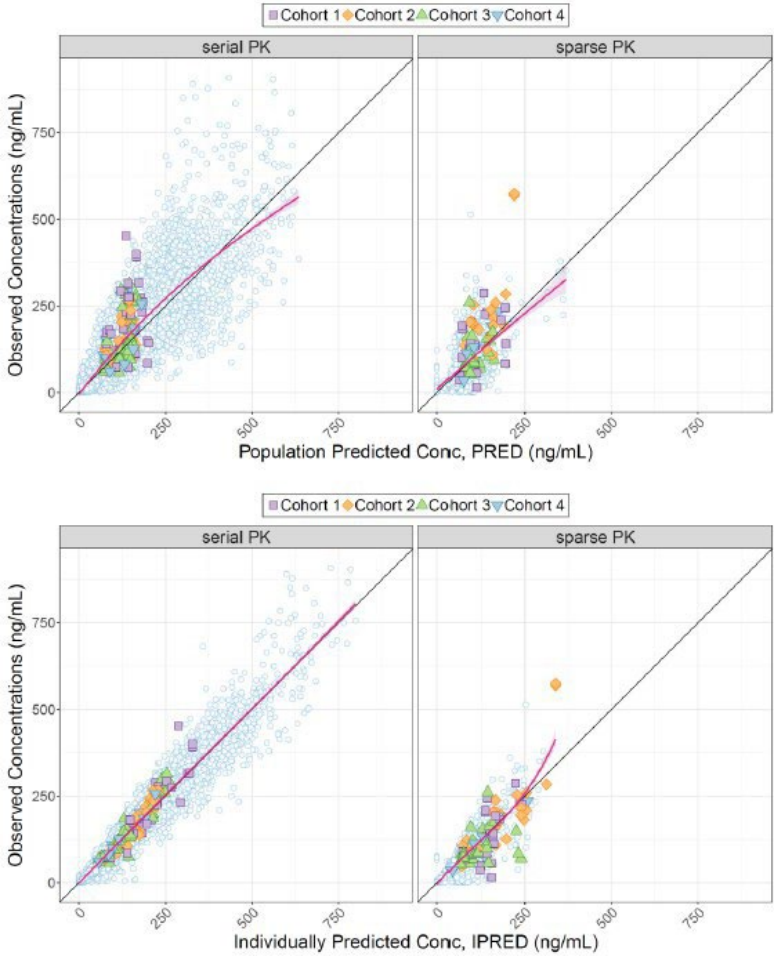
Figure 9. GoF Plots for the Final Population PK Model



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 6, pg. 64)
Note: Each black dot represents a PK record. Solid line is line of identity or zero line; dashed lines indicate absolute CWRES thresholds of 5; blue line is a smoothing function
Abbreviations: CWRES, conditional weighted residuals; IWRES, individual weighted residuals; GoF, goodness-of-fit; PK, pharmacokinetic

Parameter	Details

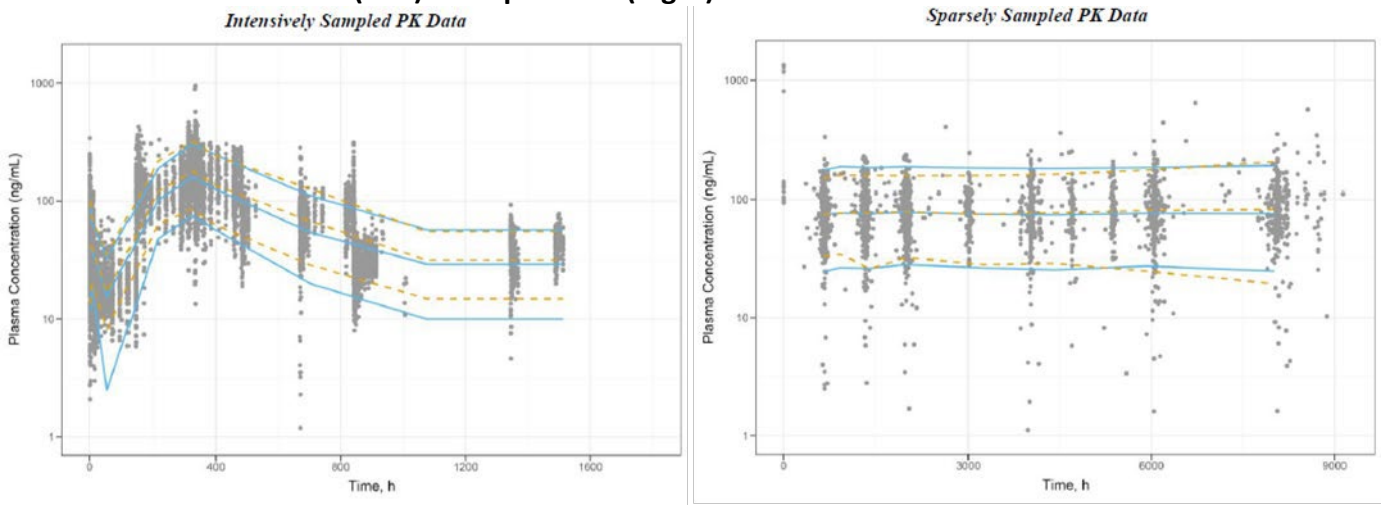
Figure 10. GoF Plots for Final Population PK Model, Stratified by Trial 304 Cohort



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 7, pg. 65)
Note: Small blue circles represent PK records for trial participants other than pediatric participants in Trial 304; larger colored symbols represent PK records, grouped by cohort, in pediatric participants in Trial 304
Abbreviations: GoF, goodness-of-fit; IPRED, individually predicted concentrations; PK, pharmacokinetic; PRED, population predicted concentrations

