25 February 2021
EMA/153239/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orladeyo

International non-proprietary name: berotralstat

Procedure No. EMEA/H/C/005138/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

Administrative information

Name of the medicinal product:	Orladeyo
applicant:	BioCryst Ireland Limited Rocktwist House, Block 1 Western Business Park Shannon Co. Clare V14 FW97 IRELAND
Active substance:	Berotralstat dihydrochloride
International Non-proprietary Name/Common Name:	berotralstat
Pharmaco-therapeutic group (ATC Code):	other hematological agents, drugs used in hereditary angioedema (B06AC)
Therapeutic indication(s):	Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Pharmaceutical form(s):	Capsule, hard
Strength(s):	150 mg
Route(s) of administration:	Oral use
Packaging:	blister (ACLAR/PVC-Alu)
Package size(s):	28 capsules 98 capsules

Table of contents

1. Background information on the procedure....7
1.1. Submission of the dossier....7
1.2. Steps taken for the assessment of the product....8
2. Scientific discussion....9
2.1. Problem statement....9
2.1.1. Epidemiology....9
2.1.2. Biologic features/Aetiology and pathogenesis....10
2.1.3. Clinical presentation, diagnosis....10
2.1.4. Management....10
2.2. Quality aspects....12
2.2.1. Introduction....12
2.2.2. Active substance....12
General information....12
Manufacture, characterisation and process controls....13
Stability....14
2.2.3. Finished medicinal product....15
Description of the product and Pharmaceutical development....15
Stability of the product....16
Adventitious agents....17
2.2.4. Discussion on chemical and pharmaceutical aspects....17
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects....17
2.2.6. Recommendations for future quality development....17
2.3. Non-clinical aspects....18
2.3.1. Introduction....18
2.3.2. Pharmacology....18
2.3.3. Pharmacokinetics....20
2.3.4. Toxicology....23
2.3.5. Ecotoxicity/environmental risk assessment....30
2.3.6. Discussion on non-clinical aspects....30
2.3.7. Conclusion on non-clinical aspects....34
2.4. Clinical aspects....34
2.4.1. Introduction....34
2.4.2. Pharmacokinetics....40
2.4.3. Pharmacodynamics....54
2.4.4. Discussion on clinical pharmacology....59
2.4.5. Conclusions on clinical pharmacology....66
2.5. Clinical efficacy....66
2.5.1. Dose response study....71
2.5.2. Main study....75
Ancillary analyses....93
Analysis performed across trials (pooled analyses and meta-analysis)....107

2.5.3. Discussion on clinical efficacy....119
2.5.4. Conclusions on the clinical efficacy....122
2.6. Clinical safety....123
Patient exposure....123
Adverse events....125
Serious adverse events and deaths....134
Laboratory findings....135
Safety in special populations....138
Immunological events....146
Safety related to drug-drug interactions and other interactions....146
Post marketing experience....148
2.6.1. Discussion on clinical safety....148
2.6.2. Conclusions on the clinical safety....153
2.7. Risk Management Plan....153
Safety concerns....153
2.8. Pharmacovigilance....159
2.9. New Active Substance....159
2.10. Product information....159
2.10.1. User consultation....159
2.10.2. Additional monitoring....159
3. Benefit-Risk Balance....160
3.1. Therapeutic Context....160
3.1.1. Disease or condition....160
3.1.2. Available therapies and unmet medical need....160
3.1.3. Main clinical studies....160
3.2. Favourable effects....161
3.3. Uncertainties and limitations about favourable effects....161
3.4. Unfavourable effects....162
3.5. Uncertainties and limitations about unfavourable effects....163
3.6. Effects Table....164
3.7. Benefit-risk assessment and discussion....165
3.7.1. Importance of favourable and unfavourable effects....165
3.7.2. Balance of benefits and risks....166
3.8. Conclusions....167
4. Recommendations....167

List of abbreviations

Alu	Aluminium
CoA	Certificate of Analysis
CMA	Critical material attribute
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Standard
DVS	Dynamic Vapour Sorption
EP	European Pharmacopoeia
GMP	Good Manufacturing Practice
HAE	Hereditary Angioedema
HDPE	High-density polyethylene
HPLC	High-performance liquid chromatography
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control
IR	Infrared spectroscopy
JP	Japanese Pharmacopoeia
KF	Karl Fischer
LDPE	Low-density polyethylene
LOQ	Limit of quantitation
MDD	Maximum daily dose
MO	Major objection
MS	Mass Spectrometry
MW	Molecular weight
NF	National formulary
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OoS	Out of Specification
PCTFE	Polychlorotrifluoroethylene
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PSD	Particle size distribution
PVC	Polyvinyl chloride

QC	Quality Control
QP	Qualified Person
QSAR	Quantitative structure–activity relationship
QTPP	Quality Target Product Profile
REC	Recommendation
RRF	Relative Response Factor
RRT	Relative Retention Time
SEM	Scanning electron microscope
SM	Starting material
TTC	Threshold of toxicological concern
USP	United States Pharmacopeia
UV	Ultraviolet
XRPD	X-ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioCryst Ireland Limited submitted on 9 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Orladeyo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

Orladeyo, was designated as an orphan medicinal product EU/3/18/2028 on 27 June 2018 in the following condition: Treatment of hereditary angioedema (HAE).

The applicant applied for the following indication: for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0061/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0061/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 30 March 2021 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/Orladeyo.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

applicant's request for consideration

New active Substance status

The applicant requested the active substance berotralstat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
12 October 2017	EMEA/H/SA/3647/1/2017/SME/III	Prof Bloechl-Daum/Dr Weis-Bjerrum/Dr Janssens

The Protocol assistance pertained to the following *non-clinical, and clinical* aspects:

- Carcinogenicity investigations
- Need to measure Phospholipidosis marker in phase 3 programme
- Plans to exclude QT time effects
- Management of Drug-Drug interactions and concomitant medications
- Liver safety monitoring during the phase 3 programme
- Management of rash during the phase 3 programme
- ADME characterisation
- Bioequivalence demonstration between Phase 2 and proposed commercial formulation
- Statistical analysis plan for phase 3 study BCX7353-302
- Study population to be included in phase 3 study BCX7353-302, including whether patients who experienced an acute HAE in a previous phase 2 study can be enrolled
- Inclusion of adolescent patients (12-17 years of age) in phase 3 study BCX7353-302
- Safety database for MAA
- Extent of envisaged efficacy data to be generated to support benefit/risk assessment

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Margareta Bego

The application was received by the EMA on	9 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	16 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	30 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 November 2020
The Rapporteurs circulated the updated Assessment Report on the	27 November 2020

responses to the List of Questions to all CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	01 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 February 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Orladeyo on	25 February 2021
The CHMP adopted a report on similarity of Orladeyo with Takhzyro on (Appendix 1)	25 February 2021

2. Scientific discussion

2.1. Problem statement

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

The great majority of cases are caused by mutations in *SERPINGrade 1*, the gene for the major regulator of the contact activation pathway, complement 1 esterase inhibitor (C1-INH), leading to dysregulation of bradykinin (BK) (Cicardi and Zuraw 2018). Insufficiency of C1-INH results in abnormally upregulated cleavage of high-molecular-weight kininogen (HK) by plasma kallikrein, releasing BK, which mediates angioedema (Kaplan and Joseph 2014).

The applicant proposes that Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema in patients aged 12 years and older.

2.1.1. Epidemiology

In several European epidemiology studies, the prevalence of HAE has been reported as between 1: 64,000 and 1: 92,000 and has shown no apparent ethnic variation.

It is estimated that HAE affects approximately 0.15 in 10,000 inhabitants of the EU/EEA. Based on a population of 516 million, it can be estimated that there are about 8000 people currently affected with HAE in the EEA.

The frequency of attacks in patients not taking a prophylactic medication varies, from rarely in some to every few days in others, with 59% of subjects reporting at least 1 attack per month (Caballero, Aygoren-Pursun et al. 2014).

2.1.2. Biologic features/Aetiology and pathogenesis

Hereditary angioedema is caused by mutations in the gene coding for C1 esterase inhibitor (C1-INH), resulting in deficiency (HAE type I) or dysfunction (HAE type II) of C1-INH protein.

The primary inhibitor of kallikrein in plasma is the *SERPIN Grade 1* gene product, C1-INH (Cicardi, Bork et al. 2012). C1-INH is a serine protease inhibitor that normally prevents uncontrolled contact activation and bradykinin (BK) production by covalently binding to and inactivating kallikrein (Patston, Gettins et al. 1991). Patients with C1-INH-HAE have mutations in the C1-INH gene that result in either a failure to produce C1-INH or the production of non-functional C1-INH (Pappalardo, Cicardi et al. 2000). The amount of functional C1-INH produced by the unaffected allele is insufficient to control serine protease activity, including that of kallikrein, that is induced by even asymptomatic levels of vascular endothelial contact activation (Cicardi, Bork et al. 2012). As a result, even when a patient does not experience any symptoms, plasma Kininogen (HK)levels may be lower than normal and BK is detectable (Cugno, Hack et al. 1993, Nussberger, Cugno et al. 1998, Kaplan, Joseph et al. 2002, Nussberger, Cugno et al. 2002, Suffritti, Zanichelli et al. 2014). During symptomatic attacks, kallikrein activation, HK cleavage, and BK production increase, and circulating BK levels are dramatically elevated (Cugno, Nussberger et al. 2003, Bork, Meng et al. 2006, Cicardi, Bork et al. 2012, Martello, Woytowish et al. 2012).

2.1.3. Clinical presentation, diagnosis

In patients with hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired, which leads to uncontrolled increases in plasma kallikrein activity and bradykinin release, resulting in HAE attacks consisting of swelling (angioedema), pain, and limitation of functions.

HAE is characterized clinically by recurrent episodes of angioedema of the skin, pharynx, larynx, gastrointestinal (GI) tract, genitals, and extremities (attacks) (Longhurst and Cicardi 2012).

Angioedema attacks may or may not be precipitated by a stimulus (such as stress, trauma, infection, or changes in hormonal levels with menses) and typically progress over several hours, with symptoms, if left untreated, subsiding gradually over the following 3 to 5 days (Zuraw and Christiansen 2011).

Oropharyngeal and especially laryngeal swelling can be life-threatening, and the progression of symptoms in laryngeal attacks is more rapid than in other locations due to the anatomy of the upper airway (Bork, Hardt et al. 2012).

Attacks at other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring. Abdominal attacks are especially painful and may result in unnecessary surgical procedures if HAE is not recognized as causal. HAE has a significant impact on functionality and quality of life (QoL).

2.1.4. Management

The management of HAE involves both the prevention of attacks and treatment of attacks (Cicardi, Bork et al. 2012, Craig, Aygoren-Pursun et al. 2012, Horiuchi, Ohi et al. 2012, Zuraw, Banerji et al. 2013, Maurer, Magerl et al. 2018).

The International World Allergy Organization/European Academy of Allergy and Clinical Immunology Guideline for the Management of HAE recommends that all patients be evaluated for long-term prophylaxis at every visit, have sufficient medication for on-demand treatment of 2 attacks, and carry on-demand treatment at all times (Maurer, Magerl et al. 2018).

As the focus of this application is prevention, a summary of approved/withdrawn treatments for the prevention of HAE attacks in the EU, the US, and Japan is provided below.

Drug, Route of Administration	**European Union** (Date of Approval if Available)	**United States** (Date of Approval)	**Japan**
Danazol PO	Approved in some member states	Approved (1976)	Not approved
Stanozolol PO	Withdrawn	Not approved; discontinued (1984)	Not approved
Tranexamic acid PO	Approved in some EU member states (1969) CHMP advised member states to delete this indication (2012)[a]	Not approved	Not approved
Cinryze® IV	Approved (2011)	Approved (2008)	Not approved
Haegarda® SC	Not approved	Approved (2017)	Not approved
Tahkzyro™ SC	Approved (2018)	Approved (2018)	Not approved

In spite of available medicinal products for the treatment of acute attacks, HAE still is a disorder with high mortality. Berotralstat is the first oral product that has been submitted for marketing authorisation for the prophylaxis of HAE attacks.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. The applicant claimed that the already authorised therapies were associated with significant safety or tolerability concerns with long term administration but this was not substantiated as no direct safety data was provided. In addition, due to the clinical trial designs no comparison in terms of safety, tolerability or even compliance is possible between Orladeyo and the other approved medicinal products for the prevention of HAE attacks.

From a safety perspective it is agreed that an oral formulation does not have the administration site reactions associated with IV or SC injection. However, GI side effects were noted with Orladeyo which do not appear to be as common with other licensed therapies such as Cinryze or Takhzyro.

Furthermore, the applicant claimed that the approved therapies are most likely reserved as a second line setting (i.e. not responding to other therapies), nevertheless no supporting evidence were provided. These claims were not agreed as the currently approved indications for Cinryze or Takhzyro are not restricted to patients in a second line setting.

In terms of efficacy, a statistically significant improvement was seen compared to placebo however it cannot be concluded that Orladeyo is more efficacious compared to other authorised medicinal products.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 150 mg of berotralstat (as dihydrochloride) as active substance.

Other ingredients are:

Capsule filling: crospovidone (type A), magnesium stearate, silica (colloidal anhydrous), starch (pregelatinised);

Capsule shell: gelatin, titanium dioxide (E 171), indigo carmine (E 132), black iron oxide (E 172), red iron oxide (E 172);

Printing ink: black iron oxide (E 172), potassium hydroxide, shellac, propylene glycol (E 1520).

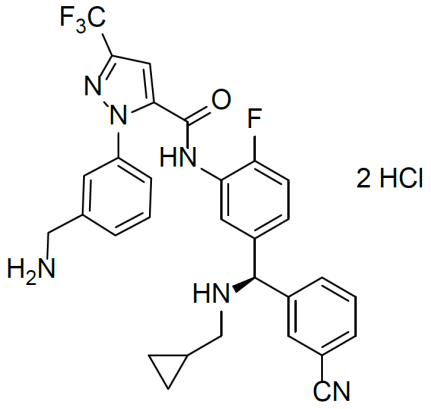
The product is available in PCTFE/PVC-Alu blisters in a carton, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of berotralstat is (*R*)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)((cyclopropylmethyl)amino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride corresponding to the molecular formula $C_{30}H_{26}F_4N_6O \cdot 2HCl$. It has a relative molecular mass of 635.48 and the structure depicted in Figure 1.

Figure 1: Active substance structure



The structure of berotralstat was elucidated by a combination of methods.

Berotralstat is an off-white hygroscopic powder, with pH dependent solubility Berotralstat dihydrochloride is considered a variable hydrate since the amount of water bound to the molecule is correlated to the environmental relative humidity

Berotralstat exhibits stereoisomerism due to the presence of one chiral centre. The (*R*)-enantiomer is the active isomer. Enantiomeric purity is controlled routinely in the specification of the starting material and of the active substance by isocratic RP-HPLC.

Polymorphism has not been observed for berotralstat. The proposed manufacturing method of berotralstat consistently generates only one form. Acceptable data have been provided demonstrating that there is no change in polymorphism during stability and when subjected to mechanical stress as mentioned in the pharmaceutical development section. The variable hydrate nature of the active substance does not impact the solid state form and the physico-chemical characteristics of the active substance, as demonstrated through a study

Manufacture, characterisation and process controls

The active substance is synthesized using well defined starting materials with acceptable specifications. Two active substance manufacturers are proposed. No reprocessing, reworking, recycling, regeneration, or other operations are permitted. The chemical synthetic process of berotralstat hydrochloride adopted at both proposed sites is the same with minor differences in the process parameters and some solvents; the differences, mainly due to regional availability, have been adequately justified. Adequate in-process controls (IPCs) applied during the synthetic steps monitor conversion rates, related substances and residual solvents. Two steps include process parameters considered to be critical. The specifications and control methods for SMs, reagents and intermediate products have been presented and revised during the procedure to address a MO on genotoxic impurities further described below; they are now considered satisfactory. Although a comprehensive justification for not controlling a class 1 residual solvent in the active substance specification has been provided, levels above the ICH limit cannot be excluded. Since the proposed omission of a non-routine test for this class 1 solvent, on a suitable intermediate or on the final active substance, has not been fully justified in line with Annexes to the Guideline for residual solvents (CPMP/ICH/283/95 Impurities), the applicant is recommended to include a routine test for this class 1 residual solvent in the specification for 2-propanol and methanol. Alternatively, batch data on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches of the active substance, generated using a validated method, should be provided demonstrating that the class 1 residual solvent is not more than 30 % of the specified limit in the final active substance (REC 1). In addition, in the last step of the process, three solvents are used. These solvents can form the corresponding alkyl halides which are known to be potentially genotoxic. Their presence is controlled in the active substance at levels justified in line with ICH M7 and supported by data generated throughout the development program, including the batches of the active substance manufactured using the proposed commercial manufacturing process. Additionally, to address the MO on the control of mutagenic impurities, QSAR assessment of specified impurity has concluded that specified impurity is non-mutagenic (Class 5), justifying the proposed control limit. A QSAR assessment, in line with ICH M7, has also been carried out for a solvent used in the manufacture of the SM BCX9297, confirming that this solvent is non-mutagenic (Class 5) and hence its control, in line with ICH Q3A qualification threshold, is adequate. To address the same MO, new impurity limits in intermediates have been introduced and existing ones have been tightened. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and fate.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Minor changes introduced have been presented in sufficient detail and have been justified. The overall chemistry is unchanged; the impurity profile of batches manufactured using the proposed commercial process is tighter than earlier batches, confirming that the quality has been improved with the changes made to the process through the development program. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double low-density polyethylene (LDPE) bags or liners contained in a high-density polyethylene (HDPE) standard open-top drum that is tightly closed. The LDPE complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification, includes tests for: description (in-house), identification (IR and RP-HPLC), assay and impurities (RP-HPLC), chiral impurity (isocratic RP-HPLC), chloride content (potentiometric titration), water content (KF – Ph. Eur.), residual solvents (GC), residue on ignition (Ph. Eur.), alkyl chlorides (GC), microbial quality (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies; appropriate specifications have been set and limits have been tightened during the procedure in line with batch data. Unspecified impurities limits are set in line with ICH Q3A identification threshold. Alkyl chloride limits are set in line with ICH M7, as described above.

As discussed above, although the applicant proposed not to include a limit for a class 1 residual solvent in the active substance specification this was not considered fully acceptable, despite the justification provided; REC1 is raised, recommending the applicant to fully control its presence at the level of the solvents used or to provide sufficient data to demonstrate its routine control can be omitted, since the theoretical presence of the solvent cannot be excluded

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three full scale batches of the active substance from each proposed manufacturer are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three production scale stability batches of active substance from each of the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as those used for release and were stability indicating.

All tested parameters were within the specifications. The water content is observed to gradually increase with time as the material equilibrates with its environment and then remains constant after the equilibration point. The specification was not exceeded. The stability profile of batches from both sites is similar.

Photostability testing following the ICH guideline Q1B was performed

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months with no specific storage conditions when stored in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as hard capsules containing 150 mg of berotralstat (as dihydrochloride) as active substance.

The hard capsule is a size 1 capsule (19.4 mm × 6.9 mm) with white opaque body imprinted with “150” and light blue opaque cap imprinted with “BCX”.

The function of the excipients chosen have been fully described. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, as applicable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility of the excipients with the active substance has been demonstrated. The acceptability of the pharmaceutical form for the intended paediatric patient population (children 12 years or older) has been discussed and agreed during the PIP procedure EMEA-002449-PIP02.

The chosen QC dissolution method is considered acceptable.

A bioequivalence study was performed showing bioequivalence between the early clinical formulation The primary packaging is PCTFE/PVC-Alu blisters, as described in section 6.5 of the SmPC. The material of the primary container closure systems complies with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Berotralstat capsules manufacturing process is considered to be a standard manufacturing process, it has been described in sufficient detail All relevant process parameters have been included in the description. The critical step has been identified.

An assessment of the powder blend uniformity and stratified content uniformity was performed. The three PPQ batches met the protocol acceptance criteria which supports the conclusion of content uniformity of the final blend and the homogeneity of the active substance content throughout the encapsulation process. Therefore, it is not necessary to perform blend uniformity testing during routine commercial manufacture. The in-process controls are adequate for this type of manufacturing process pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data is provided for batches of each strength and the data indicate that the process is capable of reproducibly producing product of consistent quality. Bulk holding times have been validated and are acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications, include appropriate tests for this kind of dosage form: description (visual), identification (HPLC and UV by HPLC), assay and degradation products (HPLC), uniformity of dosage units by content uniformity (Ph. Eur.), dissolution (in house, apparatus II), water Content (KF, Ph. Eur.), microbial limits (Ph. Eur.).

The specification criteria meet the requirements of ICH Q6A.

The dissolution specification limit has been justified based on data. However, the applicant is recommended to review the dissolution specification in line with the principles of the reflection paper (EMA/CHMP/CVMP/QWP/336031/2017) and taking into consideration the data from 10 additional subsequent production batches, including future process validation batches. In line with the Ph. Eur. 2.9.3. compliance with stage S1, S2 and S3 (Ph. Eur. 2.9.3.) should be considered acceptable, and thus it is expected to be possible to tighten the limit to Q=80% at 15 min (REC2). The water content limit has been justified based on development studies and is supported by batch data. The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, as requested, considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for six commercial scale batches manufactured by the proposed finished product manufacturer, using active substance from both suppliers, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches from each manufacturer of finished product, using active substance from both of the proposed suppliers, stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, chiral impurity, dissolution, water content and microbial attributes. The analytical procedures used are stability indicating.

No significant changes were observed in product description, assay or degradants at both long term and accelerated conditions. The dissolution met the specification criteria. The water content was observed to increase slightly over time at both the long-term and accelerated conditions, but eventually levelled off; it remained below the proposed specification at all time points.

Forced degradation studies were performed to demonstrate the stability indicating ability of the HPLC method to separate degradants generated in berotralstat capsules during stability. The finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Berotralstat 150 mg capsules are stable after exposure to fluorescent and ultra-violet light.