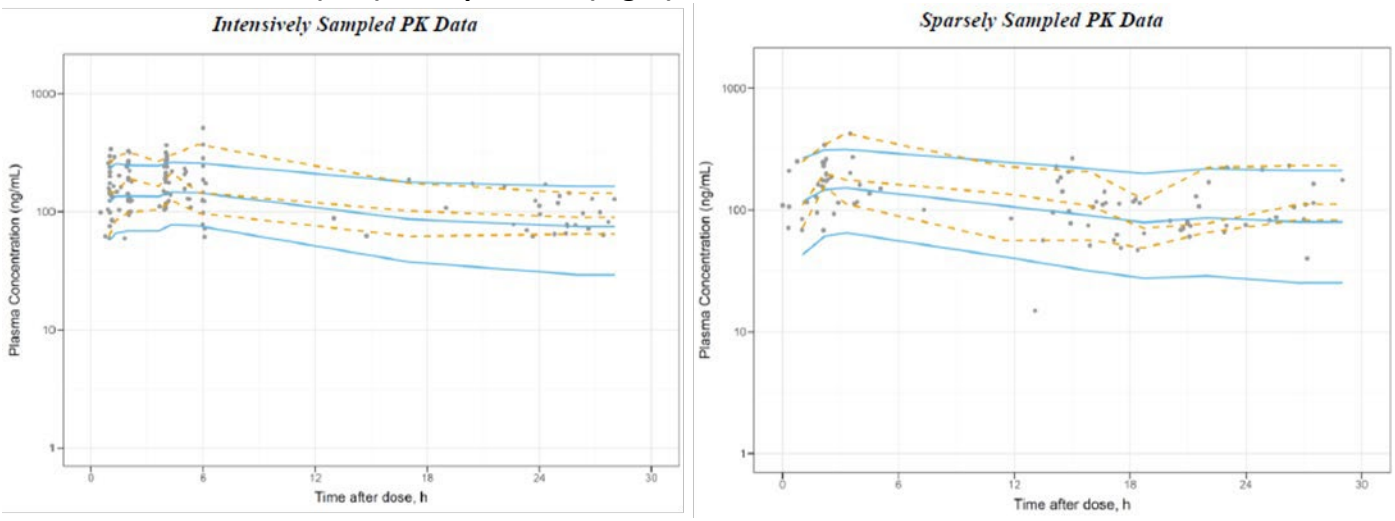
Parameter	Details
	Additionally, prediction-corrected VPC plots of berotralstat PK versus time based on both intensive and sparse PK sampling are shown below for all trials and Trial 304 in Figure 11 and Figure 12, respectively. Based on these VPC plots, the model slightly underestimates berotralstat exposure at lower concentrations (i.e., 5th percentile). Additionally, underestimation was also observed at early timepoints in Trial 304. Overall, it appears that the final model reasonably describes the observed data.

Figure 11. Prediction-Corrected VPC of Berotralstat PK vs. Time Across All Studies Using the Final Population PK Model for Intensive PK (Left) and Sparse PK (Right) Data



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 8, pg. 66)
Note: Points are observed plasma concentrations. Time is time since first dose administration in hours. Gold dashed lines are the 50th, 5th, and 95th percentile of measured concentrations. Blue lines are the 50th, 5th, and 95th percentile of 1000 simulated subjects
Abbreviations: PK, pharmacokinetic; VPC, visual predictive check

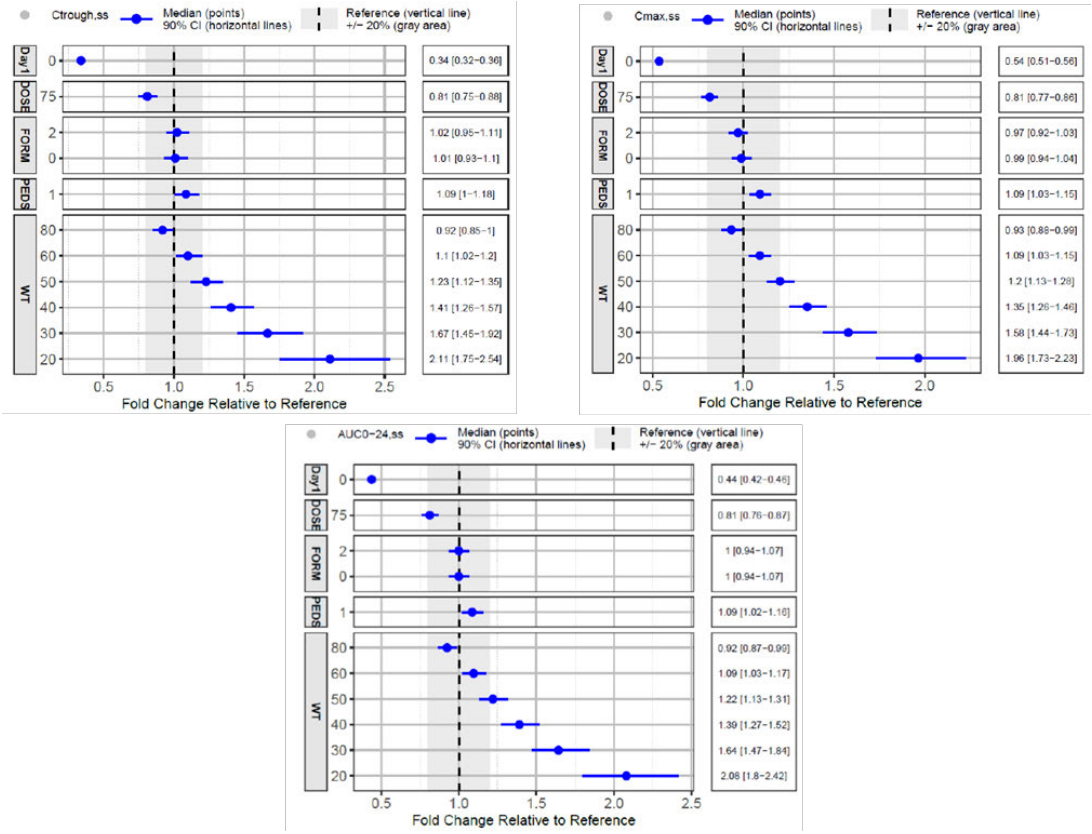
Parameter	Details
	Figure 12. Prediction-Corrected VPC of Berotralstat PK Versus Time in Trial 304 Using the Final Population PK Model for Intensive PK (Left) and Sparse PK (Right) Data