Based on available stability data, the proposed shelf-life of 3 years, without special storage conditions, as stated in the SmPC (sections 6.3 and 6.4), is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The MOs linked to the potential presence of genotoxic impurities and nitrosamine risk evaluation have been adequately resolved.

At the time of the CHMP opinion, two minor quality issue, related to the control of a class I solvent in the active substance and to tightening the dissolution specification limits in the finished product, remained unsolved, having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to include a routine test for a class I solvent in the specification for 2 solvents (with limits that will ensure that the worst-case scenario contamination of the active substance cannot exceed 2 ppm). Alternatively, batch data on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches of the active substance, generated using a validated method, should be provided demonstrating that benzene is not more than 30% of the specified limit. This should be completed by Q3 2021.
2. The applicant is recommended to review the dissolution specification in line with the principles of the reflection paper (EMA/CHMP/CVMP/QWP/336031/2017) and taking into consideration the data from 10 additional subsequent production batches, including future process validation batches. In line with the Ph. Eur. 2.9.3. compliance with stage S1, S2 and S3 (Ph. Eur. 2.9.3.) should be considered acceptable, and thus it is expected to be possible to tighten the limit.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Berotralstat (BCX7375) is a synthetic small molecule inhibitor of plasma kallikrein, intended for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years or older. HAE is a disorder of dysregulation of the contact activation pathway, characterized by recurrent episodes of tissue swelling. Plasma kallikrein is a serine protease integral to the contact activation pathway, it circulates in plasma as a zymogen, pre-kallikrein (PKK), bound to one of its main substrates, high-molecular-weight kininogen (HK). During contact activation, PKK is cleaved by activated factor XIIa forming the active protease kallikrein. Kallikrein in turn cleaves HK, producing bradykinin (BK). The activation of the BK B2 receptor by BK results in vasodilatation, increased vascular permeability, and smooth muscle contraction, leading to the tissue swelling that characterizes HAE. The great majority of cases of HAE are caused by mutations in SERPINGrade 1, leading to an insufficiency of C1 esterase inhibitor (C1-INH), the major regulator of the contact activation pathway. This results in abnormally upregulated cleavage of HK by plasma kallikrein, releasing BK, which mediates angioedema. In asymptomatic HAE plasma HK levels may be lower than normal and BK is detectable, while symptomatic attacks are characterized by uncontrolled contact activation, with increased kallikrein production, HK cleavage, and dramatic increases in circulating BK.

Primary pharmacodynamic studies

A limited primary pharmacodynamics package was presented in this application. It included 8 in vitro studies, 3 of which were conducted to develop the fluorogenic assay used to measure plasma kallikrein activity.

No *in vivo* primary pharmacodynamics have been conducted with BCX7353. However, the *in vitro* data demonstrate that BCX7353 is a potent inhibitor of purified plasma kallikrein, with a Ki of 44nM (Study BR-7353-001). BCX7353 has also been shown to have acceptable selectivity for plasma kallikrein over other related serine proteases, with an IC50 of 0.88 nM against plasma kallikrein and IC50 ranging from 3967nM (against plasmin) to >50,000nM against other related serine proteases (Study BR-7353-002). There is theoretical possibility of pharmacodynamic action with other human serine proteases, however, this was not tested. As serine proteases are a very broad group of enzymes, it is not possible to rule out inhibition of all other serine proteases in primary pharmacodynamics. From in vitro studies, there appeared to be no detectable clinical consequences of any such theoretical inhibition.

BCX7353 was also shown to suppress HK/PKK-dependent BK production on human endothelial cells, with an EC_{50} of 5.56nM (Study BR-7353-004), indicating that BCX7353 potently suppresses BK production after contact system activation by endothelial cells, supporting its proposed mode of action in HAE. Furthermore, BCX7353 was shown to inhibit kallikrein activity ex-vivo, in activated human plasma from healthy human volunteers and in monkey and rat plasma with mean EC_{50}s of 5.4, 5.2, and 7.2 nM (Study BR-7353-005-REV-01), supporting the suitability of monkey and rat as the non-clinical species used for toxicology studies. Finally, BCX7353 was shown to inhibit kallikrein activity ex-vivo from subjects with HAE, with a range of EC_{50}s slightly higher than in normal human plasma, ranging from 11.7 to 20.0 nM, and a mean EC_{50} of 15.9 ± 0.57 nM (Study BR-7353-006-REV-01).

Secondary pharmacodynamic studies

As plasma kallikrein is an upstream regulator of the coagulation pathway, *in vitro* secondary pharmacology studies examined the effect of BCX7353 in plasma-based coagulation assays. The effect

of BCX7353 on prothrombin time (Study BR-7353-003) and activated partial thromboplastin time (Study TD-BR-18-5353-010) was evaluated in human and animal plasma from various species. PT doubling as a result of BCX7353 treatment was not seen at the highest concentration tested of 100 µM, and aPTT doubling was observed at 73.4 µM, representing an estimate of > 17,000-fold and > 12,000-fold higher than the EC_{50} of 5.83 nM to inhibit kallikrein activity in human plasma, respectively. Hence, BCX7353 was shown to prolong PT and aPTT only at very high, supra-therapeutic, drug concentrations, not considered relevant for human safety. *In vivo* secondary pharmacodynamics studies were not conducted.

Safety pharmacology studies

In vitro safety pharmacology studies included radioligand binding studies to assess the interaction of BCX7353 with 103 subtypes of GPCRs (Study AB26402). The affinity of BCX7353 for all targets was low, relative to the potency of BCX7353 at plasma kallikrein (0.44 nM). A Ki > 3 µM is reported for all GCPRs tested, with the exception of the cannabinoid CB1, melanocortin MC5, and somatostatin SST1 receptors (Ki= 1.56, 1.92, and 2.09 µM, respectively), indicating an acceptable selectivity of at least 3545-fold for the target enzyme.

BCX7353 was shown to inhibit the hERG channel *in vitro*, with an IC_{50} of 0.29 µM (Study 806-125) and to reduce the action potential amplitude (APA), depolarize the resting membrane potential and slow the dV/dt max in isolated rabbit Purkinje fibers at concentration of 0.9, 9.4, and 93.7 µM (Study 141030.CDS). Although, BCX7353 did not prolong action potential duration (APD) at concentrations up to 93.7µM, 300-fold greater than that required to block hERG channels, significant shortening of the APD is reported at 1 and 100µM concentrations. The applicant considered reductions in APA and dV/dt max may be due to the inhibition of hNav1.5, while depolarization of the RMP may be due to the inhibition of hKir2.1. BCX7353 was shown to inhibit hNav1.5 (peak) with an IC_{50} of 4.79 µM (Study 150123.CDS). According to the applicant the lack of increase in APD may be due to inhibition of both hERG and L-type calcium channels and BCX7353 was shown to inhibit cloned human hCav1.2 in CHO cells with an IC_{50} of 1.30 µM (Study 150123.CDS). The applicant cited also literature data indicating that inhibition of both hERG and hCav1.2 is also a property of the antihypertensive agent, verapamil, which does not appear to have any propensity for Torsades de Pointes (Redfern 2003).

However, in human cardiomyocytes, the beat period and field potential duration (a surrogate for the QT interval of an ECG) was increased by BCX7353 at concentrations > 0.3 µM, suggesting that BCX7353 has the potential to increase QT interval (Study 150217.CDS). The selectivity margin would be estimated to 51-fold in reference to the inhibition of kallikrein in human plasma (5.83nM).

In vivo, respiratory and CNS safety pharmacology studies conducted in the rat report a no observable effect level (NOEL) of 450 mg/kg, the highest dose tested, indicating that BCX7353 has a low potential to affect these systems (Study 806-124 and Study 806-123). A single dose of 15 mg/kg BCX7353 had no adverse effects on the cardiovascular system in conscious monkeys (Study 806-135). However, doses of 50 and 150 mg/kg decreased blood pressure (diastolic, systolic and mean) and increased ECG intervals, including RR, PR, QRS and QTc. Emesis/vomitus also occurred at ≥50 mg/kg, with watery faeces reported at 150mg/kg.

In the monkey single-dose toxicology study (Study 806-116), the Cmax and AUC_{0-24} associated with a single dose of 150 mg/kg were 852 ng/mL and 15,600 ng.h/mL, respectively. The human exposure (Cmax and AUC_{0-24}) at 150 mg, the dose for which approval is being sought, is 157 ng/mL and 2640 ng.h/mL, respectively (Study BCX7353-112), suggesting an approximately 5-fold safety margin from the exposure reported at the NOAEL in monkeys to the anticipated clinical exposure. Furthermore, in a chronic repeat-dose toxicology study in cynomolgus monkeys, 80 mg/kg/day BCX7353 administered for 39 weeks had no effects on ECG parameters, with a Cmax and AUC_{0-24} following 39 weeks of dosing of 692 ng/mL and 13,500 ng.h/mL, respectively (Study 806-162). Hence, the *in vitro* and *in vivo*

safety pharmacology data identify the cardiovascular system as a target organ for toxicity but no ECG findings are reported from the chronic repeat-dose toxicology study in monkeys.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetics of BCX7353 was studied in mice, rats, rabbits, and monkeys, the species used in the general and reproductive toxicology studies, and carcinogenicity studies. Several studies to evaluate the absorption, distribution, metabolism and excretion were conducted using [14C]BCX7353.

Absorption

Pharmacokinetic parameters reported following single oral dosing of [14C] BCX7353 (radiolabel A) in Wistar Han (WH) rats, demonstrate that BCX7353 was efficiently absorbed, with a time to maximum concentration (Tmax) of 2 hours. Terminal elimination was slow with a mean t1/2 of 18.5 hours. The oral bioavailability (F) relative to an IV dose was estimated to be 33%. Similarly, in cynomolgous monkeys oral doses of BCX7353 were absorbed with a Tmax of 2 to 6 hours. Terminal elimination was slow with a mean t1/2 of 22.7 hours. The oral F relative to an IV dose was estimated to be 45%. In PK studies in albino Sprague-Dawley (S-D) rats and cynomolgus monkeys, using [14C] BCX7353 with radiolabel B, the fraction absorbed was 62% and 52% in rats and monkeys, respectively.

The PK of BCX7353 following repeat dosing was evaluated as part of the general and reproductive toxicity studies in mice, rats, pregnant rats, pregnant rabbits, and monkeys. In mice and monkeys, there was no evidence of a sex difference in BCX7353 exposure (Cmax or AUC0-24). In 28-day and 13-week studies in rats the data suggested Cmax and AUC0-24 were greater in females than in males. However, in the 26-week rat study and the 2-year rat carcinogenicity study, no sex differences were observed. Accumulation was evident following repeat dosing in rats and pregnant rabbits, but not in mice or monkeys, with the exception of systemic exposure reported for the 2 highest doses of 55mg/kg/day and 80mg/kg/day in the chronic monkey toxicity study which showed evidence of accumulation.

Placental transfer of BCX7353 was demonstrated in pregnant rats and rabbits with a Cmax in foetal plasma of 4% to 7%, and 7% to 11%, of the maternal plasma Cmax in rats and rabbits, respectively. Exposure due to breast milk was evaluated in rats; the Cmax of BCX7353 in pup plasma on lactation day (LD) 14 was < 5% of the maternal plasma Cmax.

Distribution

The *in vitro* plasma protein binding of BCX7353 (3µM) was determined to be 98.7%, 98.9%, 99.4%, 74.1%, and 81.9% in human, rat, mouse, monkey, and rabbit plasma, respectively. Although, the applicant indicated that the values in monkey and rabbit plasma may be underestimated due to instability of BCX7353 in these matrices. The *in vitro* red blood cell (RBC) to plasma partitioning ($K_{RBC/P}$) for BCX7353 was estimated in human, rat, mouse, monkey, and rabbit blood. BCX7353 has roughly similar affinities for RBCs and plasma proteins in human, rat, and rabbit (as defined by $K_{RBC/P}$ > 1 but < 2), whereas in mouse and monkey blood there appears to be a relatively lower uptake into red cells ($K_{RBC/P}$ < 0.5).

A mass balance and distribution study was performed in albino male WH rats and pigmented Long-Evans (LE) rats following a single oral dose (30 mg/kg) of [^{14}C]BCX7353 (radiolabel A). After oral dosing to WH rats, the radioactivity was widely distributed to all tissues by the first collection time point (0.5 hours post dose) and most of the tissues reached maximum radioactive concentrations by the 8-hour time point. The tissues showing the highest maximum concentrations of radioactivity included liver, kidney medulla, spleen, adrenal gland(s), kidney(s), lungs, and pituitary gland.

Similarly, in male pigmented LE rats, radioactivity was also widely distributed to all tissues by the first collection time point (1-hour post dose) and most of the tissues reached the maximum radioactive concentrations by the 8-hour time point. At 1440 hours post-dose, the highest concentration of radioactivity was quantified in the uveal tract of the eye, suggesting [14C] BCX7353-derived radioactivity bound to melanin. However, the possibility of accumulation of BCX7353 in the eye associated with melanin binding was not considered relevant for human safety on the basis that there were no microscopic or ophthalmological effects reported in the eyes of rats or monkeys from the chronic repeat-dose toxicity studies. In addition, BCX7353 was not cytotoxic in the mouse fibroblast assay in the absence or presence of ultraviolet radiation.

Low levels of radioactivity were detected in testes, suggesting [14C] BCX7353-derived radioactivity crossed the blood/testes barrier. A similar distribution pattern of radioactivity in both albino and pigmented rats was found in distribution studies using radiolabel B.

Metabolism

In vivo metabolism of [^{14}C]BCX7353 was evaluated in rats and monkeys using 2 radiolabelled forms of BCX7353. Following a single oral dose of BCX7353 with radiolabel A to WH rats, multiple radioactive peaks were observed in plasma and eleven metabolites were identified. Of these 11 metabolites, only 3 constituted ≥ 5 % of the total radioactivity. These were unchanged BCX7353 (61% of total dose), and N-desmethylcyclopropyl]-BCX7353 (M3) and hydroxy-BCX7353 (M9), which were the major circulating metabolites contributing 13.5% and 13.0% of the total radioactivity exposure, respectively. In bile there were small amounts of multiple metabolites and < 0.3% of the dose was recovered as unchanged BCX7353; M3 and [N-desmethylcyclopropyl]-BCX7353 carboxylic acid (M5) were the 2 most abundant metabolites in bile, accounting for 2.27% and 3.08% of the dose, respectively. Unchanged BCX7353 was the major component recovered in faeces, accounting for 20.7% of the dose. M3, M5, BCX7353-carboxylic acid (M7), and N-acetyl-BCX7353 (M8) were the abundant components identified in faeces, accounting for 4.55, 4.89, 6.59, and 3.45% of the dose, respectively. A low level of unchanged BCX7353 (0.5% of the dose) was detected in urine; M3 was the most abundant component in urine, accounting for 1.4% of the dose. To summarize, [^{14}C] BCX7353 was metabolized in rats after oral administration via oxidation, reduction, hydrolysis, dealkylation, N-acetylation, oxidative deamination, N-carbamoylation, and glucuronidation.

Following a single oral gavage dose of radiolabel A to monkeys, there were no quantifiable levels of unchanged parent BCX7353 in either individual time-point or in pooled plasma samples.

The metabolism of BCX7353 was also evaluated in rats and monkeys using radiolabel B. In both rats and monkeys, the predominant metabolites identified in plasma and urine were carnitine and glycine conjugates of CPCA. In pooled plasma from rats and monkeys, the carnitine conjugate (M2) accounted for 44.9% and 41.7% of the total radioactivity in the sample, respectively, while the glycine conjugate (M1) was, respectively, 18.5% and 11.5% of the total radioactivity in the plasma sample. These data suggest N-dealkylation, cleaving the cyclopropyl ring from the purine ring is involved in the metabolism of BCX7353. This indicates the ^{14}C position on radiolabel B is in a metabolically sensitive position on the core molecule. The signal from the radiolabelled metabolite is based on the CPCA cleavage and does not follow the metabolic fate of the principal part of the molecule.

*In vitro m*etabolism of BCX7353 was slow, and thus hampered the identification of metabolites and metabolic pathways. In a cross-species study using cryopreserved hepatocytes, BCX7353 was stable for > 120 minutes in human, monkey, rat, rabbit, and mouse, suggesting no major species differences. In studies using human liver S9 fractions BCX7353 was also stable for > 120 minutes. When incubated with human cryopreserved hepatocytes for 360 minutes there was a small amount of metabolism (< 10% loss of BCX7353). Four metabolites were isolated chromatographically; the proposed identities

were bio-transformational products of amide hydrolysis, N-methylation, oxidation to yield a carboxylic acid, N-dealkylation, glucuronidation, acetylation, or a combination thereof.

Using fresh isolated primary rat and human hepatocytes, incubations with BCX7353 for up to 24 hours produced 12 chromatographic peaks that could represent putative metabolites. In rat, the principle peaks were identified as CPCA-carnitine conjugate, [*N*-desmethylcyclopropanoyl]-BCX7353, hydroxy-BCX7353, and BCX7353-aldehyde with relative abundance accounting for 3.76%, 4.56%, 2.63%, and 3.23% of the total peak area, respectively, at 24 hours. In human hepatocytes, BCX7353-aldehyde and CPCA-carnitine conjugate were the most abundant components at 6 and 24 hours, respectively, accounting for 2.66% and 2.18% of the total peak area.

After incubation with a panel of recombinant human cytochrome P450 (CYP) isoenzymes the greatest loss of BCX7353 was observed with CYP2D6 and CYP3A4 (15.0% and 22.4% loss, respectively, of which approximately 10% was non-specific). Less than 10% substrate loss was observed with the other CYP enzymes evaluated (1A2, 2A6, 2B6, 2C8,2C9, 2C19, 2E1), and the half-lives were > 60 minutes for each CYP. Metabolite identification following incubation with recombinant CYP2D6 and CYP3A4 found 9 BCX7353-related components, which were proposed to form by oxidative deamination, N-dealkylation, oxidation, reduction, and defluorination or a combination thereof.

Excretion

The excretion of BCX7353 was evaluated in rats and monkeys using [^{14}C]BCX7353. Following a single oral dose of BCX7353 with radiolabel A in intact rats, the mean cumulative excretion of radioactivity in the urine and faeces was 2.5% and 94%, respectively, of the administered dose up to 168 hours. In bile duct cannulated (BDC) rats, 22.6% of the administered dose was recovered in bile up to 96 hours post dose. The excretion in monkeys was similar to rats; following a single oral dose of radiolabel A, 4.2% and 85.3% of the administered radioactivity were excreted in urine and faeces, respectively, by 336 hours post-dose. In both rats and monkeys, the principal component in faeces was unchanged BCX7353.

The excretion profiles in rats and monkeys were different using radiolabel B. Following a single oral dose in rats, the mean cumulative excretion of radioactivity in the urine and faeces was 41.1% and 44.7%, respectively, and was 24.1% and 59.6% in monkeys, respectively, of the administered dose through 168 hours. In the urine of rats and monkeys, conjugates of CPCA were the only major metabolites, but in faeces of rat and monkey these conjugates were each less than 5% of the total radioactivity; unchanged BCX7353 was the major component. Thus, urine is the principal elimination pathway of the carnitine- and glycine-CPCA conjugates following N-dealkylation.

These studies indicated that faecal, biliary and urinary pathways are important for the elimination of BCX7353 in rats and monkeys, although there is some variability in the findings resulting from use of the 2 different radiolabels.

Pharmacokinetic Drug Interactions

The ability of BCX7353 to inhibit CYP enzymes was evaluated in pooled human liver microsomes (PHLM). The IC_{50} of BCX7353 were < 1 µM for CYP450: CYP2C9 (0.24 µM) and CYP2C19 (0.36 µM); between 1 and 10 µM for CYP2D6 (2.3 µM) and CYP3A (2.5 µM with midazolam as the probe substrate). The IC_{50}s against all other CYP isozymes (1A2, 2A6, 2B6, 2C8, 2E1) were > 10 µM. Further studies found that BCX7353 is likely a time-dependent inhibitor of CYP3A but not a time-dependent inhibitor of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1.

The induction of CYP enzymes was investigated by measuring CYP enzyme activity and messenger ribonucleic acid (mRNA) expression for CYP1A2, CYP2B6, CYP3A4, and CYP3A4/5 in cryopreserved human hepatocytes cultured for 3 days with BCX7353. Cultures from 3 donors were evaluated. The

highest, non-cytotoxic, concentration of BCX7353 was 2.66 µM, which caused > 2-fold increases in CYP enzyme activity and/or mRNA activity in at least 1 culture of CYP1A2 and CYP2B6; there was > 2-fold CYP3A4 mRNA activity but not CYP 3A4/5 enzyme activity. However, a BCX7353 concentration of 0.886 µM, which is still > 200-fold higher than the worst-case concentrations expected to be in the hepatocytes in vivo, did not result in changes in CYP2B6 mRNA of > 20%, indicating no cause for concern for clinical safety with CYP2B6 substrates. Also, BCX7353 was found to be a weak to moderate inhibitor of CYP3A4 in clinical trials (BCX7353-102, BCX7353-112, BCX7353-115) at BCX7353 doses of both 350 mg and 150 mg, and appropriate wording has been included in the SmPC to recommend monitoring for drugs which have a narrow therapeutic window, such as cyclosporine or fentanyl.

A series of studies evaluated BCX7353 as an inhibitor and as a substrate of key human transporters. BCX7353 inhibited transport by P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein (MATE)1, and MATE2-K with calculated IC50s of 0.49, 12.0, 3.53, and 4.60 µM, respectively. BCX7353 was an inhibitor of organic anion transporting polypeptide (OATP)1B1, organic cation transporter (OCT)2 and OATP1A2 with IC50s of 13.2, 13.3, and 11.3 µM, respectively. The IC50 was > 30 µM for inhibition of OATP1B3, organic anion transporter (OAT)1, OAT3, and OATP2B1, and > 100 µM for multidrug resistance protein (MRP)2. BCX7353 was not an inhibitor of the bile-salt export protein (BSEP) transporter at 10 µM.

BCX7353 is a substrate of P-gp and BCRP but is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity is reported from the acute phase of non-GLP compliant, 7-day, dose range finding studies in rats (Study 806-111) and monkeys (Study 806-116). The maximum tolerated single dose in rats is reported as 450mg/kg, with higher dosing associated with mortality (n=3/9 females), treatment-related clinical signs; including decreased activity, diminished pupillary reflex, vocalization (females only), hunched posture, piloerection, and skin cold to the touch, and decreased body weight. The maximum tolerated single dose in monkeys is reported as 300mg/kg. While higher doses were tolerated, they were associated with extensive vomitus and emesis which may have impacted on exposure. Minimal, mostly reversible body weight decreases occurred after each dose and some reversible, minimal to mild decreases in mean arterial BP (20 to 30 mmHg) are reported in the male and female at 500 mg/kg.

Repeat dose toxicity

Mice

A GLP compliant repeat dose range finding study was conducted in CByB6F1 hybrid mice (Study 20088903) to evaluate the potential toxicity and assess the TK of BCX7353 when given orally for 5 and 28 days. Dosing was well tolerated for 28 days at dose levels up to 50/mg/kg/day, with mortality observed at the high dose of 125mg/kg/day. Clinical observations prior to mortality included decreased activity, dehydration, and/or hunched posture, decreased mean body weight, mean body weight gain, and food consumption. Possible slight non-adverse test article-related decreases in leukocytes, lymphocytes, MCV, and MCH were noted but no target organs were identified. The maximum tolerated dose (MTD) was considered to be ≥ 50 and < 125 mg/kg/day, and the NOAEL was 50 mg/kg/day with a Cmax of 2000 ng/mL and an AUC_{0-24} of 21,800 ng.h/mL on Day 28. This study supports the 6-month carcinogenicity study conducted using transgenic mice (Study 20088905), for which a high dose of 50mg/kg/day was chosen.

Rats

A 7-day dose range finding study in rats (Study 806-111) indicated that multiple doses of BCX7353 were not tolerated at 150mg/kg/day, with mortality, clinical observations and changes in clinical and anatomical pathology occurring at this dose level in the study. The 7-day NOAEL in rats is reported as 50mg/kg/day (AUC_{0-24hr} = 15,300 ng•hr/mL; Cmax = 1060 ng/mL, on Day 7). Subsequently, a 28-day repeat-dose study in rats included doses up to 75mg/kg/day (Study 806-131). The results indicate that BCX7353 was well tolerated at dose levels up to 25 mg/kg/day, but adverse clinical effects such as audible or difficult breathing and hunched posture, body weight loss, decreased food consumption, morbidity, and mortality were observed at 75 mg/kg/day. Clinical pathology data demonstrated evidence of inflammation and changes secondary to hepatocellular and myocyte damage that were mostly observed at 75 mg/kg/day in both sexes. Adverse histopathology changes including tubular regeneration and vacuolation were present in the kidneys, myofiber degeneration/necrosis (heart, skeletal muscle, tongue, larynx, oesophagus, and the glandular stomach), and/or bile duct hyperplasia and degeneration/necrosis was observed in males and females at 75 mg/kg/day. The NOAEL after dosing BCX7353 by oral gavage for 28 days in rats is considered to be 10 mg/kg/day on the basis of adverse bile duct degeneration/necrosis in males and females at ≥ 25 mg/kg/day. At the NOAEL, the combined male and female Cmax and AUC_{0-24} on Day 28 were 186 ng/mL and 2230 ng.h/mL, respectively.

Results from the GLP-compliant 13- and 26-week repeat-dose toxicity studies in rats indicate that BCX7353 was generally well tolerated, with dosing up to 20mg/kg/day (Study 806-144 and Study 8001291 respectively). The primary target organ for BCX7353-toxicity in rats was the liver. Bile duct hyperplasia was observed at the highest doses of 20mg/kg/day evaluated in 13- and 26-week studies but was considered non-adverse due to the limited incidence and severity, and the lack of change of clinical pathology parameters. The kidney was also identified as a target organ at the high dose of 75mg/kg/day in the 28-day rat study, but kidney toxicity was not apparent in 13- or 26-week studies with dosing up to a maximum of 20mg/kg/day.

A consistent finding in the sub-chronic and chronic toxicity studies was the presence of foamy/ vacuolated macrophages in several organs and tissues, including the liver, lung, small intestine, spleen, and lymph nodes, together with increased urinary concentrations of the exploratory phospholipidosis (PLD) biomarker, di-22:6-bis(monoacylglycerol) phosphate (BMP). Vacuolated macrophages and increased urinary BMP were suggestive of PLD, which was confirmed in the 13-week rat toxicity study using electron microscopic evaluation of the liver. Of note, a frequent clinical observation at higher dose levels was audible, shallow, and difficult breathing and sometimes open-mouth breathing. In rat studies evaluating doses > 20 mg/kg/day (28-day, carcinogenicity studies) these clinical observations occasionally preceded moribundity and mortality. In the 26-week rat study, there were microscopic changes in the nasal cavity (epithelial degeneration of the nasal and olfactory tissue), which were consistent with local irritation secondary to gastric-related reflux. The applicant suggests that this irritation of the upper respiratory system is due to BCX7353 in the nasal cavity and not due to systemic effects of the test item. The NOAEL in the 13 and 26-week toxicity studies in rats was 20 mg/kg/day. At this NOAEL, AUC_{0-24} was 9710 ng.h/mL, which represents a safety margins of 3.8, over the exposure in humans receiving 150 mg once daily (QD), the dose being sought for approval.

Monkeys

A 7-day dose range finding study in monkeys included dosing at, 0, 10, 75 and 200mg/kg/day, with n=2 monkeys per sex per group (Study 806-116). There was no reported mortality but vomitus occurred in both sexes at 75 and 200mg/kg/day, with test-article related decreased body weight at 200mg/kg/day in both sexes which would likely become adverse over a longer treatment duration than

7 days. Reversible, minimal to mild post-dose (4 hours) decreases in mean arterial blood pressures (20 to 30 mmHg) in one male each at 10 and 75 mg/kg/day and one female each at 10 and 200 mg/kg/day were reported of uncertain relationship to treatment, due to the low number of animals in this study. There was evidence of hepatocellular and/or hepatobiliary injury in both sexes administered ≥ 75 mg/kg/day. The NOAEL in Phase B was considered to be 75 mg/kg/day ($AUC_{0\text{-}24hr}$ = 7,120 ng• hr/mL; Cmax = 369 ng/mL, on Day 7) on the basis of decreases in electrolytes associated with the high incidence of emesis/vomitus and inappetence at 200mg/kg/day.

Subsequently, a 28-day repeat-dose study in monkeys included daily oral doses of 0, 10, 30 and 100mg/kg/day (Study 806-132). The results indicated the liver and kidney as primary target organs for toxicity. A NOAEL of 10mg/kg/day was reported on the basis of adverse liver findings at ≥ 30mg/kg/day, including increases in ALT and AST that correlated with increased liver weights, hepatocyte vacuolation, large hepatocytes, hyperplasia of oval cells, increased mononuclear cell infiltrates, and increased numbers of individual necrotic hepatocytes. Other toxicity occurred as higher doses levels, with increased kidney weights, degeneration/regeneration of renal tubules, infiltrates of mononuclear cells and basophilic renal tubules, and degeneration/regeneration of skeletal muscle myofibers considered adverse in animals at 100 mg/kg/day. Furthermore, infiltrates in the villi of the small intestine were noted in males and females at 30 and 100 mg/kg/day and were considered adverse at 100 mg/kg/day. Follicular hyperplasia was also observed in the spleen of males at 30 and 100 mg/kg/day, and in females at 10, 30, and 100 mg/kg/day. Increases in spleen weights, hepatocyte necrosis, infiltrates in the small intestine, degeneration with regeneration of renal tubules and increases in ALT and AST were all noted at 30 mg/kg/day. At the NOAEL of 10 mg/kg/day, the combined male and female mean Cmax and AUC0-24 on Day 28 were 86.4 ng/mL and 1350 ng.h/mL respectively.

Results from a GLP-compliant 13-week repeat dose study in monkeys demonstrated administration of BCX7353 at 2.5, 7.5, and 20 mg/kg/day by oral gavage for 91 days was well tolerated in cynomolgus monkeys (Study 806-145). The only test article-related findings were increases in ALT in both sexes at 20 mg/kg/day, and increases in the urinary PLD biomarker in both sexes at 7.5 and 20 mg/kg/day, both findings were considered non-adverse as they showed evidence of recovery and no microscopic correlates are reported. Hence, a NOAEL of 20/mg/kg/day is reported, the highest dose level administered. The Cmax and AUC0-24 on Day 91 were 192 ng/mL and 3350 ng.h/mL, respectively at the NOAEL of 20mg/kg.

Two chronic 39-weeks repeat-dose studies were conducted in monkeys. In the first study (Study 8001292) there was no toxicity at a high dose of 20 mg/kg/day. Therefore, this study was repeated using higher doses of 30, 55, and 80 mg/kg/day (Study 806-162). In the second 39-week study in monkeys BCX7353 was generally tolerated at doses up to 80mg/kg/day, with no treatment-related mortality reported. The liver was also a primary target organ for BCX7353-related toxicity in this study, and hepatocellular hypertrophy was noted, together with increases in transaminase levels. The maximum increases of AST and ALT were observed after 1 and 3 months of dosing and were lower following 39 weeks of dosing. Consistent with findings in the rat and the 28-day monkey study, the kidney was also a target organ at higher doses than those affecting the liver. Renal tubular hyperplasia and/or mononuclear cell infiltration was observed at doses ≥ 55 mg/kg/day in the 39-week study. Also consistent with the rat study results, in monkeys the presence of foamy/vacuolated macrophages is also reported in several organs and tissues, including the liver, lung, small intestine, spleen, and lymph nodes, together with increased urinary concentrations of the exploratory PLD biomarker, di-22:6-bis(monoacylglycerol) phosphate (BMP), suggestive of PLD. At higher doses evaluated in the 28-day studies, there was degeneration/regeneration of skeletal, cardiac and smooth muscle. These effects were not observed in 13-week or chronic toxicity studies, nor were there any changes in creatine kinase (CK) isoenzymes in these latter studies. The NOAEL in chronic toxicity studies in monkeys was

30 mg/kg/day. At this NOAEL, the AUC_{0-24} was 3950 ng.h/mL, which represents a narrow safety margins of 1.5, over the exposure in humans receiving daily 150 mg doses of BCX7353.

Toxicokinetics

TK data were acquired in all pivotal repeat-dose toxicity studies. In rats, data from the 28-day repeat dose study indicate that systemic exposure increased with increasing dose in a greater than dose-proportionate manner on Days 1 and 28. A trend towards higher exposure in females was also noted at lower doses only (5 to 25 mg/kg/day). Also, BCX7353 appeared to accumulate in plasma (2.18- to 4.83-fold) following repeated administration of BCX7353 for 28 days. Similarly, TK data from the 13-week rat study indicate that systemic exposure to BCX7353 appeared to be sex dependent. Individual plasma concentrations, Cmax, and AUC were generally greater in females than in males (female: male ratios based upon AUC_{0-last} ranged from 1.12 to 2.42; female/male ratios based upon AUC_{0-24} ranged from 1.12 to 2.53). Following daily administration of BCX7353, AUC_{0-24} and Cmax increased with increasing dose. At the NOAEL of 20mg/kg/day, the Cmax and AUC_{0-24} on Day 90 (sexes combined) were 567 ng/mL and 11200 ng.h/mL, respectively; in males the Cmax and AUC_{0-24} on Day 90 were 341 ng/mL and 6330 ng.h/mL, respectively; in females the Cmax and AUC_{0-24} on Day 90 were 792 ng/mL and 16000 ng.h/mL, respectively. In the rat 26-week repeat dose study, AUC_{0-24} increased in a more than dose-proportional manner between 2.5 and 20 mg/kg. The exposure to BCX7353 on Days 91 and 182 increased after 26 weeks of daily administration, indicating accumulation occurred. Mean accumulation ratios ranged from 1.73 to 8.23 on Day 91, and from 2.38 to 11.3 on Day 182 for AUC_{0-24}. Steady-state conditions appeared to have been reached by Day 91. However, no sex differences were observed for AUC_{0-24} in this study. Gender ratios (female: male) ranged between 0.693 and 1.95 for AUC_{0-24}.

In monkeys, data from the 28-day repeat dose study indicate systemic exposure initially increased with increasing dose in a slightly greater than dose-proportionate manner (Day 1), but in a dose-proportionate manner on Day 28. Systemic exposure to BCX7353 appeared to be independent of sex. Further, BCX7353 did not accumulate in plasma following repeated administration of BCX7353 for 28 days. The t½ could only be determined in a limited number of animals due to insufficient data in the terminal elimination phase. In these animals, individual t½s ranged from 13.0 to 19.6 hours at 10 mg/kg, 11.3 to 56.8 hours at 30 mg/kg, and 321 hours for the single animal at 100 mg/kg. At the NOAEL of 10 mg/kg/day, the combined male and female mean Cmax and AUC_{0-24} on Day 28 were 86.4 ng/mL and 1350 ng.h/mL respectively. Similarly, TK data from the 13-week monkey study indicate that systemic exposure to BCX7353 appeared to be independent of sex. Median Tmax appeared to be dose-dependent and were observed at 2 hours post dose at 2.5 mg/kg on all study days, 4 hours post dose at 7.5 mg/kg on all study days, and 8 hours post dose at 20 mg/kg on all study days. Following daily administration of BCX7353, mean AUC_{0-24} and Cmax increased with increasing dose in an approximate dose-proportional manner from 2.5 to 7.5 mg/kg and in a slightly greater than dose-proportional manner from 2.5 to 20 mg/kg on Days 1, 28, and 91. Systemic exposure to BCX7353 did not appear to change following repeated administration of BCX7353 for 28 or 91 days. Mean accumulation ratios (based upon AUC0-24) were 1.31, 0.89, and 0.95, at 2.5, 7.5, and 20 mg/kg, respectively, on Day 28; and 1.51, 1.03, and 1.03, at 2.5, 7.5, and 20 mg/kg, respectively, on Day 91. At the NOAEL of 20 mg/kg/day, the combined male and female mean Cmax and AUC0-24 on Day 91 were 192 ng/mL and 3350 ng.h/mL, respectively.

Two chronic 39-weeks repeat-dose studies were conducted in monkeys. In the first, following dosing up to 20mg/kg/day, Tmax ranged between 1 and 8 hours post-dose and tended to increase with the increase in dose but did not increase over time. The Cmax was followed by a sustained level of BCX7353 where t½ was not estimable. In general, on Days 1, 91 (Week 13), 182 (Week 26), and 273 (Week 39), the AUC_{0-24} increased in a dose-proportional manner. The exposure to BCX7353 on Days

91, 182, and 273 did not change substantially when compared with Day 1 indicating that accumulation did not occur. Sex-specific mean accumulations ratios ranged from 0.785 to 1.32 on Day 91, from 0.877 to 1.30 on Day 182, and from 0.675 to 1.40 on Day 273, for AUC0-24. Steady-state conditions appeared to have been reached by Day 91 (Week 13), indicating there were no sex-dependent differences in exposure (AUC_{0-24}). At the NOAEL of 20mg/kg/day on Day 273, a sex-averaged Cmax of 197 ng/mL and AUC_{0-24} of 2880 ng.h/mL was reported. In the second chronic monkey toxicity study with dosing up to 80mg/kg/day, TK assessment was conducted for the test article on Days 1, 90, and 270. Systemic exposure to BCX7353 appeared to be independent of sex. Also, systemic exposure (AUC_{0-24} and Cmax) did not appear to increase with increasing dose on Day 1; however, exposure appeared to increase with increasing dose in an approximately dose-proportional manner on Days 90 and 270. Systemic exposure to BCX7353 generally did not appear to increase following repeated administration of BCX7353 for 90 or 270 days at 30 mg/kg, but generally appeared to increase following QD administration at 55 and 80 mg/kg for 90 or 270 days. At the NOAEL of 30 mg/kg/day, the mean Cmax and AUC_{0-24} on Day 270 (sexes combined) were 277 ng/mL and 3950 hr.ng/mL respectively.

In summary, TK data from the pivotal repeat-dose toxicology studies in rats indicate sex-dependent exposures that were higher in female rats in the 28-day and 13-week studies, although this finding was not replicated in the chronic rat toxicity study. A greater than dose-proportional increase in exposures with increasing dose was also apparent in the 28-day and 26-week rat studies, with evidence of BCX7353 accumulation after repeated dosing for 28 days, up to 26-weeks. However, TK data from all pivotal repeat-dose toxicology studies in monkeys indicates that exposure to BCX7353 was independent of sex. In monkeys, Tmax appeared to be dose-dependent and increased with increasing dose, ranging between 1-8 hours post-dose but exposure increased with increasing dose approximately dose-proportionally. Furthermore, BCX7353 did not accumulate with repeated dosing in the majority of pivotal monkey toxicity studies, although systemic exposure reportedly increased following daily administration at the 2 highest doses of 55mg/kg/day and 80mg/kg/day in the second chronic monkey toxicity study.

Interspecies comparison

The principal target organs in rats and monkeys are the liver and kidney. Phospholipidosis (PLD) was also observed in the liver via electron microscopy and suspected in the small intestine, lung, spleen, and lymphoid tissue at clinically relevant exposures. There were no direct toxicities associated with its presence and the clinical relevance of these findings is unknown. These findings are included in section 5.3 of the SmPC.

The respiratory system is affected at higher doses and considered an indirect effect of irritant properties of BCX7353 in the nasal cavity following gavage-related gastric reflux, causing breathing related difficulties. High doses of BCX7353 in the 28-day studies were associated with findings of skeletal and cardiac (rat only) muscle degeneration which was not observed in longer duration studies. The human exposure (Cmax and AUC_{0-24}) at 150 mg, the dose for which approval is being sought, is 157 ng/mL and 2640 ng.h/mL, respectively (Study BCX7353-112). Hence, the safety margin based on exposures at the NOAELs in the chronic toxicity studies in rat (20mg/kg/day) and monkey (30mg/kg/day) is 3.8 and 1.5 respectively. While these safety margins could be considered acceptable to support berotralstat 150 mg once daily (QD) administered to humans, BCX-7353-related decreased survival was noted in WH rats administered 20mg/kg/day in the 104-week carcinogenicity study, with audible breathing, decreased body weight, and lower food consumption also observed. The amended pathology report indicated that the decreased survival occurring at 20mg/kg/day was not statistically significant, this increase in mortality was not attributed to any particular probable cause of death, with pituitary and uterus tumours considered the most likely cause of death in males and females at 20mg/kg dosing respectively. In addition, deleterious effect on muscles were seen mostly in higher

doses in the repeat dose toxicity studies in rat and monkey, with 20 mg/kg considered NOAEL in study 806-144 and 8001291 repeat-dose toxicity rat studies.

Genotoxicity

The genotoxicity of BCX7353 has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in GLP-compliant studies in-vitro and in-vivo. No positive findings in either in-vitro or in-vivo tests are reported with BCX7353. It is concluded that BCX7353 is not genotoxic.

Bacterial reverse mutation studies were also conducted with 3 drug substance impurities; BCX7611, BCX7499, and BCX6634. Under the conditions of the respective studies, BCX7499 and BCX6634 were concluded to be negative in the bacterial reverse mutation assay. However, BCX7611 was positive for the ability to induce reverse mutations at the selected locus of S. typhimurium tester strain TA98 in the presence of an exogenous metabolic activation system. BCX7611 is a starting material in the synthesis of berotralstat hydrochloride and unreacted BCX7611 is a potential impurity but a limit of NMT 4ppm has been set to ensure human exposure is less than the TTC of 1.5ug/day, which is acceptable.

Carcinogenicity

Carcinogenicity studies include a 6-month transgenic mouse study and a 2-year rat carcinogenicity study. In CByB6F1/Tg rasH2 Hemizygous mice, daily oral administration of BCX7353 at doses up to 50 mg/kg for 26 weeks did not result in any treatment-related clinical signs, gross pathology findings, neoplastic histopathology findings, or significant effects on survival (Study 20088905). Dose-related statistically significant decreases in body weight gain and body weights with corresponding reductions in food consumption were noted at 20 and 50 mg/kg/day. Also, treatment-related non-neoplastic histopathology findings in the nasal cavity occurred at ≥ 8 mg/kg BCX7353 which were considered related to local irritant properties of BCX7353 as a result of gavage-related reflux, rather than a direct effect of BCX7353.

In WH rats daily oral administration of BCX7353 was reportedly tolerated for 104 weeks at doses up to 20 mg/kg/day (Study 806-161). A higher dose group of 60/40mg/kg/day was also included, but increased incidence of salivation, thin appearance, audible breathing, decreased body weight, and decreased food consumption were noted, leading to an increase in morbidity and mortality in this group. Consequently, this group was terminated at Week 28. At the highest remaining dose of 20 mg/kg/day, decreased survival, audible breathing, decreased body weight, and lower food consumption were observed. The decreased survival was not attributable to a predominant cause of death and was not statistically significant. The decreased body weight was also considered treatment-related but non-adverse, due to the magnitude of change (Week 53: < -10% versus control, Week 101: -17.6% and -13.5% less than controls, in males and females respectively).

In the uterus, a low incidence of malignant endometrial stromal sarcomas in females at 8 mg/kg/day (2/60 affected – 3.33%) and 20 mg/kg/day (3/60 affected – 5%) is reported. Malignant sarcomas of the skin were present in 3/60 (5%) of males treated with 20mg/kg/day, compared to 0/60 control males and this increase was statistically significant at 20mg/kg/day using the Poly-3 pairwise test for rare tumours (p=0.033).