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 9, pg. 67)
Note: Points are observed plasma concentrations. Time is time since first dose administration in hours. Gold dashed lines are the 50th, 5th, and 95th percentile of measured concentrations. Blue lines are the 50th, 5th, and 95th percentile of 1000 simulated subjects
Abbreviations: PK, pharmacokinetic; VPC, visual predictive check

Significant Covariates and Clinical Relevance	Forest plots depicting the effects of retained covariates on berotralstat PK parameters ($C_{trough,ss}$, $C_{max,ss}$, and $AUC_{0-24h,ss}$) compared to a typical adult reference subject are presented below in Figure 13. Based on these plots, dose, formulation (i.e., oral capsule versus oral pellet), and age group (i.e., adult versus pediatric) did not have a significant impact on berotralstat exposure. However, body weight ≤40 kg appeared to contribute to significantly higher berotralstat exposure based on $C_{trough,ss}$, $C_{max,ss}$, and $AUC_{0-24h,ss}$.

Parameter	Details
	Figure 13. Covariate Effects on Predicted Berotralstat PK Parameters ($C_{trough,ss}$, $C_{max,ss}$, and $AUC_{24h,ss}$) Relative to Reference Subjects Using the Final Population PK Model



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 10, 11, and 12 [pg. 69-71])
Note: Reference subject defined as a 70 kg adult who received 150 mg QD capsule at steady state. Blue dot and horizontal bar represent the fold-change (median and 90% CI) of the covariate effect. Gray shaded region corresponds to fold-change of 0.8 to 1.2.
Abbreviations: $AUC_{0-24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours at steady state; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; DOSE, dose in mg; FORM, formulation (0 = oral capsule, 2 = oral pellet); PEDS, pediatric population; PK, pharmacokinetic; WT, body weight

Monte-Carlo Simulations to	In order to inform the adult exposure-matching approach to pediatric dose selection, the covariate effect of body weight on berotralstat PK was characterized further. The Applicant performed a series of Monte-Carlo simulations using the final

Parameter	Details
Support Proposed Pediatric Dosing	population PK model, whereby berotralstat PK parameters ($C_{trough,ss}$, $C_{max,ss}$, $AUC_{0-24h,ss}$, and $C_{ave,ss}$) were predicted under various dosing scenarios according to berotralstat dose and weight band stratification. (b) (4) each oral pellet contains 6 mg of berotralstat as free base, potential berotralstat oral pellet doses ranging from (b) (4) mg QD were simulated in (b) (4) Additionally, dosing paradigms consisting of up to 9 weight bands were considered for pediatric patients with body weight ranging from (b) (4) kg (Table 32).

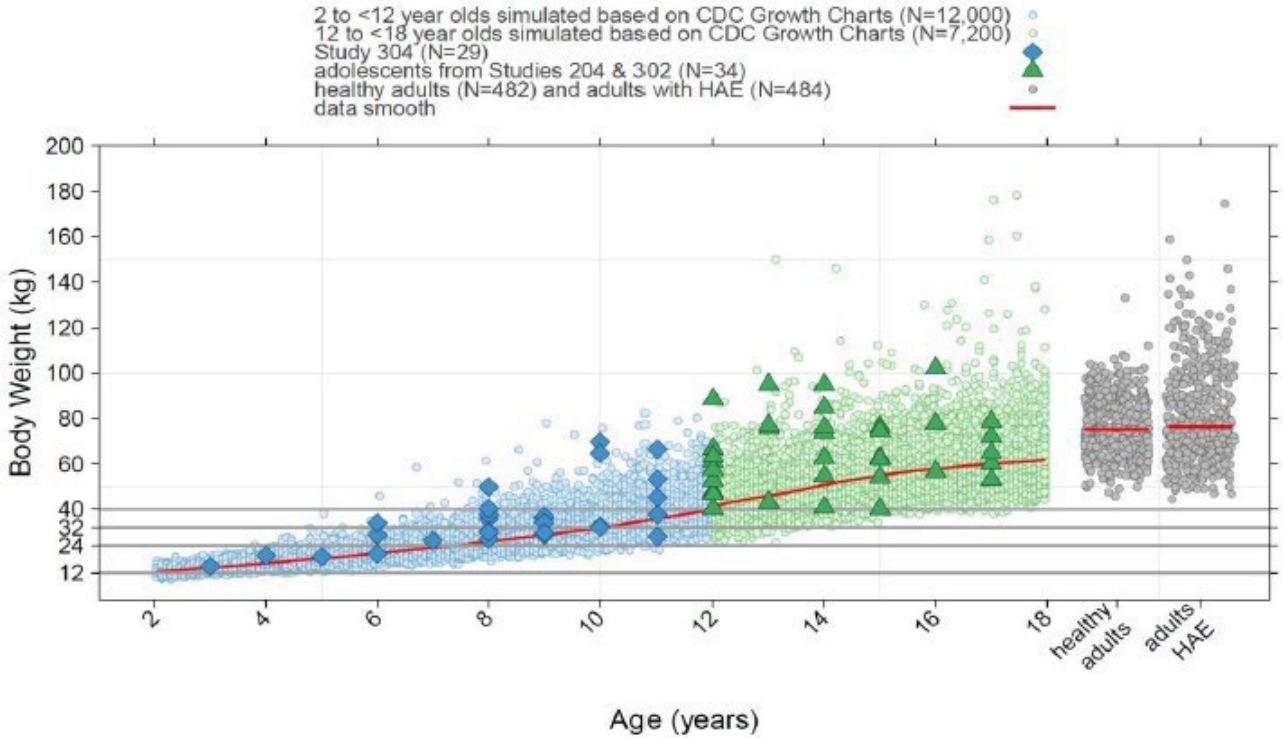
Table 32. Summary of Potential Berotralstat Dosing Scenarios Considered by the Applicant to Inform Pediatric Dose Selection