BCX7353 is not genotoxic and the applicant cites an article from the literature proposing a mechanism for non-genotoxic compounds to cause hemangiosarcomas in rodents, via the induction of hypoxia, which stimulates proliferation of new blood vessels and occasional neoplasms of blood vessels (Cohen, Storer et al. 2009). It is thought that gavage-related gastric reflux of BCX7353 may have led to the nasal epithelial degeneration, causing the breathing-related difficulties which were observed, possibly

leading to hypoxia. The applicant considered the relevance of this rodent tumour to human safety as unlikely.

Reproductive and developmental toxicity

The completed package of reproductive and developmental toxicity for BCX7353 includes a fertility and early embryonic development study in male and female rats, embryo-foetal development (EFD) studies in rats and in rabbits, and a pre- and post-natal development study in rats. All pivotal reproductive toxicity studies were GLP-compliant and were conducted in an OECD member country. The reproductive and developmental toxicity package did not identify any effects of BCX7353 on fertility, pregnancy, foetal weights, malformations, embryolethality, embryo-foetal growth or teratogenicity.

A GLP-compliant fertility and early embryonic development study was conducted in rats to evaluate the potential toxicity of BCX7353 on female oestrous cycle, tubal transport, implantation, and development of the embryo, and to detect functional effects on male fertility (Study 806-156). Daily doses of 0, 10, 25, and 45 mg/kg/day were administered to males from 28 days prior to pairing until euthanasia on Day 63, dosing in females began 14 days prior to pairing and continued through GD 7. A NOAEL for parental toxicity of 25mg/kg/day is reported, based on adverse findings of lower terminal body weights, lower body weight gain, and lower food consumption in males at 45mg/kg/day. The NOAEL level for reproductive performance and fertility was 45 mg/kg/day, the highest dose level evaluated.

Embryo-foetal development (EFD) studies were conducted in rats and rabbits to evaluate the effects of BCX7353 on pregnant females and on the development of the embryo and foetus consequent to exposure of the female from implantation to closure of the hard palate. In the pivotal rat EFD study, daily doses of 0, 10, 25, and 75 mg/kg/day were administered from Days 6 to 17 post-mating (Study 9000644). The NOAEL for maternal toxicity was 25 mg/kg/day, based on adverse treatment-related clinical signs of decreased body weight, body weight gain and food consumption at 75mg/kg/day. Breathing irregularities and salivation were also reported at 75mg/kg/day. No evidence of embryo-foetal mortality, foetotoxicity, or teratogenicity was reported at any dose level and the NOAEL for EFD was 75 mg/kg/day, the highest dose administered. Placental transfer of BCX7353 appeared to be limited in rats, as the maximum mean foetal plasma concentrations at 4 hours post-dose were 3.8%, 7.1%, and 5.1% of the maternal Cmax at 10, 25, and 75 mg/kg/day, respectively.

In the pivotal rabbit study, daily doses of 1, 20, 20 and 100mg/kg/day were administered from post-mating day 17 to 19 (Study 9000815). The NOAEL for maternal toxicity was 50mg/kg/day, on the basis that the 100m/kg/day dose was poorly tolerated, with 4 pre-terminal deaths (including 2 abortions) and adverse effects on clinical condition, body weights, and food intakes reported. Decreased food consumption was also noted at 50mg/kg/day but was not considered adverse, as values recovered after dosing and no other maternal parameters were affected. No evidence of embryo-foetal mortality, foetotoxicity, or teratogenicity was reported at any dose level and the NOAEL for EFD was 100 mg/kg/day, the highest dose administered. Placental transfer was also limited in rabbits. The mean concentrations in foetal plasma at 3 hours post maternal dose were 7%, 11%, and 11% of the maternal Cmax for the 20, 50, and 100 mg/kg dose groups, respectively.

Berotralstat crossed the placental barrier in rats and rabbits. An embryo-foetal development study conducted in pregnant rats administered berotralstat at exposures 9.7 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose revealed no evidence of harm to the developing foetus. A second embryo-foetal development study in a relevant non-rodent species was not conducted.

A pre- and postnatal development (PPND) study was conducted in rats to evaluate the possible adverse effects of BCX7353 on the pregnant/lactating females and on the development of the conceptus and the offspring following exposure of the female from implantation through weaning

(Study 806-157). Daily doses of 1, 10, 25 and 45mg/kg/day were administered from gestational day (GD) 6 to lactation day (LD) 20. The NOAEL for maternal toxicity was 25mg/kg/day on the basis of treatment-related effects at 45 mg/kg/day in the parental females, included lower gestation body weight gain, lower lactation body weights (LD 14 and 17), lower lactation food consumption, and lower F1 pup body weights at LD 14, LD 21, and PND 28. The lower pup body weights on LD 14, 21, and PND 28 were considered adverse, but in the parental females, no effect of BCX7353 was observed on pregnancy rate, parturition parameters, litter size, F1 pup pre-weaning development (physical, sensory, reflex testing), sex ratios, survival, or clinical findings. Also, in the F1 animals retained on study, no effect was observed on body weights (growth or gestation), sexual maturation, clinical findings, behaviour (motor activity, learning, and memory), reproductive performance/fertility indices, GD 13 uterine implantation data, or macroscopic findings. BCX7353 was detected in the plasma from pups at all dose levels on LD 14, confirming that there was lactational exposure. Similar plasma concentrations were recorded in male and female pups at each collection interval but the maximum mean plasma concentrations were substantially lower (< 5%) in pup plasma relative to maternal plasma.

Phototoxicity

The results from the completed GLP-compliant Neural Red Uptake Phototoxicity assay in BALB/c 3T3 mouse fibroblasts indicate that BCX7353 has no phototoxic potential (Study 20088288). Radiolabelled BCX7353 was found to bind to melanin-containing tissues of LE rats in a distribution study. However, there were no microscopic or ophthalmological effects reported in the eyes of rats or monkeys from the chronic repeat-dose toxicity studies.

2.3.5. Ecotoxicity/environmental risk assessment

The predicted environmental concentration was calculated using a revised Fpen, based on the estimated prevalence of hereditary angioedema, giving a value of 0.00375 µg/l, which falls below the action limit of 0.01 µg/l.

Substance (INN/Invented Name): Berotralstat			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	pH metric method	4.19 ± 0.02	Potential PBT (N)
Phase I			
Calculation	Value	Unit	Conclusion
PEC $_{surfacewater}$, refined (prevalence)	0.00375	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Berotralstat is not a PBT substance as log Kow does not exceed 4.5.

Therefore, the applicant considered that Berotralstat is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Following a single oral gavage dose of radiolabel A to monkeys, there were no quantifiable levels of unchanged parent BCX7353 in either individual time-point or in pooled plasma samples. Since these results were unexpected and contrary to all other evaluations, these results required further scrutiny. No technical issues were identified concerning the conduct of this study. However, these findings clearly contrast with those from several other PK, toxicology, and metabolism studies in monkeys, which demonstrated BCX7353 is detectable in plasma for many hours following oral dosing. This

finding is unexplained. According to the applicant, no errors were found with the conduct of the study. One of proposed explanations for lack of quantifiable systemic berotralstat is rapid first pass metabolism, as non-naïve animals were used in this study. However, considering unchanged berotralstat is found in urine samples of the same animals this is highly unlikely. The applicant suggests limited stability of berotralstat in monkey plasma as an explanation for the lack of unchanged drug in monkey plasma, possibly due to mishandling of the radiolabelled plasma samples.

Pharmacology

Berotralstat (BCX7375) is a synthetic small molecule inhibitor of plasma kallikrein, intended for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years or older. A limited primary pharmacodynamics package was presented and no in vivo studies were included, but the scientific rationale for inhibiting plasma kallikrein activity in the treatment of in HAE is accepted, and the in vitro proof of concept data are considered sufficient non-clinical data to support the use of BCX7353 in HAE.

A complete package of safety pharmacology studies was conducted. BCX7353 was shown to inhibit the hERG channel in vitro, with an IC50 of 0.29 µM. Although, BCX7353 did not prolong action potential duration in isolated rabbit Purkinje fibers at the concentrations up to 93.7µM, 300-fold greater than that required to block hERG channels. However, in human cardiomyocytes, the beat period and field potential duration (a surrogate for the QT interval of an ECG) was increased by BCX7353 at concentrations > 0.3 µM, suggesting that BCX7353 has the potential to increase QT interval, albeit with a 51-fold selectivity margin relative to the inhibition of kallikrein in human plasma (5.83nM). Furthermore, decreased blood pressure (diastolic, systolic and mean) and increased ECG intervals, including RR, PR, QRS and QTc were reported in the vivo safety pharmacology study in conscious monkeys, following doses of 50 and 150 mg/kg BCX7353. The applicant did not consider these blood pressure and ECG effects to be adverse as the maximum increase was generally <11% vs the control mean. Therefore, the applicant reports a NOEL for cardiovascular safety of 150mg/kg in this study. The NOEL is not agreed, but 150mg/kg is accepted as the no observable adverse effect level (NOAEL) for cardiovascular effects under the conditions of this study.

These data identify the cardiovascular system as a potential target organ for BCX7353 toxicity. Decreased mean arterial pressure (20 to 30 mmHg) was also identified in the 7-day repeat dose toxicity study in monkeys at ≥10mg/kg and reversible decreased HR and lengthened RR, QT, QTc, QRS were reported at 100mg/kg/day in the 4-week monkey repeat-dose study. However, no effects on ECG parameters are reported from the chronic repeat-dose toxicology study in cynomolgus monkeys, with dosing up to 80 mg/kg/day BCX7353 administered for 39 weeks.

Pharmacokinetics

The nonclinical pharmacokinetics of BCX7353 was studied in mice, rats, rabbits, and monkeys, the species used in the general and reproductive toxicology studies, and carcinogenicity studies. A sex-dependent difference in BCX7353 exposure was reported in 28-day and 13-week studies in rats, the data suggested Cmax and AUC_{0-24} were greater in females than in males. However, there was no evidence of a sex difference in BCX7353 exposure in mice and monkeys and the rat finding was inconsistent, with no sex differences observed in the 26-week rat study and the 2-year rat carcinogenicity study. Following repeat dosing, accumulation was observed in rats and pregnant rabbits, but not in mice nor monkeys, with the exception of systemic exposure reported for the 2 highest doses of 55mg/kg/day and 80mg/kg/day in the chronic monkey toxicity study which showed evidence of accumulation. Hence, a potential for BCX7353 accumulation following repeated dosing is identified from the non-clinical pharmacokinetic data. This issue was addressed further in the clinical PK studies, therefore no further non-clinical queries were raised on this matter.

Placental transfer of BCX7353 was demonstrated in pregnant rats and rabbits (Cmax in foetal plasma was 4% to 7%, and 7% to 11%, of the maternal plasma Cmax in rats and rabbits, respectively). Exposure due to breast milk was evaluated in rats; the Cmax of BCX7353 in pup plasma on lactation day (LD) 14 was < 5% of the maternal plasma Cmax. This finding is included in sections 4.6 and 5.3 of the SmPC which is acceptable.

In the rat mass balance and distribution study, following a single oral dose of [^{14}C]BCX7353 (radiolabel A) in male pigmented LE rats, BCX7353 was found to bind to melanin-containing tissues. At 1440 hours post-dose, the highest concentration of radioactivity was quantified in the uveal tract of the eye. While accumulation of BCX7353 in the eye associated with melanin binding is possible, this was not considered relevant for human safety on the basis that there were no microscopic or ophthalmological effects reported in the eyes of rats or monkeys from the chronic repeat-dose toxicity studies and BCX7353 was not cytotoxic in the mouse fibroblast assay in the absence or presence of ultraviolet radiation.

Following a single oral gavage dose of radiolabel A to monkeys, there were no quantifiable levels of unchanged parent BCX7353 in either individual time-point or in pooled plasma samples. Since these results were unexpected and contrary to all other evaluations, these results required further scrutiny. No technical issues were identified concerning the conduct of this study. However, these findings clearly contrast with those from several other PK, toxicology, and metabolism studies in monkeys, which demonstrated BCX7353 is detectable in plasma for many hours following oral dosing. However, berotralstat is relatively unstable ex vivo in monkey plasma at room temperature and this finding may be the result of mishandling of the radiolabelled plasma samples. The CHMP considered that there was no need to explore this further.

Pharmacokinetic drug interaction studies indicated that BCX7353 is an inhibitor of CYP2C9 and CYP2C19 at concentrations < 1 µM, and an inhibitor of CYP2D6 and CYP3A at concentrations between 1 and 10 µM. Further, BCX7353 is likely a time-dependent inhibitor of CYP3A but is not likely a time-dependent inhibitor of other principal CYP isoenzymes. These results suggest that BCX7353 may interfere with the disposition of drugs metabolized by these enzymes. This issue has been addressed by a clinical drug-drug interaction (DDI) study and therefore no further non-clinical queries are raised on this issue.

BCX7353 also caused a 2- to 3-fold induction of mRNA and enzyme activity of human CYPs 2B6, and 3A4 but a lower concentration of BCX7353, (e.g. corresponding to > 200-fold than the expected worst-case concentrations in hepatocytes in vivo), did not result in changes in CYP2B6 mRNA of more than 20%. The potential drug-drug interaction with CYP3A4 substrates was tested in 3 clinical trials and BCX7353 was found to be a weak to moderate inhibitor of CYP3A4, appropriate wording for drugs which have a narrow therapeutic window has been included in the SmPC section 4.5.

Furthermore, BCX7353 inhibits P-gp, BCRP, MATE1, and MATE2-K , and is a substrate of P-gp and BCRP. The ability of BCX7353 to inhibit or act as a substrate for Pgp and BCRP has also been addressed in clinical DDI studies. This information has also been reflected in SmPC sections 4.5 and 5.2.

Toxicology

The applicant has submitted an acceptable package of toxicology studies for Orladeyo in line with the requirements of the respective ICH guidances. Rats and monkeys were selected as species for general toxicity studies, on the basis of their pharmacology and metabolism, which is acceptable.

Concerns were identified regarding the rabbit as a pharmacologically relevant species for toxicology evaluation of berotralstat. With regards to pharmacodynamics, kinetics and metabolism, the rabbit

seems to have a different pharmacologic response to berotralstat; an inhibitor of plasma kallikrein activity in humans, nonhuman primates and rats with half-maximal inhibition of plasma kallikrein observed at concentrations less than 10 nM, while in rabbit plasma, berotralstat did not inhibit kallikrein at concentrations less than 1000 nM. At the same time, it seems that the rabbit is the most sensitive species regarding prolongation of aPTT. Concentration for doubling aPTT was 9.6-10.3 µM while berotralstat treatment resulted in prolongation of PT and aPTT only at very high supratherapeutic drug concentrations in standard human plasma-based assays of coagulation (PT doubling was not observed at concentrations up to 100 µM [56.2 µg/mL]; aPTT doubling was observed at 73.4 µM [41.3 µg/mL]). There is no PK data available for rabbit with the exception of the study showing the instability of berotralstat in rabbit plasma and the reproductive toxicity studies. In reproductive toxicity studies the rabbit has a substantially lower exposure than rat at the same doses (i.e. Cmax and AUC on day 17 post-mating at 50 mg/kg – 1130 ng/ml and 20700 hr*ng/mL, respectively; while rabbit values at day 19 post-mating at 50 mg/kg are 266 ng/ml and 2350 hr*ng/mL), due to lower bioavailability and/or metabolism in plasma. Hence, in EFD studies in rabbits potential on-target effect in the dams may not have been assessed due to the low exposure but exposures causing some maternal toxicities are achieved (reduced food consumption and lower bodyweights leading to abortions), with an margin of 1.7 to the exposure achieved at the human 150 mg berotralstat dose. However, considering the inadequate pharmacological activity in rabbits, these data are considered insufficient evidence of lack of toxicity in non-rodent species and the rabbit data will not be included in the SmPC.

The principal target organs for BCX7353 toxicity in rats and monkeys are the liver and kidney. Phospholipidosis (PLD) was also observed in the liver via electron microscopy and suspected in the small intestine, lung, spleen, and lymphoid tissue. There were no direct toxicities associated with its presence and the clinical relevance of these findings is unknown, however this has been reflected in section 5.3 of the SmPC. The respiratory system is affected at higher doses and considered an indirect effect of irritant properties of BCX7353 in the nasal cavity following gavage-related gastric reflux, causing breathing related difficulties. High doses of BCX7353 in the 28-day studies were associated with findings of skeletal and cardiac (rat only) muscle degeneration. Based on the exposure in male and female rats at the NOAEL of 20mg/kg/day for skeletal myofibre degeneration/ necrosis, the applicant reported a safety margin to the clinical dose of 150mg QD of 4.5. These findings are included in section 5.3 of the SmPC.

Carcinogenicity

In a 6-month transgenic mouse carcinogenicity study, toxicity findings consistent with those seen in the repeat-dose toxicity package are reported. However, no evidence for BCX7353-related increases in tumours at the high dose of 50 mg/kg/day are observed. The 50mg/kg/day dose corresponding to an AUC0-24 and Cmax of 23,100 ng.h/mL and 2280 ng/mL in males, 31,800 ng.h/mL and 2970 ng/mL in females, respectively, on Day 182. The human exposure (AUC0-24 and Cmax) at 150 mg, the dose for which approval is being sought, is 2640 ng.h/mL and 157 ng/mL, respectively (Study BCX7353-112), indicating an approximately 10-fold margin from the high dose in mice to the clinical exposure following a 150 mg berotralstat dose on an AUC basis. This information is included in section 5.3 of the SmPC.

In the 2-year rat carcinogenicity study, a finding of malignant endometrial stromal sarcomas at 8 mg/kg/day (2/60 affected) and 20 mg/kg/day (3/60 affected) is reported. The possibility that this is a BCX7353-related finding could not be ruled out, due to the low incidence of this tumour in historical controls and the statistical significance of this finding. In addition, malignant sarcomas of the skin were present in 3/60 (5%) of males treated with 20mg/kg/day, compared to 0/60 control males and this increase was statistically significant at 20mg/kg/day using the Poly-3 pairwise test for rare tumours (p=0.033). Although there were no undifferentiated sarcomas in females at 8 or 20 mg/kg/day, and 1 of 60 control females (1.7%) were affected, there is a documents sex effect in rats, with males known

to be more sensitive to skin tumours. In support of this, skin neoplasms are more common in males than in females (Bomhard, 1992; Bomhard, 1994; Zwicker, 1992; Weber, 2017, NTP data). Hence, the role of berotralstat in carcinogenesis of rare malignant skin sarcomas cannot be excluded. The findings of malignant skin sarcoma, together with the margin of safety for these finding have been included in section 5.3 of the SmPC.

With regards to environmental risk, no specific studies were conducted for berotralstat, which is acceptable in line with the relevant guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.7. Conclusion on non-clinical aspects

The non-clinical data support an authorisation in HAE and are adequately reflected in section 5.3 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Type of Study	Study Id	Locat'n of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (# subjects dosed)	No. of Subjs Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Phase 1	BCX7353-101	5.3.3.1	To characterize the PK profile of single (Part 1) and multiple (Part 2) ascending doses of berotralstat in healthy subjects To characterize the anticipated PD effects of single (Part 1) and multiple (Part 2) ascending doses of berotralstat in healthy subjects To evaluate the effect of a high-fat meal on the single dose PK of berotralstat in a pilot evaluation in healthy subjects To characterize the PK profile of single and multiple doses of berotralstat in healthy subjects of Japanese origin (Part 3) To characterize anticipated PD effects of single and multiple doses of berotralstat in healthy subjects of Japanese origin (Part 3)	Randomized, double-blind, placebo-controlled, 3 Part study	Part 1 – single dose: C1: 10 mg [SN] (6) C2: 30 mg [SN] (4) C3: 100 mg [SN] (6) C4: 250 mg [SN] (6) C5: 500 mg [SN] (6) C6: 1000 mg [SN] (6) Part 2- multiple dose (# of subjects exposed to berotralstat): C1: 125 mg [SN] × 7 d (10) C2: 250 mg [SN] × 7 d (10) C3: 500 mg [SN] × 7 d (10) C4: 350 mg [SN] × 14 d (10) Part 3 -Japanese ethnobridging (# of subjects exposed to berotralstat): Single dose: C1:100 mg [SN] (6) C2: 500 mg [SN] (6) Multiple dose: 250 mg [SN] × 7 d (10) *Note:* 250 mg group in Part 1 received 2 doses for food effect evaluation	46 subjects enrolled 48 Subjects enrolled 28 Subjects enrolled	Healthy subjects	Part 1: Single dose, except for Cohort 4 where patients received 2 single doses Part 2: 7 days (Cohorts 1 to 3), 14 days (Cohort 4) Part 3: Single dose (2 Cohorts) and 7 days (1 Cohort)	Complete

Type of Study	Study Id	Locat'n of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (# subjects dosed)	No. of Subjs Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Phase 1	BCX7353-103	5.3.1.2	The primary objective was to determine the relative oral bioavailability of berotralstat when administered in 2 different capsule formulations (SN or base content) to healthy subjects Secondary PK objectives: To estimate the effect of a high-fat meal on the PK of berotralstat following single dose administration of berotralstat blend in capsules To characterize the PK of 2 berotralstat formulations when administered with or without food to healthy subjects To estimate the effect of a moderate- and low-fat meal on the PK of berotralstat following single-dose administration of berotralstat blend in capsule (Part 2)	Open-label, randomized 2 part, 3 period crossover	Treatment A: berotralstat API 350 mg (SN) as 3 × 116.67 mg (SN) capsules following an overnight fast (23) Treatment B: berotralstat blend 300 mg (free base) as 3 × 100-mg capsules following an overnight fast (22) Treatment C: berotralstat blend 300 mg (free base) as 3 × 100-mg (22)	24 subjects were enrolled	Healthy subjects	Single dose with at least 14 days between dosing periods	Complete
Phase 1	BCX7353-104	5.3.3.1	The primary objective was to determine the mass balance of [14C]-BCX7353 PK secondary objectives: To determine the radioprofile and identify metabolites of [^{14}C]-BCX7353 in plasma, urine, and feces following a single oral dose of [^{14}C]-BCX7353 To assess the PK of berotralstat in plasma and urine following administration of an oral dose of [^{14}C]-BCX7353 To assess the PK of total radioactivity in plasma To assess the exposure of notable radiolabeled components using AUC pooling	Open-label, non-randomized	Single oral solution dose of 350 mg of [^{14}C]-BCX7353 diHCl salt that consisted of a mixture of [^{14}C]-BCX7353 that contained 100 µCi 14C (3.7 MBq) and unlabeled berotralstat diHCl salt that contained approximately 300 mg of berotralstat (7)	7	Healthy subjects	Single dose	Complete
Phase 1	BCX7353-105	5.3.3.4	The primary PK objectives were as follows: To characterize the effect of berotralstat on the single dose PK of the P-gp substrate, digoxin, in healthy subjects To characterize the effect of berotralstat on the single-dose PK of the BCRP substrate, rosuvastatin, in healthy subjects To characterize the effect of the P-gp and BCRP inhibitor, cyclosporine, on the single dose PK of berotralstat in healthy subjects The secondary objectives of the study were as follows: • To evaluate the safety and tolerability of berotralstat in healthy subjects • To evaluate the safety and tolerability of digoxin when dosed concomitantly with berotralstat • To evaluate the safety and tolerability of rosuvastatin when dosed concomitantly with berotralstat	Open-label, fixed sequence, non-randomized	Each berotralstat dose was administered as 3 × 116.7-mg oral capsules (total dose of 350 mg berotralstat [SN]). Each subject received the following orally administered treatments in an open-label, fixed-sequence design: Cohort 1: • Day 1: digoxin 0.25 mg • Days 11 to 18: berotralstat 350 mg • Day 19: berotralstat 350 mg followed 1 hour later by digoxin 0.25 mg • Days 20 to 21: berotralstat 350 mg (18) Cohort 2: • Day 1: rosuvastatin 10 mg • Days 7 to 14: berotralstat 350 mg • Day 15: berotralstat 350 mg followed 1 hour later by rosuvastatin 10 mg • Day 16: berotralstat 350 mg (18) Cohort 3: • Day 1: berotralstat 350 mg • Day 14: single dose of cyclosporine 600 mg followed 1 hour later by berotralstat 350 mg (18)	54 subjects were enrolled	Healthy subjects	Cohort 1: 11 days Cohort 2: 10 days Cohort 3: 2 single doses	Complete

Type of Study	Study Id	Locat'n of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (# subjects dosed)	No. of Subjs Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Phase 1	BCX7353-106	5.3.4.1	Primary objectives were to characterize: The steady-state effects of berotralstat on the QT/ QTc interval of the 12-lead ECG The torsadogenic potential of berotralstat at steady-state by evaluating the effects of berotralstat on the QT subintervals The secondary objectives were to characterize the PK of berotralstat and of berotralstat on other ECG intervals, as well as assess the safety and tolerability of multiple doses of berotralstat in healthy subjects.	Randomized, double-blind, placebo-controlled	Cohort 1: 150mg/day administer orally as 2 x 75mg capsules (14) Cohort 2: 450mg/day administered orally as 6 x 75mg capsules (14)	40	Healthy subjects	14 days of dosing	Complete
Phase 1	BCX7353-107	5.3.3.3	The primary objective was to characterize the single-dose PK of berotralstat in subjects with varying degrees of renal impairment compared to matched healthy subjects. *Note:* due to the per protocol study design, only severe renal impairment was evaluated in this study. The secondary objectives of the study were to: • To assess the safety and tolerability of single doses of berotralstat in subjects with varying degrees of renal impairment. • To determine the extent of removal of berotralstat via hemodialysis, if applicable. • To provide dosage adjustment guidance based upon the degree of renal impairment, if applicable.	Open-label, non-randomized	Two 100mg capsules for oral administration were given to each subject for a total dose of 200 mg. (14)	14	Subjects with severe renal impairment and matched healthy controls	Single dose	Complete
Phase 1	BCX7353-108	5.3.3.3	The primary objective of the study was to characterize the single dose PK of berotralstat in subjects with varying degrees of hepatic impairment compared with matched healthy subjects. The secondary objectives of this study were to assess the safety and tolerability of single doses of berotralstat in subjects with varying degrees of hepatic impairment and to provide dose adjustment guidance for berotralstat based upon the degree of hepatic impairment, if applicable.	Open-label, non-randomized	Each subject received 1 single oral dose of a berotralstat capsule containing 150 mg of berotralstat (24)	24 subjects were enrolled in the study	Subjects with mild, moderate and severe hepatic impairment and matched healthy controls	Single dose	Complete
Phase 1	BCX7353-109	5.3.4.2	A primary objective of this study was to characterize the PK profile of berotralstat in subjects with HAE A secondary objective of this study was to provide additional safety and tolerability information for berotralstat in subjects with HAE	Open-label, non-randomized	Regimen B: Single oral dose of BCX7353 750 mg [SN] in a capsule formulation Regimen C: Single oral dose of BCX7353 750 mg [SN] in a liquid formulation (6)	6 subjects	HAE	Single dose	Complete

Type of Study	Study Id	Locat'n of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (# subjects dosed)	No. of Subjs Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Phase 1	BCX7353-110	5.3.5.4	1. To evaluate whether prophylactic inhibition of plasma kallikrein with a single 700 mg oral dose of the plasma kallikrein inhibitor BCX7353 significantly reduced the volume of a wheal provoked by intradermal forearm skin prick tests (SPTs) of: a. Codeine (non-immunoglobulin E [IgE] mediated mast-cell [MC] activation) b. Histamine c. A subject-relevant allergen (IgE-mediated MC activation) 2. To evaluate whether prophylactic inhibition of plasma kallikrein with a single 700 mg oral dose of the plasma kallikrein inhibitor BCX7353 significantly reduced the intensity of a flare provoked by intradermal forearm SPTs of: a. Codeine (non-IgE mediated MC activation) b. Histamine c. A subject-relevant allergen (IgE-mediated MC activation) 3. To evaluate the safety and tolerability of a single 700 mg oral dose of BCX7353 in healthy subjects	Phase 1b, exploratory proof of concept study. Randomized double-blind, placebo-controlled	Subjects received a single oral dose of BCX7353 700 mg or matching placebo	12 subjects were randomized and completed the study; 7 subjects received placebo and 5 subjects received BCX7353	Male subjects 18 to 70 years of age with a known allergy (wheal ≥ 4 mm) to at least 1 of the allergens of the pan-European SPT at the Day 1 visit	Subjects received a single oral dose of BCX7353 700 mg or matching placebo on Day 7 (± 2 days).	Complete
Phase 1	BCX7353-112	5.3.3.4	The primary objectives of the study were to characterize the effect of berotralstat on the PK of: Danazol in healthy male subjects (Cohort 1) Amlodipine in healthy subjects (Cohort 2) Desipramine in healthy subjects (Cohort 3) The secondary objectives of the study were to evaluate the safety and tolerability of berotralstat and Danazol (Cohort 1), berotralstat and Amlodipine (Cohort 2) and berotralstat and Desipramine (Cohort 3) when administered concomitantly	Open-label, fixed sequence, non-randomized	Subjects were administered orally 3 capsules of BCX7353 dihydrochloride containing 50 mg free base weight of BCX7353, for a total dose 150 mg QD. Subjects received the following treatments in an open-label, fixed sequence: Cohort 1 Day 1: Danazol 200 mg Days 7 to 15: BCX7353 150 mg Day 16: Danazol 200 mg + BCX7353 150 mg (19) Cohort 2 Day 1: Amlodipine 5 mg Days 14 to 25: BCX7353 150 mg Day 23: Amlodipine 5 mg + BCX7353 150 mg (14) Cohort 3 Day 1: Desipramine 50 mg Days 10 to 20: BCX7353 150 mg Day 19: Desipramine 50 mg + BCX7353 150 mg (19)	52 subjects were enrolled in this study	Healthy subjects	Cohort 1: Subjects received 2 single doses of danazol and 10 daily doses of BCX7353. Cohort 2: Subjects received 2 single doses of amlodipine and 12 daily doses of BCX7353. Cohort 3: Subjects received 2 single doses of desipramine and 11 daily doses of BCX7353.	Complete

Type of Study	Study Id	Locat'n of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (# subjects dosed)	No. of Subjs Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Phase 1	BCX7353-113	5.3.1.2	The primary objective of this study was to determine whether 2 berotralstat capsule formulations (Phase 3 formulation and commercial formulation) at 2 dosage strengths are bioequivalent in healthy subjects. Secondary objectives of this study were to characterize the PK of 2 berotralstat formulations at 2 dosage strengths when administered to healthy subjects and to evaluate the safety and tolerability of berotralstat when administered to healthy subjects.	Open-label, randomized	Cohort 1 • Regimen A: berotralstat Phase 3 formulation – 110 mg as 2 × 55 mg capsules, taken once by mouth following an overnight fast (reference formulation) • Regimen B: berotralstat commercial formulation – 110 mg as 1 × 110 mg capsule, taken once by mouth following an overnight fast (test formulation) (30) Cohort 2 • Regimen C: berotralstat Phase 3 formulation – 150 mg as 2 × 75 mg capsules, taken once by mouth following an overnight fast (reference formulation) • Regimen D: berotralstat commercial formulation – 150 mg as 1 × 150 mg capsule, taken once by mouth following an overnight fast (test formulation) (30)	60 subjects enrolled	Healthy subjects	Subjects received 1 dose of each formulation within their cohort, separated by a minimum 30-day washout period	Complete
Phase 1	BCX7353-114	NA	The primary objective of the study was to determine the relative oral bioavailability of BCX7353 when administered in 2 different formulations (liquid and mini-tablet formulations) in healthy subjects.	Open-label, randomized	Cohort 1 • Regimen A: BCX7353 liquid formulation – 650 mg taken once by mouth following an overnight fast, reconstituted in an oral vehicle prior to administration (reference formulation) • Regimen B: BCX7353 mini-tablets formulation – 675 mg as mini-tablets, taken once by mouth following an overnight fast (test formulation)	18	Healthy subjects	1 dose of each formulation separated by 21 days	Ongoing
Phase 1	BCX7353-115	5.3.3.4	The primary objective of the study was to determine the effect of berotralstat on the PK of midazolam, omeprazole, dextromethorphan, and tolbutamide in healthy subjects The secondary objective of the study was to evaluate the safety and tolerability of midazolam, omeprazole, dextromethorphan, tolbutamide, and BCX7353 when administered concomitantly	Open-label, fixed sequence, non-randomized	Berotralstat 150 mg oral capsule Midazolam 4 mg oral solution (2 mg/mL) Tolbutamide 500 mg oral tablet Omeprazole 40 mg oral capsule Dextromethorphan 30 mg (30 mg/5 mL) (21)	21 subjects	Healthy subjects	Subjects received 11 oral doses of berotralstat 150 mg QD on Days 3 to 13. Subjects received 2 oral doses of midazolam 4 mg, tolbutamide 500 mg, omeprazole 40 mg, and dextromethorphan 30 mg on Days 1 and 12.	Complete
Phase 2	BCX7353-202	5.3.5.1	**Primary:** • To evaluate the efficacy of single oral doses of BCX7353 in treating acute attacks in subjects with hereditary angioedema (HAE) The secondary objectives of this study were as follows: • To evaluate the safety and tolerability of single oral doses of BCX7353 in subjects with HAE • To evaluate the relationship of BCX7353 dose with clinical responses • To evaluate subject satisfaction with BCX7353 treatment • Substudy: to describe the natural history and temporal pattern of symptoms of untreated attacks and those treated with commercially available attack medications	Randomized, double-blind, placebo controlled	BCX7353 powder and matching placebo powder for reconstitution as oral solutions. 750mg [SN] (36), 500mg [SN] (15), 250 mg [SN] (12)	63 subjects were randomized, 58 of which received at least 1 dose of study drug/active	HAE	3 separate attacks were treated; 2 with active drug and 1 with placebo	Complete

Type of Study	Study Id	Locat'n of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (# subjects dosed)	No. of Subjs Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Phase 2	BCX7353-203	5.3.5.1	The primary objective of this study was to evaluate the efficacy of once-daily prophylactic berotralstat up to 5 dose levels, as measured by the number of attacks of HAE observed in subjects with HAE enrolled in each treatment group The secondary objectives of this study were as follows: • To evaluate the safety and tolerability of berotralstat over 28 days in subjects with HAE • To describe the PK profile of daily berotralstat in subjects with HAE • To characterize the anticipated PD effects of berotralstat in subjects with HAE • To characterize the dose-response relationship of berotralstat in subjects with HAE • To evaluate effects of berotralstat on QoL	A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study	Part 1: 350mg [SN] berotralstat or placebo orally QD (18) Part 2: 250mg [SN] berotralstat, 125mg [SN] berotralstat or placebo orally QD (13) Part 3: 250mg [SN] berotralstat, 125mg [SN] berotralstat, 62.5 mg [SN] berotralstat or placebo orally QD (22)	Part 1: 36 subjects were enrolled Part 2: 15 subjects were enrolled Part 3: 24 subjects were enrolled	HAE	Subjects were dosed orally with berotralstat capsules and/or matching placebo QD for 28 days.	Complete
Phase 2	BCX7353-204 Interim	5.3.5.2	Primary Objective • To evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 in subjects with HAE Secondary Objectives • To assess the effectiveness (ie, HAE attack frequency, severity, and disease activity over time) of BCX7353 during long-term administration • To evaluate QoL during long-term administration of BCX7353 • To evaluate subject's satisfaction with medication during long-term administration of BCX7353	2-arm, open-label study	The doses of BCX7353 used in this study are 110 mg QD (100) and 150 mg QD (127) initially, transitioning to single-arm, 150 mg QD dosing based on results of Part 1 of Study BCX7353-302. Beroltralstat capsules administered orally.	227; 100 subjects randomized to receive 110 mg berotralstat and 127 subjects randomized to receive 150 mg berotralstat	HAE	Ongoing	Interim CSR available, study enrollment is ongoing
Phase 3	BCX7353-301 Interim	5.3.5.1	Part 1 Primary objective: • To determine the efficacy of prophylactic berotralstat (BCX7353) 110 and 150 mg administered once daily (QD) for 24 weeks compared to placebo in subjects with hereditary angioedema (HAE) Part 1 Secondary objectives: • To assess the safety and tolerability of berotralstat 110 and 150 mg administered QD for 24 weeks • To assess the effects of berotralstat on HAE disease activity and angioedema event characteristics • To evaluate the effects of berotralstat on quality of life (QoL) • To characterize the pharmacodynamic (PD) effects of berotralstat	Randomized, double-blind, placebo-controlled, parallel-group study in subjects with hereditary angioedema	Two capsules of berotralstat at 55 mg or 75 mg were administered orally QD for 24 weeks in Part 1	A total of 25 subjects were screened, 19 subjects were randomized (intent-to-treat [ITT] population) and treated (safety population).	HAE	Subjects received 24 weeks of berotralstat or placebo in Part 1 of the study.	Interim CSR available, study enrollment is ongoing
Phase 3	BCX7353-302 Interim	5.3.5.1	Part 1 Primary Objective • To determine the efficacy of prophylactic berotralstat 110 mg and 150 mg administered QD for 24 weeks compared to placebo in subjects with HAE Part 1 Secondary Objectives • To assess the safety and tolerability of berotralstat 110 mg and 150 mg administered QD for 24 weeks • To assess the effects of berotralstat on HAE disease activity and HAE attack characteristics • To evaluate the effects of berotralstat on QoL • To characterize the PD effects of berotralstat	Randomized, double-blind, placebo-controlled, parallel-group, 3-part study in subjects with Type I or II HAE.	Two capsules of berotralstat at 55 mg (41) or 75 mg (40) were administered orally QD for 24 weeks in Part 1	121 subjects were randomized (stratified by baseline attack rate, < 2 vs. ≥ 2 per 28 days), and 120 randomized subjects (99%) were treated.	HAE	Subjects received 24 weeks of berotralstat or placebo in Part 1 of the study.	Interim CSR available, study enrollment is ongoing

2.4.2. Pharmacokinetics

Bioanalytical Methods

Bioanalytical Method Validation

LC-MS/MS based methods for the determination of BCX7353 in human plasma were validated at LGC and Q2 Solutionslaboratories, respectively. Additional method validation was also provided for the assessment of BCX7353 in urine at LGC laboratories. Analytical methods for the determination of BCX7353 in plasma, and associated internal standards (IS), utilised LC-MS/MS with protein precipitation extraction, while methods investigating urine used solid phase extraction (SPE). The % fraction of unbound (%fu) BCX7353 in human plasma was quantitated using a rapid equilibrium dialysis (RED) chamber combined with LC-MS/MS.

The calibration curve for each method was established by a weighted (1/x2) linear regression of the ratio of the peak area of the analyte to that of the (IS). Linear responses in the analyte and IS ratios were observed in spiked calibration standards (CS) and quality control (QC) samples, respectively, for each method. Bioanalytical method validation reports provide data pertaining to selectivity; lower limit of quantification (LLOQ); characterisation of potential matrix interference; intra- and inter-assay accuracy and precision; dilution integrity; carryover and analyte stability.

Back calculated CS were within ±20% of the nominal value at the LLOQ, and ±15% for all other concentration levels above the LLOQ, using a minimum of 6 non-zero concentration levels. Intra- and inter-assay precision (%CV) was acceptable for the QC sample concentrations presented (i.e. %CV for low, medium and high QC samples <15%, respectively). The intra- and inter-assay accuracy (percent relative error [%RE]) was within ±15% of the nominal values for low, medium and high QC samples were utilised, and within ±20% for the LLOQ.

Bioanalytical Analysis of Samples

During the analysis of participant samples, spiked CS and QC standards were extracted to permit the determination of the concentration of BCX7353 and its respective IS, in addition to the assessment of accuracy and precision. Information pertaining to transportation, handling and storage of samples was provided. All samples were analysed within the established stability range following long-term storage. Incurred sample reanalysis (ISR) was performed during assessment of BCX7353 in participant samples from clinical studies to ensure method reproducibility.

Population pharmacokinetic analysis (BCX7353-PPK-01)

Twelve (12) clinical studies were included in a dataset for population pharmacokinetic (PK) analysis of BCX7353. These studies included healthy subjects, subjects with HAE, and subjects with renal or hepatic impairment.

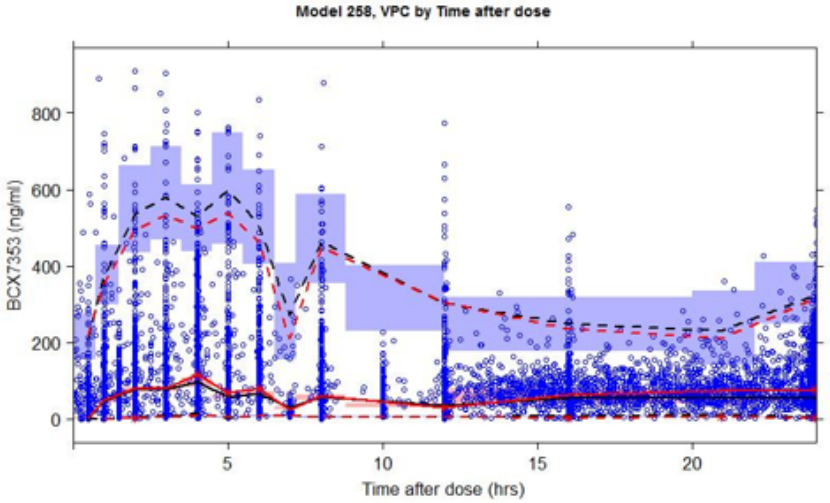
The final updated model was a 3-compartment model with first-order absorption with an absorption lag time and linear elimination. Body weight was included as a covariate on clearance and volume of distribution. Dose was included as a covariate effect on bioavailability. PK parameters for the final model are provided in Table 7. VPC for the first 24 hours after dose is given in Figure 2.

Table 2: Model 258, Fixed Parameter Estimates (THETA) PK Model of BCX7353 - Pooled

Parameter	Parameter Estimate (RSE%)	Between subject variability (CV%) and RSE (%)
THETA(1) CL (L/hr for 75.2 kg subject*)	47.3 (2.4)	37.6 (2.69)
THETA(2) V (L for 75.2 kg subject)	1650 (2.49)	32.5 (4.68)
THETA(3) Additive error (ng/mL)	0.483 (3.75)	NA
THETA(4) Proportional error	0.286 (0.404)	NA
THETA(5) Ka (1/hr)	1.12 (0.0891)	83.2 (6.79)
THETA(6) K23 (1/hr)	0.0812 (2.32)	NA
THETA(7) K32 (1/hr)	0.0309 (2.52)	NA
THETA(8) ALAG1 (hr)	0.468 (2.15)	48.7 (4.55)
THETA(9) K24 (1/hr)	0.00281 (17.7)	NA
THETA(10) K42(1/hr)	0.00136 (25.4)	NA
THETA(11) Dose on relative bioavailability	0.497 (5.51)	BA
THETA(13) V~Weight	1.00 (8.28)	NA
THETA(15) CL~Weight	0.480 (14.3)	NA

Abbreviations: ~ = "is a function of"; CI = confidence interval; CL = clearance; F1 = bioavailability for dose in compartment 1; Ka = absorption rate; NA = not available; RSE = relative standard error; V = volume.
*75.2 was the median weight across all studies

Figure 2: Model 258, VPC for the First 24 Hours after Dose



Absorption

- Bioavailability

Study BCX7353-101 (Part 1, 2 and 3)

This study was a 3-part, Phase 1, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, PK, and PD of single and multiple doses of BCX7353 in healthy subjects of Western and Japanese origin.

Part 1 and 3 – Single Ascending Dose in Healthy Western and Japanese Participants

The PK characteristics of single ascending oral doses of BCX7353 [10, 30, 100, 250, 500 and 1000 mg] were assessed in healthy Western volunteers during Part 1, and Japanese participants [100 and 500 mg] during Part 3 of this study. All study drug was administered under fasting conditions in all parts, except for one cohort in Part 1 who received drug under both fasting and fed conditions. PK samples were collected through 96 hours post dose.