Dosing Scenario	# Weight Bands	Simulated Pediatric Weight Bands (Simulated Berotralstat Oral Pellet Dosing Regimens)[a]
		(b) (4)

Source. Compiled by reviewer from Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Table 11 [pg. 84-87] and Tables 21-32 [pg. 219-268])
[a] All dosing regimens explored were administered QD
Abbreviations: PK, pharmacokinetic; QD, once daily

Parameter	Details
	To inform the dosing scenario simulations outlined above in Table 32, a virtual pediatric population of subjects 2 to less than 12 years of age was generated based on the CDC weight-for-age growth charts, with body weights ranging from 9 to 77 kg (N=12,000). Actual body weights of subjects enrolled in Trial 304 were generally higher than the 50th percentile of the expected body weights for age based on CDC growth charts (Figure 14).

Figure 14. Simulated Body Weights for Pediatric HAE Subjects Based on CDC Growth Charts Overlaid With Observed Body Weights From Trial 304 Compared to Observed Body Weights of Adults and Adolescents ≥12 Years of Age

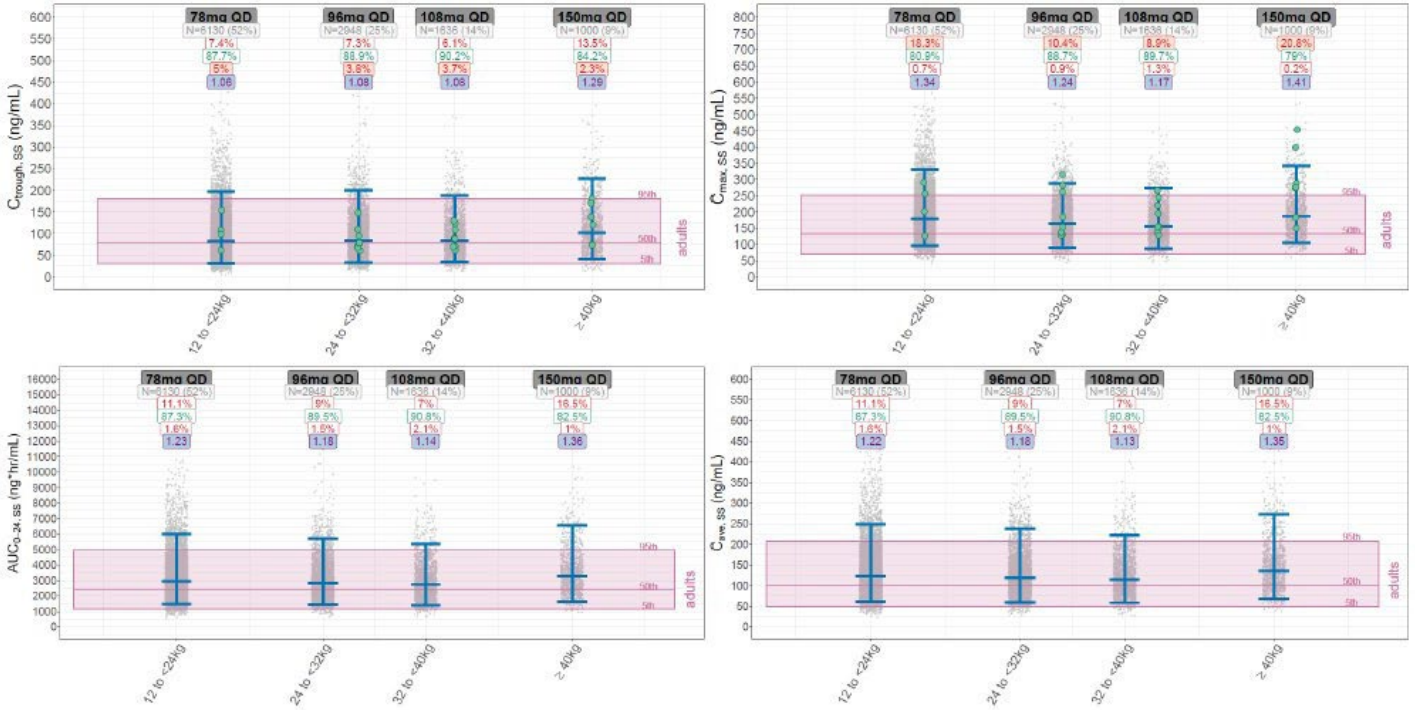


Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 13, pg. 76)
Abbreviations: CDC, Centers for Disease Control and Prevention; HAE, hereditary angioedema; N, number of subjects; PK, pharmacokinetic

Parameter	Details
	Using the final population PK model and simulated pediatric population, steady-state berotralstat PK parameters were simulated for pediatric subjects 2 to less than 12 years of age at the doses and weight bands administered in Trial 304 and compared to the adult reference range (Figure 15). Based on observed PK data from Trial 304 as well as PK simulations according to the berotralstat dosing scenarios described in Figure 15, the Applicant initially proposed the dosing scenario outlined below in Figure 16 upon submission of the current NDA. (b) (4)