Cmax was reached in both Western and Japanese subjects approximately 2 to 6 hours following single oral doses under fasting conditions. A second peak occurred approximately 5 hours after dosing in both Western and Japanese participants, which coincided with the timing of a meal, suggesting that berotralstat may undergo enterohepatic recirculation. Berotralstat plasma concentrations then declined biphasically. Urinary excretion and renal clearance (CLR) of berotralstat was low with <3% of the dose excreted in urine as unchanged parent across dose cohorts.

In Western participants (Part 1), C_{max} ranged from 3.75 to 680 ng/mL, while AUC0-inf ranged from 25.0 to 16800 (ng·h/mL) for 30-1000 mg doses. $T_{1/2}$ was 2.75 h for the 30 mg dose, and 45.1 to 62.2 hours for 100 to 1000 mg doses. For Japanese participants (Part 3), C_{max} was 37.9 and 311 ng/mL, $AUC_{0\text{-}inf}$ was 720 and 6940 (ng·h/mL), while $T_{1/2}$ was 55.6 and 45.8 for 100 and 500 mg doses, respectively.

Part 2 and 3 – Multiple Ascending Doses in Healthy Western and Japanese Participants

In Part 2 and 3, participants of Western (Part 2) and Japanese (Part 3) origin were treated with either a 7 or 14-day course of study drug. Participants recruited in Part 2 received 125, 250 or 500 mg QD for 7 days, while an additional cohort received 350 mg QD for 14 days. Participants in Part 3 received 250 mg of study drug or placebo QD for 7 days. For 7 days of fasted dosing (Parts 2 and 3 multiple dose), PK samples were collected for 24-hours post dose on Day 1 and for 96 hours post dose on Day 7. For 14 days of fasted dosing (Part 2 Cohort 4), PK samples were collected for 24-hours post dose on Day 1 and for 120 hours post dose on Day 14.

There was approximately 3- to 5-fold accumulation in exposure in both Western and Japanese participants following multiple dosing over 7 or 14 days. For Western participants dosed for 7 days (Part 2), there was a slightly greater than dose-proportional increase in exposure (AUC_{tau} and C_{max}) over the 125-mg to 500-mg dose range. Steady-state conditions were achieved from 6 to 12 days post first dose. Geometric mean BCX7353 AUC_{tau} and C_{max} were approximately 13% and 20% higher, respectively, in Japanese subjects as compared to Western subjects following multiple doses of BCX7353 at 250 mg QD.

- Bioequivalence

Study BCX7353-103

This Phase 1, single-dose, open-label, randomized, crossover study evaluated the relative bioavailability of 2 BCX7353 capsule formulations. A minimum 14-day washout period separated treatments.

- Treatment A: BCX7353 API 350 mg [SN] (fasted)
- Treatment B: BCX7353 Blend 300 mg [free base] (fasted)

Following single-dose administration, the BCX7353 API 350-mg (SN) capsule was shown to be bioequivalent to the BCX7353 blend 300-mg (fasted) capsule formulation in all PK parameters of interest; Cmax, AUC0-last, and AUC0-inf.

Table 3: Statistical Analysis of Selected PK Parameters for BCX7353 Blend 300 mg (Fasted) vs. BCX7353 API 350 mg (SN) – PK Population.

Parameter	n1/n2	Treatment B/ Treatment A GLSM	Ratio (%) [a]	90% CI [b] (%)
$AUC_{0\text{-}last}$ (ng.h/mL)	22/23	2415/2297	105.2	(97.5, 113.4)
$AUC_{0\text{-}inf}$ (ng.h/mL)	22/23	3286/3121	105.3	(96.5, 114.9)
C_{max} (ng/mL)	22/23	126/118	107.1	(98.5, 116.6)

Study BCX7353-113

This Phase 1, single-dose, open-label, randomized, two-period crossover study evaluated the bioequivalence of 2 capsule formulations (berotralstat Phase 3 formulation [reference] and berotralstat commercial formulation [test]). Subjects were enrolled in either cohort 1 (110 mg berotralstat) or cohort 2 (150 mg berotralstat). There was a minimum 30-day washout period between treatments.

Berotralstat commercial formulation was shown to be bioequivalent to the berotralstat Phase 3 formulation in both the 110 mg and 150 mg strengths in all PK parameters of interest; Cmax, AUC0-72, and AUC0-inf.

Table 4: Statistical Analysis of Bioequivalence of 110 mg Commercial Formulation vs. 110 mg Phase 3 Formulation (PK Population)

	Geometric LS mean				Geometric LS mean ratio	
	Test 110 mg		Reference 110 mg		(Test/Ref)	
Pharmacokinetic parameter	n	Test	n	Reference	Ratio Test/Reference	90% CI
C_{max} (ng/mL)	28	32.4	28	31.3	103.8	(94.0, 114.5)
AUC_{0-72} (ng.h/mL)	28	478.3	28	466.9	102.4	(98.6, 106.4)
AUC_{0-inf} (ng.h/mL)	11	615.2	11	617.7	99.6	(93.8, 105.8)

Table 5: Statistical Analysis of Bioequivalence of 150 mg Commercial Formulation vs. 150 mg Phase 3 Formulation (PK Population)

PK Parameter	GLSM				GLSM ratio (%)	
	Test 150 mg		Reference 150 mg		(Test/Reference)	
	n	Test	n	Reference	Ratio Test/Reference	90% CI
C_{max} (ng/mL)	27	51.7	27	50.2	103.0	(94.9, 111.7)
AUC_{0-72} (ng.h/mL)	27	775.6	27	759.7	102.1	(96.4, 108.1)
AUC_{0-inf} (ng.h/mL)	15	1083.7	15	1062.3	102.0	(95.2, 109.3)

- Influence of Food

Study BCX7353-101 (Part 1, Cohort 4)

Participants in Part 1 of study BCX7353-101 were administered a 250 mg oral dose of BCX7353 following an overnight fast and after consumption of a high-fat meal. There was a washout period of ≥7 days between dosing in fed versus the fasted stated.

Following consumption of a high-fat breakfast, BCX7353 AUC_{0-last} and AUC_{0-inf} increased by 19 and 41%, respectively, compared to the fasted condition. No significant difference in mean Cmax values were observed.

Table 6: BCX7353-101 Part 1: Statistical Comparisons of BCX7353Pharmacokinetic Parameters Following Single Dose Administration of BCX7353 at 250 mg under Fasted or Fed Conditions

BCX7353 Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		% Geometric Least Square Mean Ratio (90% CI)
	BCX7353 250 mg Fed (N=6)	BCX7353 250 mg Fasted (N=6)	BCX7353 250 mg Fed/Fasted
C_{max} (ng/mL)	98.1	104	94.3 (66.4, 134)
AUC_{0-last} (ng•hr/mL)	1850	1550	119 (96.5, 148)
AUC_{0-inf} (ng•hr/mL)	2720	1930	141 (108, 184)

Study BCX7353-103

This Phase 1, cross-over study evaluated the effect of a high fat meal on BCX7353 pharmacokinetics when administered in a novel capsule formulation. Subjects received a single dose of 1 of the following treatments:

Treatment B: BCX7353 blend in capsule – 300 mg (free base) following an overnight fast

Treatment C: BCX7353 blend in capsule – 300 mg (free base) following a high-fat meal

There was a minimum 14-day washout period between treatments.

Berotralstat exposure (Cmax, AUC0-last, and AUC0-inf) was similar following administration of a single dose of berotralstat blend 300 mg in capsule after a high-fat meal compared with under fasting conditions. Although time to Cmax (Tmax) was delayed by 3 hours following the high-fat meal compared to fasted administration, this did not impact overall berotralstat exposure. The 90% CIs for all 3 PK parameters were within the bounds of 80% to 125%, indicating that there was no food effect on the extent of exposure with the blend capsule formulation.

Table 7: Statistical Analysis of Selected PK Parameters for BCX7353 Blend 300 mg (High Fat) vs. BCX7353 Blend 300 mg (Fasted) – PK Population

Parameter	n1/n2	Treatment C/ Treatment B GLSM	Ratio (%) [a]	90% CI [b] (%)
$AUC_{0\text{-last}}$ (ng.h/mL)	22/22	2487/2415	103.0	(95.3, 111.2)
$AUC_{0\text{-inf}}$ (ng.h/mL)	22/22	3347/3286	101.9	(93.2, 111.3)
C_{max} (ng/mL)	22/22	142/126	112.0	(102.8, 122.0)

Metabolites of BCX7353 found in human plasma and urine were assessed qualitatively. In plasma samples collected from healthy subjects dosed orally once daily (QD) for multiple days with BCX7353 at 250, 350 and 500 mg/dose, 3 metabolites were detected along with the parent molecule. The putative metabolites found were postulated to be formed by N-dealkylation (M3), oxidative deamination, hydrogenation (M9), and oxidation, or a combination thereof (M6, M7). In urine the predominant metabolite detected was the CPCA-carnitine conjugate (M2).

Distribution

Berotralstat has a high apparent volume of distribution (Vd/F 3123 L), which suggests tissue distribution. The protein binding of berotralstat in human plasma was determined to be 98.7%.

Elimination

Study BCX7353-104 (Mass Balance)

This was a phase 1, open-label, non-randomized, mass balance study to evaluate the absorption, metabolism and excretion of BCX7353 following administration of a single 350 mg oral dose of [14C]-radiolabelled BCX7353 (100 µCi 14C [3.7 MBq]) to healthy male subjects (n=7). Participants remained on site for a minimum of 336 hours post-dose and discharged on Day 15. If insufficient radioactivity was recovered, participants remained on-site up to 480 hours post-dose and discharged on Day 21.

The arithmetic mean of the total recovered radioactivity extrapolated to infinity was 88.6% (SD, 7.0; range, 78.3 to 97.9%). The major route of excretion of total radioactivity was via faeces. A minor portion of total radioactivity was excreted in urine. The arithmetic mean radioactivity recovered in faeces and urine was 79.4% (range 71.5 to 87.0%) and 9.2% (range 6.8 to 10.9%), respectively.

BCX7353 was cleared in subjects via a combination of metabolism as well as excretion of unabsorbed parent drug. BCX7353 was the largest component of the circulating radioactivity in plasma (34% of the

total radioactivity) and all metabolites together accounted for 39%. In plasma, there were 8 metabolites of berotralstat detected, 5 of which were identified based on fragmentation pattern or prior authentic standards. The major routes of metabolism identified in humans following oral administration were oxidation, oxidative deamination, hydrogenation, N-dealkylation, N-acetylation, and N-carbamylation. No single metabolite contributed >10% of the total radioactivity exposure through 24 hours.

Dose proportionality

In subjects with HAE, AUCtau, Cmax, and Ctau of berotralstat showed a greater than dose proportional increase in exposure over the 62.5 to 350 mg dose range (Table 13).

Table 8: BCX7353-203: Statistical Analysis of Dose Proportionality of berotralstat Following Oral Administration of berotralstat at Steady State using Power Model (PK Population)

Parameter	N	Slope	90% CI Around Slope
AUC_{tau} (ng.h/mL)	51	1.473	1.322, 1.623
C_{max} (ng/mL)	51	1.437	1.268, 1.607
C_{tau} (ng.h/mL)	50	1.515	1.352, 1.678

The observed more than dose-proportional increase in exposure of berotralstat in single and multiple ascending dose studies is most likely explained by the saturation of the efflux transporters in the liver and/or intestine.

Time dependency

Berotralstat does not exhibit time-dependent PK. Accumulation in berotralstat plasma exposure with 7 or 14 days of berotralstat dosing ranges from 3- to 5-fold, which is consistent with the observed long half-life (GM 67-79 hours) (Table 13).

Table 9: BCX7353-101 Part 2: Statistical Analysis of Plasma Accumulation Ratios of BCX7353 Following Multiple Dose Administration of BCX7353 (PK Population)

BCX7353 Treatment	Geometric Least-Squares Means[a]		Accumulation Ratio (90% CI)
	Day 1 AUC_{0-tau} (ng•hr/mL) (N =10)	Day 7/14 AUC_{tau} (ng•hr/mL) (N =9)[b]	
125 mg QD	317	1600	5.07 (4.35, 5.90)
250 mg QD	750	3630	4.85 (4.13, 5.69)
500 mg QD	2640	8100	3.06 (2.61, 3.59)
350 mg QD	1580	5950	3.76 (3.21, 4.41)
Overall	-	-	4.11 (3.74, 4.52)

Pharmacokinetics in the target population

Study BCX7353-203

This was a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, PK and PD of BCX7353 in subjects with HAE. Berotralstat exposure as measured by Cmax and AUC in subjects with HAE was overall consistent with the exposure observed in healthy subjects in Study 101 following multiple daily administration for either 7 or 14 days (Table 10). In the 125 mg dose group, 55% of subjects had trough concentrations at steady-state that were above the minimum target concentration of 36 ng/mL (>4 × the kallikrein EC50 of 9 ng/mL), and 100% and 98% of subjects in the 250 and 350 mg dose groups had trough concentrations that were >4 × EC50, respectively. No subjects in the 62.5 mg dose group had trough concentrations that were >4 × EC50 at steady state.

Table 10: Study 203: Summary of Plasma PK Parameterf Following 14 Days of Multiple Oral Doses of Berotralstat in Subjects with HAE (PK Population)

PK Parameter	Berotralstat 62.5 mg QD [SN] Day14 (N=7)	Berotralstat 125 mg QD [SN] Day 7 (N=14)	Berotralstat 250 mg QD [SN] Day 7 (N=14)	Berotralstat 350 mg QD [SN] Day 14 (N=16)
C_{max} (ng/mL)[a]	31.0 (44.9)	84.6 (44.9)	262.9 (38.5)	350 (51.1)
T_{max} (h)[b]	3.8 (2.00, 7.92)	3.00 (1.08, 5.97)	3.00 (1.92, 6.00)	4.00 (2.00, 8.00)
AUC_{tau} (ng.h/mL) [a]	450 (70.2)	1350 (34.6)	4060 (25.0)	5601 (40.2)
C_{tau} (ng/mL) [a]	13.0 (77.2)	41.9 (40.9)	126.6 (30.0)	177.7 (38.7)

Study BCX7353-302

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 2 dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with HAE. Subjects received placebo (n=40), berotralstat 110 mg (n=41) or berotralstat 150 mg (n=40) QD for 24 weeks. The mean concentration of berotralstat in the berotralstat 150 mg treatment group was 94 ng/mL (range 17.6 to 266 ng/mL), with 98% of the samples with concentrations >4 × kallikrein inhibition EC50 and 89% of samples with concentrations >6 × EC50. These thresholds were more frequently met after 150 mg QD than after 110 mg QD (for which 90% of the samples had concentrations >4 × kallikrein inhibition EC50 and 59% of samples had concentrations >6 × EC50).

Special populations

- Impaired renal function

Study BCX7353-107

This was an open-label, single-dose PK study in adult male and female subjects with normal renal function and severe renal impairment (eGFR < 30 mL/min/1.73 m^2; not yet on dialysis).

Subjects in Groups A and B received a single oral dose of 200 mg berotralstat:

- Group A: normal renal function (creatinine clearance [CLCR] ≥ 90 mL/min) (n=7)
- Group B: severe renal impairment (eGFR < 30 mL/min/1.73 m2) not yet on dialysis (n=7)

The results of statistical comparisons showed that plasma berotralstat Cmax was approximately 39% higher in subjects with severe renal impairment than in matched healthy subjects, although the 90% CI encompassed 100%. Point estimates for the GLSM ratio in AUC between subjects with severe renal impairment and healthy subjects were close to unity, indicating that plasma exposure was roughly equivalent between the 2 groups (Table 16).

Table 11: Study 107: Summary of berotralstat Plasma PK Parameters (PK Population)

PK Parameters[a]	Healthy (N =7)	Severe RI (N =7)	GLSM Ratio (%) (90% CI) Healthy vs. Severe RI
$AUC_{0\text{-}inf}$ (ng.h/mL)	2070 (44)	2160 (56)	105 (66.9, 165)
$AUC_{0\text{-}last}$ (ng.h/mL)	1610 (41)	1740 (59)	109 (68.9, 171)
C_{max} (ng/mL)	88.7 (39)	123 (62)	139 (87.4, 220)
$t_{½}$ (h)	66.1 (27)	59.2 (13)	N/A
T_{max} (h)[b]	6 (1.5, 6)	5 (1.5, 6)	N/A
CL_R (mL/h)[c]	2930 (20)	508 (96)	N/A

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration vs. time curve extrapolated to infinite time; $AUC_{0\text{-}last}$ = area under the concentration vs. time curve from time zero to the last available timepoint; CI = confidence interval; CL_R = renal clearance; C_{max} = maximum plasma concentration of the drug; CSR = clinical study report; CVb% = coefficient of variation between subjects; GM = geometric mean; GLSM = geometric least squares mean; N/A = not applicable; PK = pharmacokinetic; RI = renal impairment; $t_{½}$ = estimate of the terminal elimination half-life of the drug; T_{max} = time to C_{max}.

[a] Reported as GM (CVb%)

[b] Reported as median (range)

[c] CL_R was only reported in 5 of the 7 subjects with severe renal impairment

No statistically significant correlations were identified between berotralstat PK parameters AUC0-last, AUC0-inf, and Cmax vs. CLCR, although there was a trend toward lower Cmax for higher CLCR, in alignment with the observed increase in Cmax for subjects with severe renal impairment (Pearson correlation = -0.53, p = 0.06).

Subjects with severe renal impairment excreted 4-fold lower amounts of the administered dose of berotralstat in urine as unchanged drug than matched healthy subjects (Table 11). Subjects with severe renal impairment had a 5-fold lower renal clearance (CLR) than matched healthy subjects. However, as <3% of administered drug was excreted in the urine in matched healthy subjects, the lower CLR in subjects with severe renal impairment had no clinically meaningful impact on systemic exposure.

The berotralstat unbound fraction was similar between matched healthy subjects and subjects with severe renal impairment. The median unbound fraction was 1.10 and 1.15 at 1-hour post dose or 1.10 and 0.90 at 6-hours post dose for subjects with severe renal impairment and matched healthy subjects, respectively.

- Impaired hepatic function

Study BCX7353-108

This was a single-dose, open-label study in adult male and female subjects with normal hepatic function and varying degrees of hepatic impairment.

Subjects in each of the following groups received one single oral dose of 150 mg berotralstat:

Group A: normal hepatic function (n=6)

Group B: Child-Pugh A (mild hepatic impairment) (n=6)

Group C: Child-Pugh B (moderate hepatic impairment) (n=6)

Group D: Child-Pugh C (severe hepatic impairment) (n=6)

The statistical comparisons showed that plasma exposures of berotralstat in subjects with mild hepatic impairment were similar to those in matched healthy subjects with normal hepatic function. Plasma berotralstat Cmax was approximately 27% higher in subjects with severe hepatic impairment than in matched healthy subjects with normal hepatic function, while AUCs were roughly equivalent between the 2 groups. Plasma exposure of berotralstat was increased the most in subjects with moderate hepatic impairment. Plasma berotralstat Cmax and AUC0-inf were approximately 77% and 78% higher

in subjects with moderate hepatic impairment than in matched healthy subjects, respectively. The increase in plasma berotralstat Cmax and AUC0-inf were approximately 50% and 38%, respectively, for the combined group of moderate and severe hepatic impairment (Table 17).

Table 12: Study BCX7353-108: Statistical Comparison of Plasma berotralstat PK Parameters (ANOVA) – PK Population

PK Parameter	Group	Geometric Mean	Geometric Mean Ratio (90% CI)[a]
C_{max} (ng/mL)	Healthy/normal hepatic function	45.5	
	Mild hepatic impairment	45.9	101 (54.2, 188)
	Moderate hepatic impairment	80.5	177 (95.0, 329)
	Severe hepatic impairment	57.9	127 (68.4, 237)
	Combined moderate/severe hepatic impairment	68.3	150 (87.9, 256)
$AUC_{0\text{-}inf}$ (ng.h/mL)	A	907	
	B	945	104 (60.6, 179)
	C	1620	178 (104, 307)
	D	850	93.8 (51.1, 172)
	C/D	1250	138 (82.6, 230)
$AUC_{0\text{-}last}$ (ng.h/mL)	A	737	
	B	769	104 (61.7, 177)
	C	1250	170 (100, 287)
	D	700	95.0 (56.1, 161)
	C/D	936	127 (74.8, 206)

The berotralstat unbound fraction was similar in subjects with mild hepatic impairment compared with matched healthy subjects while the unbound fraction was approximately 25% and 100% higher in subjects with moderate and severe hepatic impairment, respectively, compared with matched healthy subjects.

- Gender

There has been no direct comparison of PK parameters between sexes. Gender was tested as a covariate in the population PK model but was not found to have a significant effect on PK of berotralstat. No dose adjustments are needed based on gender.

- Race

The effect of race was tested as a covariate in the population PK model but was not found to have a significant effect on PK of berotralstat. In Study 101, the GM berotralstat AUCtau and Cmax were approximately 13% and 20% higher, respectively, in Japanese subjects vs. Western subjects following multiple doses of berotralstat at 250 mg QD (Table 18). However, there was no need for dose adjustments based on race or ethnicity.

Table 13: BCX7353-101 Part:3: Statistical Analysis of Ethnobridging of BCX7353 Following Single- and Multiple-Dose Administration of BCX7353 (Parts 1,2 and 3)

BCX7353 Treatment	BCX7353 PK Parameter	Geometric Least-Squares Means[a]				% Geometric Least Square Mean Ratio (90% CI)
		N	Japanese Subjects	N	Western Subjects	Japanese Subjects /Western Subjects
100 mg Single Dose	C_{max} (ng/mL)	6	37.9	6	22.8	166 (113, 244)
	$AUC_{0\text{-}inf}$ (ng•hr/mL)	6	720	2	391	184 (121, 282)
500 mg Single Dose	C_{max} (ng/mL)	6	311	6	245	127 (86.5, 187)
	$AUC_{0\text{-}inf}$ (ng•hr/mL)	6	6940	6	5830	119 (88.1, 160)
250 mg QD × 7 days (Day 1)	C_{max} (ng/mL)	10	114	10	77.4	147 (123, 176)
	$AUC_{0\text{-}t}$ (ng•hr/mL)	10	1050	10	750	140 (116, 170)
250 mg QD x 7 days (Day 7)	C_{max} (ng/mL)	10	261	9	217	120 (101, 143)
	AUC_{tau} (ng•hr/mL)	10	4180	9	3710	113 (95.0, 134)

Geometric least-squares means were obtained by the exponentiation of least-squares means of the parameters from a mixed effects model based on the natural logarithmic scale.
Abbreviations: CI = confidence interval; PK = pharmacokinetic; QD = once daily
Source: Section 14.4, Table 14.2.2.2.3.1 and Table 14.2.2.2.3.2

- Weight

In the updated population PK model provided upon CHMP request, simulations indicated an approximate increase of 1.42-fold in exposure in the lower weight category (down to 40 kg) compared to the higher weight category (Table 19).

Table 14: Predicted GMs of PK (CV%) for 150 mg QD Dose by Population, Based on All Data

	AUC, Initial Doses (ng.h/mL)	C_{max}, Initial Doses (ng/mL)	AUC, Steady State (ng.h/mL)	C_{max}, Steady State (ng/mL)
Under weight (40 – 60 kg)	816 (31.3)	67 (34.4)	2574 (36.7)	155 (33.9)
Low weight (60 – 80 kg)	644 (31.2)	51 (33.9)	2211 (38.3)	129 (35.6)
Normal weight (80 – 100 kg)	509 (30.1)	40 (32.5)	1951 (37.0)	111 (34.3)
Overweight (100 – 120 kg)	438 (32.0)	34 (34.0)	1818 (36.9)	101 (34.7)
Adolescent 12 – 18 years)	820 (34.4)	67 (38.2)	2515 (38.6)	153 (36.8)

Abbreviations: AUC = area under the concentration vs. time curve; C_{max} = maximum concentration; CV = coefficient of variation; QD = once daily.
Source: BCX7353-PPK-01-A2

Simulations were also conducted at the extremes of weight ranges. Subjects weighing ≥35 kg would not be anticipated to exceed tolerable exposures with regards to potential QTcF prolongation, designated as 222 ng/mL for GM Cmax.

In the combined safety population for Studies 204 and 302, subjects with lower weight had higher exposure than those in the higher weight category. Subjects weighing ≤ 70 kg had mean concentrations across visits that were approximately 17% higher than subjects weighing > 87.5 kg across active doses, but overall there was a similar general range in concentrations across subjects in each group. When comparing concentrations to the coverage of the kallikrein half-maximal effective concentration (EC50), across the weight ranges, there was a similar percentage of subjects with concentrations > 4 × EC50, > 6 × EC50 and > 8 × EC50. Therefore, although there are differences in the mean concentrations across the weight groups, and weight is a known covariate that has been shown to affect exposure in the population PK model, the concentrations after a 150 mg dose are within the efficacious window of concentrations that were targeted for kallikrein inhibition for most subjects, even in the highest weight group. Further, there was no impact of weight category on either efficacy or safety.

- Age

Berotralstat studies have enrolled predominantly adults between the ages of 18 and 64 years. The population PK dataset included 19 subjects >65 years of age (up to age 74 years) and 16 adolescent subjects (12-17 years). Age was not included as a covariate in the final (updated) population PK model. No dose adjustments are needed based on age.

Interactions

- In vitro

In vitro, BCX7353 inhibits CYP2C9 and CYP2C19, CYP2D6 and CYP3A with IC50s ranging from 0.24 µM for CYP2C9 to 2.5 µM for CYP3A4. The TDI screen with BCX7353 suggests it may irreversibly inhibit CYP3A, but not CYP2C9 or CYP2C19. BCX7353 inhibited P-gp, BCRP, MATE1, and MATE2-K with calculated IC50s of 0.492, 12.0, 3.53, and 4.60 µM, respectively. There was <50% inhibition of the OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 in the presence of BCX7353. BCX7353 is a substrate of P-gp and BCRP. In vitro experiments in recombinant enzymes showed that the greatest loss of berotralstat occurred with recombinant CYP2D6 and CYP3A4; however, the rate of metabolism and extent of loss of parent was limited and low.

- In vivo

Study BCX7353-102

This was a single-center, single-sequence, open-label drug-drug interaction study to evaluate the effect of BCX7353 on hepatic and intestinal CYP3A4 (midazolam IV and orally, respectively), CYP2C9 (tolbutamide), CYP2C19 (omeprazole), and CYP2D6 (dextromethorphan) enzyme activity using probe substrate drugs in healthy subjects.

Each subject received the following treatments:

- Day 1: 1 mg midazolam was administered as an IV bolus simultaneously to administration of 500 mg tolbutamide, 40 mg omeprazole, and 30 mg dextromethorphan orally.
- Day 2: a single oral dose of 2 mg midazolam was administered.
- Days 3 to 9: 350 mg dose of BCX7353 was administered as the dihydrochloride salt (approximately equivalent to 300 mg of BCX7353 free base) once a day.
- Day 10: 1 mg midazolam was administered as an IV bolus simultaneously to administration of 500 mg tolbutamide, 40 mg omeprazole, 30 mg dextromethorphan and 350 mg BCX7353 orally.
- Day 11: a single oral dose of 2 mg of midazolam was administered along with 350 mg BCX7353.

Midazolam

IV midazolam

The CL ratio of the Day 10 to Day 1 adjusted geometric means was 53.96%. The AUC(0-last) and AUC(0-inf) ratios of the Day 10 to Day 1 adjusted geometric means (90% CI) were 177.85% (164.41%, 192.38%) and 185.33% (171.64%, 200.12%), respectively, for IV midazolam.

Oral midazolam

The Cmax ratio of the Day 11 to Day 2 adjusted geometric means (90% CI) was 206.34% (185.00%, 230.14%). The AUC(0-last) and AUC(0-inf) ratios of the Day 11 to Day 2 adjusted geometric means

(90% CI) were 353.82% (316.39%, 395.67%) and 367.17% (331.23%, 407.02%), respectively, for oral midazolam.

Tolbutamide

The Cmax ratio of the Day 10 to Day 1 adjusted geometric means (90% CI) was 115.25% (110.08%, 120.67%). The AUC(0-last) and AUC(0-inf) ratios of the Day 10: Day 1 adjusted geometric means (90% CI) were 173.22% (155.02%, 193.56%) and 387.90% (333.74%, 450.86%), respectively.

Omeprazole

The Cmax ratio of the Day 10 to Day 1 adjusted geometric means (90% CI) was 177.79% (146.20%, 216.22%). The AUC(0-last) and AUC(0-inf) ratios of the Day 10: Day 1 adjusted geometric means (90% CI) were 206.85% (183.59%, 233.06%) and 206.73% (183.59%, 232.78%), respectively.

Dextromethorphan

The Cmax ratio of the Day 10 to Day 1 adjusted geometric means (90% CI) was 664.09% (501.57%, 879.28%). The AUC(0-last) and AUC(0-inf) ratios of the Day 10: Day 1 adjusted geometric means (90% CI) were 751.60% (570.91%, 989.48%) and 787.97% (595.80%, 1042.1%), respectively.

Study BCX7353-112

This was a Phase 1, open-label drug-drug interaction study to evaluate the effect of BCX7353 on the pharmacokinetics of danazol (CYP3A and CYP2D6 substrate), amlodipine (CYP3A substrate) and desipramine (CYP2D6 substrate) in healthy subjects (18-55 years).

Subjects were enrolled into one of the following 3 cohorts and received the following treatments:

Cohort 1

- Day 1: Danazol 200 mg
- Days 7 to 15: BCX7353 150 mg
- Day 16: Danazol 200 mg + BCX7353 150 mg

Cohort 2

- Day 1: Amlodipine 5 mg
- Days 14 to 25: BCX7353 150 mg
- Day 23: Amlodipine 5 mg + BCX7353 150 mg

Cohort 3

- Day 1: Desipramine 50 mg
- Days 10 to 20: BCX7353 150 mg
- Day 19: Desipramine 50 mg + BCX7353 150 mg

49 subjects (18 in Cohort 1, 13 in Cohort 2, and 18 in Cohort 3) were included in the PK analysis.

Danazol

The GLS mean (90% CI) ratios (BCX7353 plus danazol/danazol alone) for Cmax, AUCinf, and AUClast were 75.69% (56.66%, 101.11%), 77.7% (59.0, 102.22), and 79.8% (60.7, 104.8), respectively.

Amlodipine

The GLSM ratios (90% CI) for AUC0-inf and AUC0-last (Day 23 [amlodipine + berotralstat] / Day 1 [amlodipine alone]) were 177% (159, 198) and 177% (163, 193), respectively. The GLSM ratios (90% CI) for Cmax also increased but to a lesser extent (145% [127, 164]).

Desipramine

The GLS mean (90% CI) ratios (BCX7353 plus desipramine/desipramine alone) for Cmax, AUCinf, and AUClast were 164.29% (148.38, 181.90), 214.5% (186.6, 246.6), and 186.8% (166.5, 209.5), respectively.

Study BCX7353-115

This was a single sequence, open-label, drug-drug interaction study to evaluate the effect of steady-state BCX7353 150 mg QD on CYP3A4 (midazolam), CYP2C9 (tolbutamide), CYP2C19 (omeprazole), and CYP2D6 (dextromethorphan) enzyme activity using probe substrates in healthy subjects (18-55 years).

All subjects received the following treatments:

- Day 1: Oral doses of 4 mg midazolam, 500 mg tolbutamide, 40 mg omeprazole, and 30 mg dextromethorphan
- Days 3 to 11: Oral doses of 150 mg berotralstat QD
- Day 12: Oral doses of 4 mg midazolam, 500 mg tolbutamide, 40 mg omeprazole, 30 mg dextromethorphan, and 150 mg berotralstat
- Day 13: Oral dose of 150 mg berotralstat

Twenty-one subjects completed the study and were included in the PK analysis dataset.

Midazolam

The GLSM ratios (90% CI) (Day 12: Day 1) for midazolam Cmax, AUC0-last, and AUC0-inf were 1.45 (1.29, 1.63), 2.24 (2.05, 2.44), and 2.22 (2.03, 2.42), respectively. The GM MR AUC0-24 was higher on Day 1 (0.348) compared with Day 12 (0.135). The median t1/2 was longer on Day 12 (7.52 hours) compared with Day 1 (5.47 hours).

Tolbutamide

The GLSM ratios (90%CI) (Day 12/Day 1) for tolbutamide Cmax, AUC0-last, and AUC0-inf were 1.19 (1.11, 1.27), 1.73 (1.63, 1.85), and 2.02 (1.87, 2.19), respectively. The GM MR AUC0-24 was higher on Day 1 (0.00976) compared with Day 12 (0.00428). The median t1/2 was approximately twice as long on Day 12 (18.1 hours) compared with Day 1 (8.55 hours).

Omeprazole

The GLSM ratios (90%CI) (Day 12/Day 1) for omeprazole Cmax, AUC0-last, and AUC0-inf were 1.21 (1.00, 1.47), 1.24 (1.09, 1.40), and 1.24 (1.08, 1.44), respectively. The GM MR AUC0-24 was, similar on Day 1 (0.800) and Day 12 (0.817). The median t1/2 was similar on Day 12 (1.2 hours) compared with Day 1 (1.34 hours).

Dextromethorphan

The GLSM ratios (90%CI) (Day 12/Day 1) for dextromethorphan Cmax, AUC0-last, and AUC0-inf were 2.96 (2.48, 3.55), 2.78 (2.33, 3.33), and 2.77 (2.32, 3.31), respectively. The GM MR AUC0-24 was higher on Day 1 (1.22) compared with Day 12 (0.339). The t1/2 of dextromethorphan was unchanged.

Study BCX7353-105

This was a single-center, fixed-sequence, open-label drug interaction study to evaluate the effect of berotralstat on the PK of the P-gp substrate digoxin and the BCRP substrate rosuvastatin, as well as the effect of the P-gp and BCRP inhibitor cyclosporine on the PK of berotralstat in healthy subjects (18-55 years).

Subjects were randomly assigned to 1 of 3 cohorts and received the following treatments:

Cohort 1 (berotralstat-digoxin)

- Day 1: digoxin 0.25 mg
- Days 11 to 18: berotralstat 350 mg
- Day 19: berotralstat 350 mg followed 1 hour later by digoxin 0.25 mg
- Days 20 to 21: berotralstat 350 mg

Cohort 2 (berotralstat-rosuvastatin)

- Day 1: rosuvastatin 10 mg
- Days 7 to 14: berotralstat 350 mg
- Day 15: berotralstat 350 mg followed 1 hour later by rosuvastatin 10 mg
- Days 16: berotralstat 350 mg

Cohort 3 (cyclosporine-berotralstat)

- Day 1: berotralstat 350 mg
- Day 14: single dose of cyclosporine 600 mg followed 1 hour later by berotralstat 350 mg

51 subjects completed the study (17 subjects per cohort) and were included in the PK population.

Digoxin

The Cmax ratio of the Day 19 to Day 1 GMs (90% CI) of digoxin was 1.58 (1.20, 2.09). The AUC0-last and AUC0-inf ratios of the Day 19 to Day 1 GMs (90% CI) were 1.48 (1.22, 1.79) and 1.31 (1.15, 1.50), respectively. The t½ of digoxin was similar on Days 1 and 19. The ratio of renal clearance of digoxin on Day 19 compared to Day 1 was 0.89, suggesting that inhibition of P-gp by berotralstat had minimal impact on the overall renal elimination of digoxin.

Rosuvastatin

The Cmax ratio of the Day 15 to Day 1 GM (90% CI) of rosuvastatin was 0.760 (0.676, 0.854). The AUC0-last and AUC0-inf ratios of the Day 15 to Day 1 GMs (90% CI) were 0.802 (0.730, 0.881) and 0.844 (0.735, 0.969), respectively. The GM t½ of rosuvastatin was similar on Days 1 and 15.

Berotralstat after dosing with cyclosporine

The Cmax ratio of the Day 14 to Day 1 GM (90% CI) was 1.25 (1.05, 1.48). The AUC0-last and AUC0-inf ratios were 1.55 (1.40, 1.72) and 1.69 (1.50, 1.91), respectively. The GM t½ of berotralstat was slightly longer on Day 14. The ratio of renal clearance of berotralstat on Day 14 compared to Day 1 was 0.84, which suggests minimal impact of potential P-gp/BCRP inhibition by cyclosporine on the overall renal elimination of berotralstat.

2.4.3. Pharmacodynamics

Mechanism of action

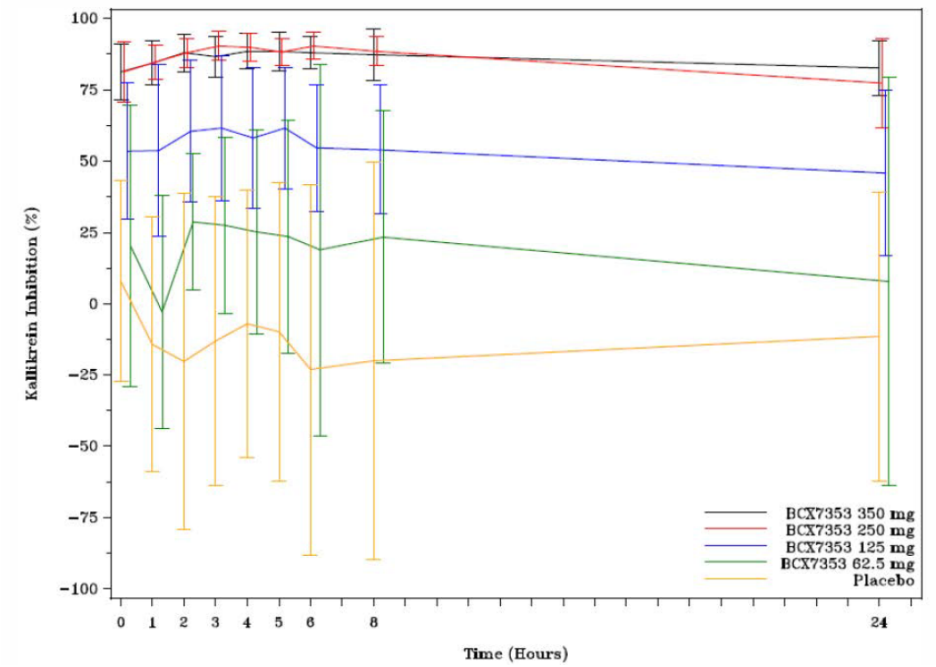
Berotralstat is a highly specific small molecule competitive inhibitor of human plasma kallikrein activity with an inhibition constant of 0.44 nM on the isolated enzyme. Berotralstat binds specifically to the active site of the plasma kallikrein enzyme. Berotralstat inhibits kallikrein activity in plasma samples obtained from healthy subjects and HAE subjects with mean EC50s of 5.4 nM (3 ng/mL) and 15.9 nM (9 ng/mL), respectively. Sustaining berotralstat concentrations near or greater than a target level over a dosing interval is expected to reduce attacks of HAE in subjects with little or no functional C1-INH, the endogenous inhibitor of kallikrein and ultimately, bradykinin production.

Primary pharmacology

Study BCX7353-203

A total of 70 subjects were included in the PD analysis. A dose dependent inhibition of kallikrein inhibition was observed with berotralstat treatment over the dose range. In subjects with HAE administered berotralstat 250 and 350 mg QD, mean kallikrein inhibition was sustained above 75% through the dosing interval, with a maximum mean inhibition of approximately 90% at Tmax. In subjects administered a 125-mg dose QD, maximum mean kallikrein inhibition observed was approximately 62%, with mean kallikrein inhibition at 24 hours of approximately 46%, whereas at 62.5-mg dose QD, maximum mean inhibition was only about 29%, with mean kallikrein inhibition of 8% at 24 hours, compared to −7% and −12% respectively for placebo (Figure 3). C1-INH and C4 levels were generally stable over time and no clinically meaningful differences were observed between dose groups.

Figure 3: BCX7353-203: Mean (± SD) Kallikrein Inhibition-Time Profiles following Administration of Multiple Doses of Berotralstat (Kallikrein PD Population)



Study BCX7353-302

The mean (SD) percent inhibitions of plasma kallikrein for all post-baseline visits were 62% (± 15.0), 68% (± 33), and -21% (± 48) for the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The proportion of subjects with >50% kallikrein inhibition averaged

across all visits was 35 of 41 subjects (85%) and 34 of 35 subjects (97%) for the berotralstat 110 and 150 mg treatment groups, respectively, with no subjects in the placebo group having 50% kallikrein inhibition. Fewer subjects had >80% kallikrein inhibition, a threshold considered to be maximal suppression of kallikrein activity, with the proportion of subjects with >80% kallikrein inhibition averaged across all visits being 2 of 41 subjects (5%) and 9 of 35 subjects (26%) for the berotralstat 110 and 150 mg treatment groups, respectively.

Study BCX7353-301

The mean (SD) percent inhibition of plasma kallikrein for all post-baseline visits were 49% (± 28), 63% (± 20), and -11% (± 19) for the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The proportion of subjects with >50% kallikrein inhibition averaged across all visits was 2 of 6 subjects (33%) and 3 of 7 subjects (43%) for the berotralstat 110 and 150 mg treatment groups, respectively. The proportion of subjects with >80% kallikrein inhibition at all visits was 0 of 6 subjects and 2 of 7 subjects (28.6%) for the berotralstat 110 and 150 mg treatment groups, respectively.

Secondary pharmacology

Study BCX7353-106

This was a randomized, double-blind, placebo-controlled multiple dose study to evaluate the effects of berotralstat at therapeutic and supratherapeutic doses and exposures on the QTc (Fridericia's method; QTcF) and QTcF subintervals in healthy adult subjects.

- Cohort 1 (therapeutic dose): berotralstat 150 mg (n=14) or placebo (n=6) daily × 14 days
- Cohort 2 (supratherapeutic dose): berotralstat 450 mg (n=14) or placebo (n=6) daily × 14 days

Berotralstat concentrations used for PD exposure-response (ER) modelling are provided in Table 20. The highest clinically relevant exposure, 240 ng/mL, was determined from the average increase in berotralstat exposure (1.5-fold increase in Cmax) observed in Study 108 in a combined group of subjects with moderate and severe hepatic impairment following administration of a single dose of 150 mg berotralstat.

Table 15: BCX7353-106: GM Cmax Values Referenced in the E-R Analysis Results

Dose Group	Concentration Data Included	C_{max} (ng/mL)
Berotralstat 150 mg	Day 1	49
Berotralstat 150 mg	Day 14	158
Berotralstat 150 mg	Combined days[a]	158
Highest clinically relevant exposure estimated from hepatic impairment Study 108, berotralstat 150 mg QD		240
Berotralstat 450 mg	Day 1	257
Berotralstat 450 mg	Combined days[a]	456
Berotralstat 450 mg	Day 14	577

Abbreviations: C_{max} = maximum plasma concentration; E-R = exposure-response; GM = geometric mean; QD = once daily

[a] The combined days GM C_{max} at the therapeutic and supratherapeutic dose was determined using the greatest C_{max} for each subject on either Day 1 or 14.

Relationship between ΔΔQTcF and berotralstat concentration (first co-primary endpoint)

The E-R analysis of ΔΔQTcF vs. berotralstat concentration found a statistically significant positive slope, 0.044 msec/(ng/mL). At 158 ng/mL, the mean estimated ΔΔQTcF was 3.4 msec (2-sided 90% UB 6.8 msec). At 577 ng/mL, the mean estimated ΔΔQTcF was 21.9 msec (2-sided 90% UB 29.4

msec). At the highest clinically relevant exposure of 240 ng/mL, the estimated ΔΔQTcF was 7.0 msec (2-sided 90% UB 10.9 msec) (Table 21).