Parameter	Details

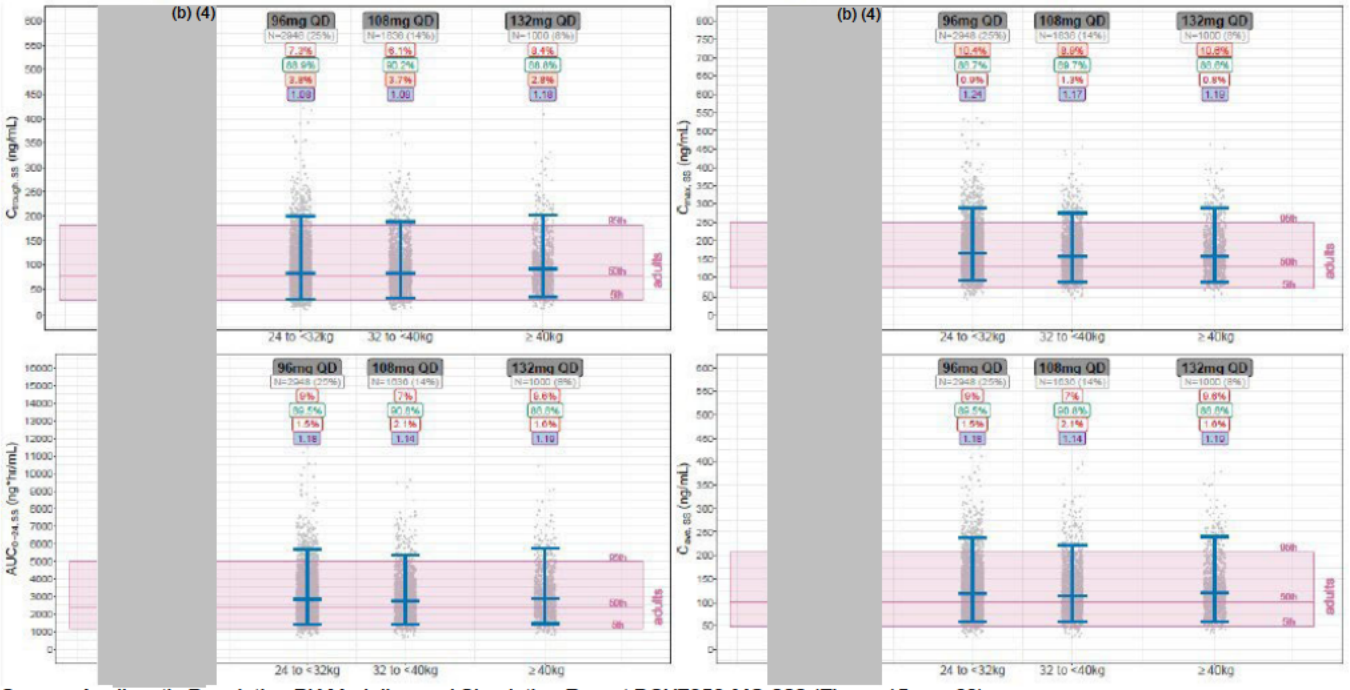
Figure 15. Simulated Steady-State Berotralstat PK Parameters for Pediatric Subjects 2 to <12 Years of Age Compared to Adult Reference Range Using the Final Population PK Model (Trial 304 Dosing)



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 14, pg. 80)
Note: Red horizontal lines correspond to 5th, 50th, and 95th percentiles of the simulated $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0-24h,ss}$, and $C_{ave,ss}$ for adults following steady-state dosing with 150 mg commercial capsule; Grey points correspond to simulated $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0-24h,ss}$, and $C_{ave,ss}$ for pediatric patients following the dose levels specified in the grey boxes above each group, which are summarized with 5th, 50th, and 95th percentiles presented in blue; Grey shaded rectangles at the top represent the dosing regimen (oral pellets formulation) for each weight bands; Light grey rectangles summarize the number and percent of simulated values for each weight band; Top red rectangle represents the percent of simulated pediatric values >95th percentile of adults; Green rectangle represents the percent of simulated pediatric values within 5th and 95th percentiles of adults; Lower red rectangle represents the percent of simulated pediatric values <5th percentile of adults; Bottom purple rectangle represents the ratio of 50th percentile of pediatric values to 50th percentile of adults; Green circle symbols represent the observed pre-dose plasma concentrations (i.e., C_{trough}) at Week 2 or the observed C_{max} at Week 2
Abbreviations: $AUC_{0-24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours at steady state; $C_{ave,ss}$, average plasma concentration at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; N, number of subjects; PK, pharmacokinetic; QD, once daily

Parameter	Details

Figure 16. Simulated Berotralstat PK Parameters for Pediatric Subjects 2 to <12 Years of Age Relative to Adult Reference Range Using the Final Population PK Model (Initially Proposed Dosing at Time of Current NDA Submission)



Source. Applicant's Population PK Modeling and Simulation Report BCX7353-MS-002 (Figure 15, pg. 89)
Note: Red horizontal lines correspond to 5th, 50th, and 95th percentiles of the simulated $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0\text{-}24h,ss}$, and $C_{ave,ss}$ for adults following steady-state dosing with 150 mg commercial capsule; Grey points correspond to simulated $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0\text{-}24h,ss}$, and $C_{ave,ss}$ for pediatric patients following the dose levels specified in the grey boxes above each group, which are summarized with 5th, 50th, and 95th percentiles presented in blue; Grey shaded rectangles at the top represent the dosing regimen (oral pellets formulation) for each weight bands; Light grey rectangles summarize the number and percent of simulated values for each weight band; Top red rectangle represents the percent of simulated pediatric values >95th percentile of adults; Green rectangle represents the percent of simulated pediatric values within 5th and 95th percentiles of adults; Lower red rectangle represents the percent of simulated pediatric values <5th percentile of adults; Bottom purple rectangle represents the ratio of 50th percentile of pediatric values to 50th percentile of adults
Abbreviations: $AUC_{0\text{-}24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours at steady state; $C_{ave,ss}$, average plasma concentration at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; PK, pharmacokinetic; N, number of subjects; NDA, new drug application; QD, once daily

Parameter	Details

However, the FDA noted concerns with the proposed dosing, particularly regarding the Applicant's proposal (b) (4) The Agency further recommended a dosage reduction to 72 mg QD for pediatric patients weighing 12 to <24 kg, given continued concern for potential concentration-dependent QT prolongation at the 78 mg QD dose level. The simulated median berotralstat $C_{trough,ss}$ and $C_{max,ss}$, with comparisons to the adult reference range, are provided below for the final proposed berotralstat dosing and weight bands (Table 33). Refer to Section 6.3.1 for additional discussion of the adequacy of the available clinical pharmacology data to support the final proposed dosing.

Table 33. Simulated Berotralstat $C_{trough,ss}$ and $C_{max,ss}$ for Pediatric Subjects 2 to <12 Years of Age Relative to Adult Reference Range Using the Final Population PK Model (Final Proposed Dosing)

		PK Parameter					
		$C_{trough,ss}$ (ng/mL)			$C_{max,ss}$ (ng/mL)		
Berotralstat Dose[a]	BW (kg)	Median (P5 – P95)	Ratio (Peds:Adults)	% < Adult P5	Median (P5 – P95)	Ratio (Peds:Adults)	% > Adult P95
150 mg QD	Adults[b]	78 (31 – 180)	Reference	Reference	133 (70 – 251)	Reference	Reference
132 mg QD	≥40	92 (38 – 202)	1.18	2.8	158 (87 – 290)	1.19	10.6
108 mg QD	32 to <40	84 (35 – 188)	1.08	3.7	156 (87 – 274)	1.17	8.9
96 mg QD	24 to <32	84 (33 – 200)	1.08	3.8	165 (91 – 289)	1.24	10.4
72 mg QD	12 to <24	77 (29 – 182)	0.99	6.1	164 (88 – 306)	1.23	13.3

Source. Adapted from Applicant's response to Agency request for information, dated October 14, 2025 (Table 1, pg. 4)
[a] 150 mg QD given as commercial oral capsule dosage form; All other doses (132, 108, 96, and 78 mg QD) given as oral pellet dosage form
[b] Adult reference range defined as the 5th to 95th percentiles of observed steady state values derived from Trials 106 and 116 (N=50)
Abbreviations: BW, body weight; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; N, number of subjects; P5, 5th percentile; P95, 95th percentile; PK, pharmacokinetic; QD, once daily

Parameter	Details
Labeling language	*Description*
8.4, Pediatric Use	The Applicant proposed to include the following language: (b) (4) The following edits in red are recommended and agreed upon in the labeling: "The use of ORLADEYO in pediatric patients aged 2 to <12 years with HAE is supported by (b) (4) f efficacy data from an adequate and well-controlled trial in adults and pediatric patients aged 12 years and older (Trial 1), and (b) (4) pharmacokinetic~~,~~ and safety, (b) (4) data from 29 pediatric patients aged 2 to less than 12 years enrolled in a multicenter, single-arm, open-label trial (b) (4) with ~~additional~~ support from population pharmacokinetic analyses (b) (4) . Pediatric patients aged 2 to less than 12 years received a dosage of ORLADEYO based on the patient's body weight, which showed no clinically significant difference in drug exposures from those observed in adults treated with ORLADEYO 150 mg [see Clinical Pharmacology (12.3)]."
12.3, Pharmacokinetics	The Applicant proposed to include the following language: (b) (4) The following edits in red are recommended and agreed upon in the labeling: "Based on population pharmacokinetics analyses that included pediatric patients 2 to <12 years of age, body weight was the only covariate with a clinically (b) (4) significant impact on the systemic exposure of berotralstat. (b) (4) (b) (4) In pediatric patients 2 to <12 years of age at the recommended dosage based on body weight, median C_{max} at steady state is expected to be up to (b) (4) 24% higher compared to adults. However, this

Parameter	Details
	difference is not considered to be clinically (b) (4) significant [see Dosage and Administration (2.2) and Use in Special Populations (8.4)].”

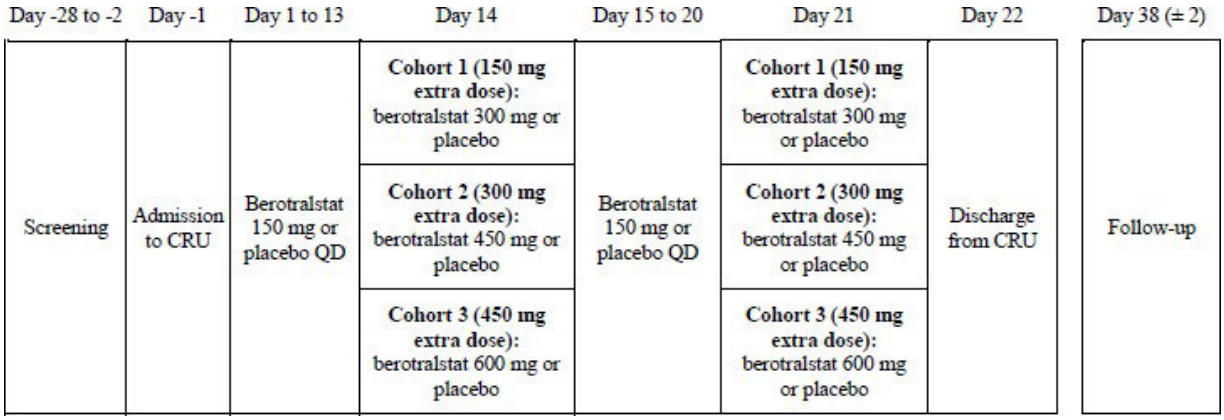
Source. Applicant’s Population PK Modeling and Simulation Report BCX7353-MS-002; Applicant response to Agency request for information, dated May 22, 2025; Proposed Labeling
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; ALT, alanine aminotransferase; API, active pharmaceutical ingredient; AST, aspartate aminotransferase; $AUC_{0\text{-}24h,ss}$, area under the plasma concentration-time curve from 0 to 24 hours at steady state; BLQ, below the limit of quantitation; BMI, body mass index; $C_{ave,ss}$, average plasma concentration at steady state; CI, confidence interval; CL/F, apparent clearance; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; CDC, Centers for Disease Control and Prevention; CWRES, conditional weighted residuals; DDI, drug-drug interaction; eGFR, estimated glomerular filtration rate; FOCEI, first-order conditional estimation with interaction; F_{rel}, relative bioavailability; GoF, goodness-of-fit; HAE, hereditary angioedema; IBW, ideal body weight; IPRED, individually predicted concentrations; IWRES, individual weighted residuals; K_a, absorption rate constant; Max, maximum; Min, minimum; N, number of subjects; NDA, new drug application; NONMEM, nonlinear mixed effects modeling; P5, 5th percentile; P95, 95th percentile; PK, pharmacokinetic; PRED, population predicted concentrations; PsN, perl-speaks-nonmem; QD, once daily; Q/F, apparent intercompartmental clearance; RSE, relative standard error; SD, standard deviation; T_{lag}, lag time in absorption; Vc/F, apparent volume of distribution in the central compartment; VPC, visual predictive check; Vp/F, apparent volume of distribution in the peripheral compartment

14.3.2 Trial 116

Trial Design

Trial 116 was a Phase 1, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the effects of extra doses of berotralstat on the QT/QTc interval in healthy adult subjects when administered at steady state following administration of the approved dosage regimen of 150 mg oral capsule QD (Figure 17). The Applicant's rationale for this trial was to explore the possibility of further development of berotralstat for the treatment of HAE patients who experience breakthrough attack symptoms while taking prophylactic doses of berotralstat.

Figure 17. Overall Trial Design for Trial 116



Source. CSR for Trial 116 (Figure 1, pg. 23)
Abbreviations: CRU, clinical research unit; QD, once daily

A total of 56 subjects were randomized in a 2:1 ratio to receive berotralstat or placebo in one of three sequential dose cohorts:

- **Cohort 1:** Berotralstat 150 mg or placebo QD on Days 1 to 21; Extra dose of 150 mg berotralstat or placebo administered on Days 14 and 21 (N=12 berotralstat; N=6 Placebo)
- **Cohort 2:** Berotralstat 150 mg or placebo QD on Days 1 to 21; Extra dose of 300 mg berotralstat or placebo administered on Days 14 and 21 (N=12 berotralstat; N=6 Placebo)
- **Cohort 3:** Berotralstat 150 mg or placebo QD on Days 1 to 21; Extra dose of 450 mg berotralstat or placebo administered on Days 14 and 21 (N=13 berotralstat; N=7 Placebo)

The trial enrolled male and female adult subjects 18 to 50 years of age (inclusive) with a body mass index of 18 and 29.9 kg/m^2 (inclusive). Subjects with eGFR <80 mL/min/1.73m^2 or AST/ALT ≥2 times the ULN were excluded, as well as those with abnormal ECG results at screening. Additionally, subjects were required to refrain from taking any over-the-counter medication, prescribed medication, vitamins, or herbal products (including St. John's wort, milk thistle) from 14 days before Day 1 until the follow-up visit. Hormonal contraception, hormone replacement therapy, acetaminophen, and COVID-19 vaccination were permitted per protocol.

Subject Disposition and Demographics

Among the 56 subjects who were enrolled, 19 participants were randomized to placebo and 37 were randomized to one of the three active berotralstat treatment arms. Of the participants randomized to receive berotralstat, 94.6% (N=35) completed the entire trial; Subjects (b) (6) (Cohort 1) and (b) (6) (Cohort 3) withdrew after Day 14 and Day 9, respectively. There were no major protocol deviations reported. A summary of baseline demographics in each treatment group is provided below in Table 34.

Table 34. Summary of Baseline Demographics in Trial 116

Demographic Statistic	All Placebo (N=19)	Cohort 1 (N=12)	Cohort 2 (N=12)	Cohort 3 (N=13)
Age (years)				
Mean (SD)	37.8 (8.1)	34.5 (9.7)	40.9 (10.9)	37.2 (5.2)
Median (Min, Max)	40.0 (26, 49)	33.0 (20, 48)	45.5 (20, 50)	37.0 (29, 47)
Sex, N (%)				
Male	15 (78.9)	7 (58.3)	5 (41.7)	10 (76.9)
Female	4 (21.1)	5 (41.7)	7 (58.3)	3 (23.1)
Weight (kg)				
Mean (SD)	78.2 (11.3)	74.9 (11.0)	73.8 (9.2)	72.9 (7.8)
Median (Min, Max)	76.4 (59.1, 101.1)	75.2 (54.9, 92.1)	74.6 (54.9, 88.3)	74.1 (58.7, 85.0)
BMI (kg/m^2)				
Mean (SD)	25.9 (2.8)	25.7 (2.9)	26.1 (3.0)	24.5 (2.6)
Median (Min, Max)	25.8 (20.2, 30.2)	26.0 (21.0, 30.2)	26.3 (20.8, 29.8)	24.5 (21.1, 29.6)

Source. Adapted from CSR for 116 (Table 14.1.3, pg. 136-137)
Abbreviations: BMI, body mass index; CSR, clinical study report; Max, maximum; Min, minimum; N, number of subjects; SD, standard deviation

PK Sampling and Analysis

The PK population consisted of subjects who received at least one dose of berotralstat with at least one measurable concentration, which included all 37 subjects randomized to receive berotralstat treatment. Mean berotralstat plasma concentration-time profiles were plotted on both linear and semi-logarithmic scales by dose cohort. PK parameters were estimated using NCA and summarized descriptively according to treatment regimen and trial day.

Plasma samples for berotralstat PK analysis relevant to this NDA were collected on Day 13 at pre-dose, and post-dose at 1, 2, 3, 4, 5, 6, 8, 12, and 24 h.

All plasma samples for determination of berotralstat concentrations were analyzed using a previously validated LC-MS/MS assay (Report 171354 (b) (4)), which was reviewed and found to be acceptable under NDA 214094 (Refer to the NDA Multidisciplinary Review and Evaluation dated December 3, 2020 [DARRTS Reference ID: 4711626]). Additionally, the in-trial bioanalysis results for Trial 116 met acceptance criteria.

Summary of PK Results

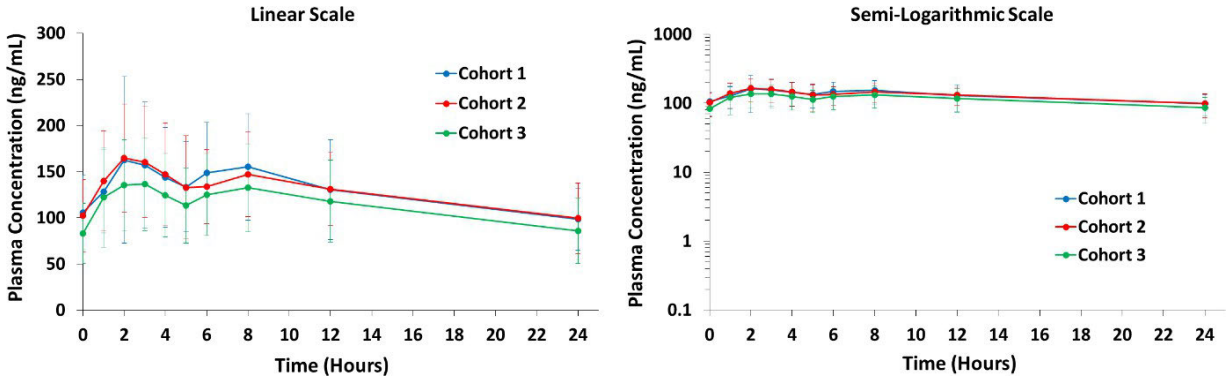
A summary of steady state berotralstat PK parameters at Day 13 according to dose cohort is provided below in Table 35. Additionally, overlayed arithmetic mean (SD) concentration-time profiles for each cohort are provided below in Figure 18. Berotralstat systemic exposure in Cohort 3 was slightly lower than that observed for Cohorts 1 and 2, although concentrations were similar to those observed across other clinical trials and are within the typical range of variability.

Table 35. Summary of Berotralstat PK Parameters on Day 13 According to Dose Cohort[a]

	Berotralstat Dose Cohort[b]		
PK Parameter	**Cohort 1 (N=12)**	**Cohort 2 (N=12)**	**Cohort 3 (N=12)[c]**
AUC_{tau} (ng*h/mL)	2932 (31.2)	2911 (34.6)	2528 (40.1)
C_{max} (ng/mL)	167.0 (36.3)	164.3 (36.2)	139.5 (40.1)
C_{trough} (ng/mL)	94.3 (30.0)	93.1 (39.0)	79.2 (46.0)
T_{max} (h)	4.5 (2.0, 8.0)	2.0 (1.0, 12.0)	3.0 (1.0, 8.0)

Source. Reviewer's analysis based on adpp.xpt for Trial 116
[a] All PK parameters reported as geometric mean (CV%), except for T_{max}, which is reported as median (min, max)
[b] All dose cohorts received berotralstat 150 mg oral capsule QD from Days 1 through 13
[c] Although 13 subjects were enrolled in Cohort 3, subject (b) (6) withdrew on Day 9; Therefore, PK parameters for Cohort 3 are calculated based on N=12
Abbreviations: AUC_{tau}, area under the plasma concentration-time curve from 0 to the end of the dosing interval; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CV, coefficient of variation; Max, maximum; Min, minimum; N, number of subjects; PK, pharmacokinetic; QD, once daily; T_{max}, time of maximum plasma concentration

Figure 18. Arithmetic Mean (SD) Berotralstat Plasma Concentration-Time Profile on Day 13 Following Administration of the Approved Oral Capsule Dosage of 150 mg QD



Source. Reviewer's analysis based on adpc.xpt for Trial 116
Abbreviations: QD, once daily; SD, standard deviation

Relevance to the Current NDA Submission

The adult reference range, upon which the Applicant's exposure-matching pediatric extrapolation approach was based, included adult PK data obtained from 50 subjects across Trials 106 and 116. The adult reference population was defined as those who were dosed to steady state with the approved berotralstat oral capsule dosage of 150 mg QD, and for whom sufficient serial PK sampling was conducted to derive PK parameters via NCA. In Trial 116, adult steady state PK data from a total of 36 subjects (N=12 from each cohort) at Day 13 were

available and contributed to the adult reference population. In Trial 106, adult steady state PK data from the 150 mg cohort were available from a total of 14 subjects at Day 14.

Since Trial 106 was previously submitted and reviewed under NDA 214094, the details pertaining to the trial design and results are not repeated here (Refer to the IRT-CS review dated April 16, 2020 [DARRTS Reference ID: 4592746]).

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