Table 16: Study 106: Berotralstat Linear Mixed-Effects Regression Analysis: Estimated Mean **ΔΔQTcF** at Highest Clinically Relevant Exposure and the GM Cmax Concentrations on Day 14 (PK/PD Population)

Concentration Level	Concentration (ng/mL)	Mean ΔΔQTcF (msec)	2-sided 90% Lower CB (msec)	2-sided 90% Upper CB (msec)
GM C_{max}, Day 14 only, 150 mg	158	3.4	0.0	6.8
Highest clinically relevant exposure	240	7.0	3.1	10.9
GM C_{max}, Day 14 only, 450 mg	577	21.9	14.4	29.4

The GM Cmax for situations of increased exposure due to intrinsic factors, as well as the extrinsic factor of co-administration of cyclosporine, are summarized in Table 1. The GM Cmax is below the 222 ng/mL drug concentration that is associated with a 90% UB on ΔΔQTcF of 10 msec for severe renal impairment, adolescents, low body weight (40 kg), and co-administration of cyclosporine. The only clinically relevant exposure is in moderate to severe hepatic impairment.

Table 17: GM Cmax and Associated 2-Sided 90% UB of **ΔΔQTcF** at Steady State for Berotralstat 150 mg QD in Subject Populations with Increased Exposure

Intrinsic Factor or Scenario	D120 Q	GM C_{max} (ng/mL)	Mean ΔΔQTcF at GM C_{max} (msec)	Is two-sided 90% Confidence Interval Upper Bound for ΔΔQTcF ≥ 10 (msec)?
Healthy subject[a]	NA	158	3.4	no
Threshold concentration scenario	Q58	222[b]	6.2	yes
Moderate or severe hepatic impairment (Worst-case exposure scenario)	Q58	240[c]	7.0	yes
Severe renal impairment	Q78	220[d]	6.1	no
Adolescent[g]	Q58	153[e]	3.1	no
Low body weight (40 kg)	Q58	183[e]	5.0	no
Co-administration of cyclosporine (P-gp, BCRP, and CYP3A4 inhibitor)	NA	198[f]	5.1	no

Abbreviations: BCRP = breast cancer resistance protein; CDC = Centers for Disease Control and Prevention; CI = confidence interval; C_{max} = maximum concentration; CYP = cytochrome P450; ΔΔ = baseline-adjusted, placebo-corrected; GM = geometric mean; NA = not applicable; NE = not estimated; P-gp = P-glycoprotein; PK = pharmacokinetic; Q = question; QD = once daily; QTcF = QT interval corrected using Fridericia's formula; UB = upper bound.

[a] Study 106

[b] Predicted C_{max} from exposure-response model associated with 10 msec ΔΔQTcF 2-sided 90% CI upper bound

[c] Simulated steady-state C_{max} based on half-life and single dose C_{max} in Study 108

[d] Simulated steady-state C_{max} based on half-life and single dose C_{max} in Study 107 (see response to Q78)

[e] Simulated based on Population PK model. Adolescent simulations utilized weight and variance of weight from CDC Weight for Ages table (CDC 2001), with simulated weight values drawn from a normal distribution. For adult subjects, the mean and variance for weight was derived from data available in the berotralstat population PK dataset.

[f] Simulated steady-state C_{max} based on exposure in Study 105

[g] In the revised population PK models, submitted with Q64, age is not a significant covariate affecting PK of berotralstat

Relationship between each ΔΔJ-Tpc and ΔΔTp-Te and berotralstat concentration (second co-primary endpoint)

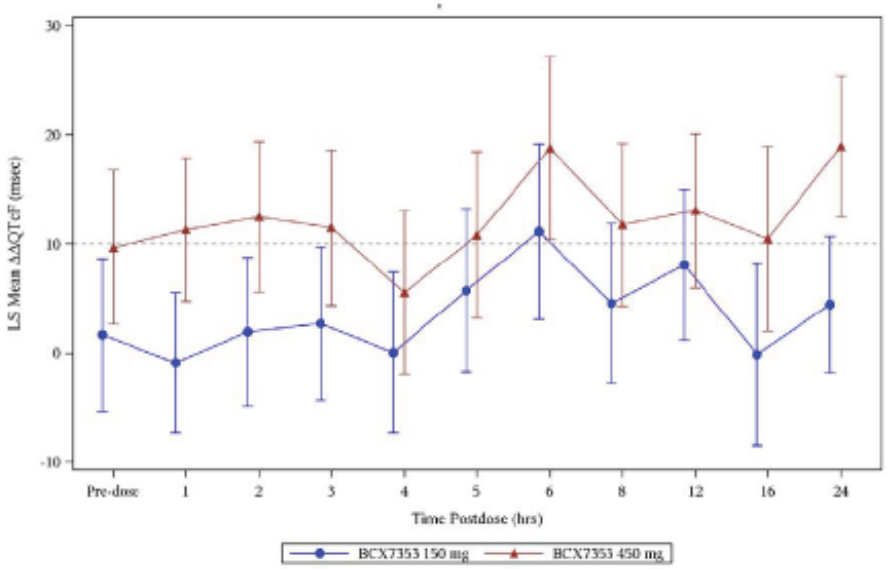
The E-R analysis of the relationship between ΔΔJ-Tpc and berotralstat concentration found a statistically insignificant, minimally positive slope, 0.010 msec/(ng/mL). For ΔΔTp-Te there was a greater positive slope, 0.020 msec/(ng/mL), with borderline statistical significance (p=0.067).

At 158 ng/mL, the mean estimated ΔΔJ-Tpc was -0.6 msec (2-sided 90% UB 3.8 msec). At 577 ng/mL, the mean ΔΔJ-Tpc was 3.5 msec (2-sided 90% UB 16.4 msec). At the highest clinically relevant exposure, the mean estimated ΔΔJ-Tpc was 0.2 msec (90% UB 5.8 msec. Corresponding values for ΔΔTp-Te were 2.4 msec (2-sided 90% UB 5.8 msec) for 158 ng/mL, and 10.8 msec (2-sided 90% UB 20.5 msec) for 577 ng/mL. At the highest clinically relevant exposure, the mean estimated ΔΔTp-Te was 4.1 msec (90% UB 8.4 msec).

Determination of the central tendency analysis (secondary endpoint)

Berotralstat LSM ΔΔQTcF and 2-sided 90% CB by dose and timepoint is shown in Figure 4. Determination of QTcF change findings by-timepoint, using a mixed model repeated measures analysis, found that on Day 14, the 2-sided 90% UB LSM ΔΔQTcFs were >10 msec at a limited number of timepoints for the therapeutic dose level, but at most timepoints for the supratherapeutic dose. For berotralstat 150 mg the maximum LSM ΔΔQTcF was 11.1 msec (2-sided 90% UB 19.2 msec) at 6 hours post-dose on Day 14; no other timepoint LSM ΔΔQTcF exceeded 10 msec. For berotralstat 450 mg on Day 14 at 24 hours post-dose, the maximum LSM ΔΔQTcF was 18.9 msec (overall 2-sided 90% UB 25.4 msec). It should be noted that this analysis was not powered based upon the enrolled subject numbers at each dose.

Figure 4: Study 106: LSM **ΔΔQTcF** and 2-sided 90% CB (msec) – Day 14 (PD Population)



Exploratory endpoints

E-R Analysis of ΔΔHR, ΔΔPR, and ΔΔQRS and change from baseline (CFB) in heart rate (HR), PR interval, and QRS interval by time point.

There was no correlation between ΔΔHR and berotralstat concentrations.

At the GM Cmax for 150mg the ΔΔPR was 4.6 msec (2-sided 90% UB 7.0 msec); the GM Cmax for berotralstat 450 mg, the ΔΔPR was between 14.1 and 25.2 msec; and at the highest clinical exposure scenario, the ΔΔPR would be between 5.0 and 11.0 msec.

At the GM Cmax for 150mg the ΔΔQRS was 2.0 msec (2-sided 90% UB 3.5 msec); the GM Cmax for berotralstat 450 mg, the ΔΔQRS was between 6.6 and 11.9 msec; and at the highest clinical exposure scenario, the ΔΔQRS would be between 2.2 and 5.1 msec.

Categorical outliers for QTcF and incidence of emergent abnormalities in ECG morphology

Minimal outlier findings were noted. Emergent abnormal morphology findings of ectopic atrial rhythm, nonspecific ST changes, T wave inverted, and nonspecific T changes, were noted in a maximum of 2 subjects for any of the findings. These were noted in subjects in both berotralstat groups but not for those who received placebo.

Pharmacodynamic interactions

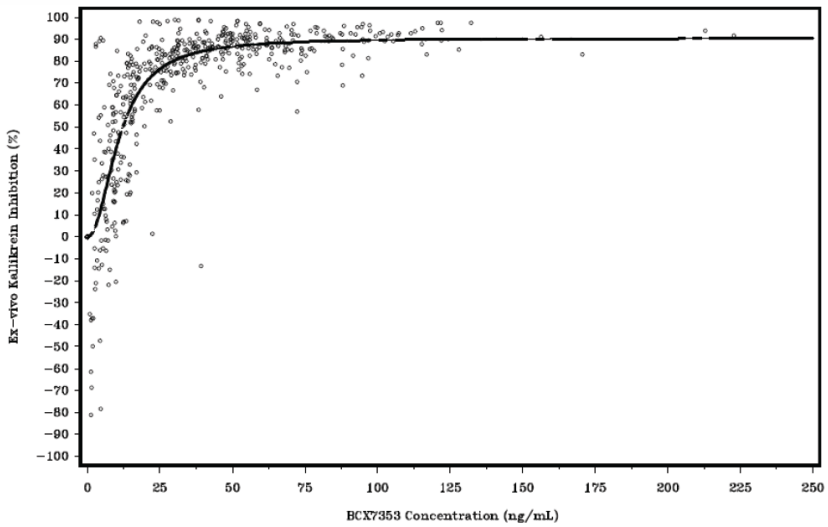
Based on mechanism of action, co-administration of berotralstat and lanadelumab (Takhzyro) would be expected to result in at least additive effects in inhibiting plasma kallikrein, without additional safety risk related to inhibition of plasma kallikrein. No PD interactions are anticipated with other medicinal products or substances.

Exposure-response analyses

Exposure-Ex Vivo Kallikrein Inhibition

Exposure-response analyses of the relationship between kallikrein inhibition and berotralstat plasma concentrations were conducted using data from subjects with HAE in Study 203. A high correlation between ex-vivo kallikrein inhibition activity and plasma concentrations of berotralstat was demonstrated, which were well described by a sigmoidal Emax model (R^2=0.75), with a calculated EC50 of 11 ng/mL (Figure 5).

Figure 5: Study 203: Correlation of Plasma berotralstat Concentrations and PD Effect on Plasma Kallikrein (PK/PD Population)



Exposure-Attack Rate Relationship in Subjects with HAE

Using data from Study 203, the relationships between the confirmed weekly attack rate and berotralstat plasma exposure explored over the entire dose range (0 to 350 mg [SN]) were evaluated graphically. None of the berotralstat steady-state PK parameters (Cmax, AUCtau, and Ctau) appeared to be correlated with the confirmed attack rate. In addition, there was no correlation between the percent of plasma berotralstat Ctau >4× and >8× kallikrein inhibition EC50 and confirmed attack rate.

Further ER analyses were conducted with the 62.5 and 125 mg dose cohorts. As shown in Figure 6 and Figure 7, steady-state berotralstat AUCtau and Ctau appeared to be moderately correlated with the confirmed attack rate in the dose range of 62.5 to 125 mg. In addition, a 125-mg dose provided a mean Ctau of 4.7-fold EC50, with a corresponding reduction in attacks of 70% ($p<0.001$) compared with placebo; a 62.5-mg dose provided a mean Ctau of 1.8-fold EC50, with no change in attack rate

vs. placebo (p=0.811). Thus, the results suggested that maintaining a minimum threshold concentration of ≥4 × EC50 or 36 ng/mL would result in clinically meaningful reductions in attacks.

Figure 6: Study 203: Confirmed Attack Rate vs. berotralstat Plasma AUCtau over the Dose Range of 62.5 to 125 mg with 95% CI for Mean Predicted Values (PK/PD Population)

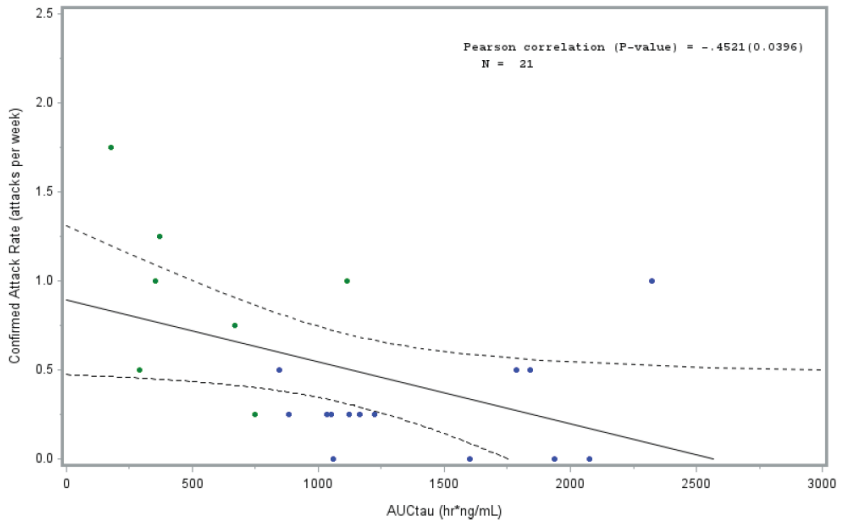
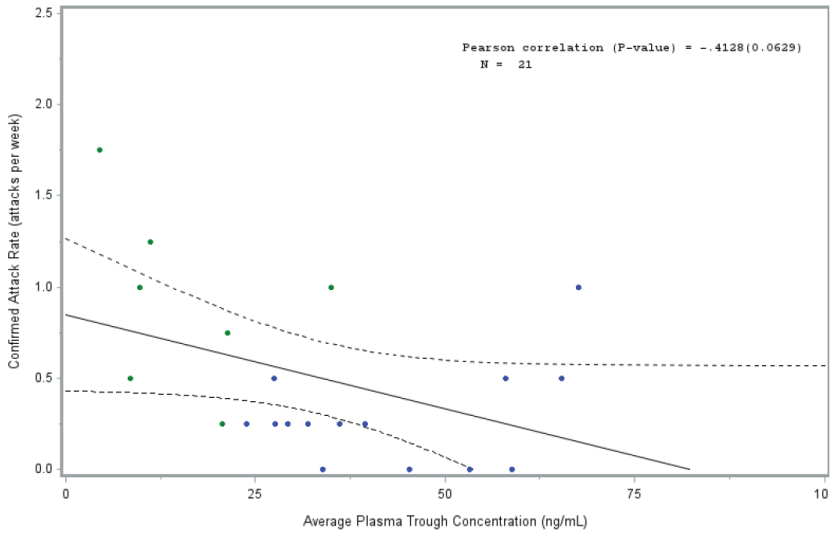


Figure 7: Study 203: Confirmed Attack Rate vs. Average berotralstat Plasma Ctau over the Dose Range of 62.5 to 125 mg with 95% CI for Mean Predicted Values (PK/PD Population)



2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical Methods

Method Validation

In general, all validation reports provide sufficient data pertaining to the appropriateness of each method to determine BCX7353 in both human plasma and urine. A cross validation study was performed to ensure there was no systematic bias in reporting of BCX7353 in plasma samples analysed between UK and US based testing facilities. The QC samples used during cross validation experiments allowed for the determination of accuracy and precision across the entire calibration range for methods LGC275284QB02 and 171354VJHM_BDN.

Bioanalytical Assessment of Samples

The bioanalytical assessment reports exhibit acceptable calibration curve and QC sample performance. Each analytical run included QC, blank and zero samples, respectively.

ISR was performed for all studies, except 204 and 302 as only interim data are presented and was acceptable.

Population PK analysis (BCX7353-PPK-01)

A 3-compartment model with first-order absorption with an absorption lag time and linear elimination provided the best fit to the data. The only covariate effects included in the updated model were body weight on clearance and volume of distribution, and dose on bioavailability.

The difference between the estimate of t1/2 from the population PK model and estimates from NCA analyses from individual studies was explained by the applicant by the very long terminal half-life of berotralstat (566 hours) which could not be captured by the individual studies. The half-life estimates from NCA analyses (80-90 hours) were likely estimates of beta half-life and not the terminal half-life, and these were in line between the PopPK and NCA analyses. Even though terminal half-life obtained by the PopPK model is long, it contributes little to the overall exposure and a third compartment is not a clinically significant reservoir.

The applicant provided VPCs stratified by weight using 10-kg bins. Overall, the observed percentiles were well within the 90%CI of the simulated percentiles, including the two lowest weight groups, which alleviated the concerns on the possible underprediction of Cmax in the underweight patients. Additionally, a plot showing observed Ctrough at steady-state vs. body weight for patients from studies 204 and 302 did not show any relationship of the observed trough values with weight.

The applicant showed that effects of age, race and sex on CL and V were not clinically nor statistically significant.

Absorption

- Bioavailability

Study BCX7353-101 (Part 1 and 3 – Single Ascending Dose in Western and Japanese Participants)

The applicant has appropriately investigated the PK profile following single ascending oral doses of BCX7353 in both Western and Japanese participants.

C_{max} ranged from 3.75 to 680 ng/mL, while AUC0-inf ranged from 25.0 to 16800 (ng·h/mL) for 30-1000 mg oral doses in Western participants. While $T_{1/2}$ was 2.75 h for the 30 mg dose, it ranged from 45.1 to 62.2 hours for 100 to 1000 mg doses. Following oral administration of 100 and 500 mg of BCX7353 in Japanese participants, C_{max} was 37.9 and 311 ng/mL; $AUC_{0\text{-}inf}$ was 720 and 6940 (ng·h/mL); while T1/2 was 55.6 and 45.8. C_{max} was reached after approximately 2 to 6 hours.

While the PK profiles are similar between cohorts, there was a trend for increased exposure in participants of Japanese origin. Following oral administration of a single 100 mg dose of BCX7353, C_{max} and $AUC_{0\text{-}inf}$ were 66 and 84% higher, respectively, in Japanese participants. For a 500 mg dose, C_{max} and $AUC_{0\text{-}inf}$ were 27 and 19% higher, respectively. Nevertheless, this is not expected to have any impact on the dose recommendation.

Study BCX7353-101 (Part 2 and 3 – Multiple Ascending Doses in Western and Japanese Participants)

The applicant has appropriately assessed the plasma and urine PK profile of BCX7353 following administration of multiple ascending oral doses of 125, 250 and 500 mg QD over a 7 day period in participants from a Western origin (Part 2) and 250 mg QD for 7 days in Japanese participants (Part

3). The applicant has also appropriately characterised the PK profile in Western participants following oral administration of 350 mg of BCX7353 QD for 14 days (Part 2).

After repeated dosing for 7 and 14 days, the accumulation ratio in BCX7353 AUC_{tau} was approximately 3- to 5-fold (Part 2 and 3). Accumulation is expected given the long $t_{1/2}$ of approximately 67 – 79 hours. Steady-state conditions were achieved after 6 to 12 days post first dose in Western participants (Part 2).

BCX7353 exposure tended to increase in Japanese subjects following the same daily oral administration of 250 mg for 7 days. BCX7353 AUC_{tau} and C_{max} were approximately 13% and 20% higher, respectively, in Japanese subjects as compared to Western participants.

Renal excretion of BCX7353 was low, with <4% of dose recovered after multiple doses.

Berotralstat concentration-time profiles showed double peaks, with second peak occurring 5 hours post-dose or 1 hour after consuming a meal. This suggests that enterohepatic recirculation occurs in humans.

- Bioequivalence

In Study 103, following single-dose administration, the BCX7353 API 350-mg (SN) capsule was shown to be bioequivalent to the BCX7353 blend 300-mg (fasted) capsule formulation in all PK parameters of interest; Cmax, AUC0-last, and AUC0-inf.

In Study 113, berotralstat commercial formulation was shown to be bioequivalent to the berotralstat Phase 3 formulation in both the 110 mg and 150 mg strengths in all PK parameters of interest; Cmax, AUC0-72, and AUC0-inf.

- Influence of Food

In Study 101, the consumption of a high-fat meal tended to increase BCX7353 AUC0-last and AUC0-inf by approximately 19 and 41%, respectively, relative to fasting conditions. However, the 90% CI were wide. There was a wash-out period of ≥7 days between feeding conditions. Given the estimated t1/2 is approximately 45-62 hours following administration of a single oral dose (study BCX7353-101 part 1), the washout period may not have been adequate.

In study 103, although Tmax was delayed by 3 hours following the high-fat meal compared to fasted administration, this did not impact overall berotralstat exposure. The 90% CIs for all 3 PK parameters were within the bounds of 80% to 125%, indicating that there was no food effect on the extent of exposure with the blend capsule formulation.

Overall, it is agreed that the effect of food on berotralstat PK is not clinically relevant. However, Orladeyo is to be administered with food to minimize gastrointestinal adverse events.

Elimination (metabolism and excretion)

In study 104 (mass balance), the amount of radioactivity recovered following administration of a single 350 mg oral dose of [^{14}C]-radiolabelled BCX7353 was100 µCi ^{14}C [3.7 MBq]. The arithmetic mean of the total recovered radioactivity extrapolated to infinity was 88.6% (SD, 7.0; range, 78.3 to 97.9%). BCX7353 was shown to be eliminated via a combination of metabolism as well as excretion of unabsorbed parent drug. The major route of excretion of total radioactivity was via faeces (extrapolated arithmetic mean, 79.4% [ranging from 71.5% to 87.0%]). Renal excretion was a minor route of elimination, accounting for approximately 9.2% (ranging from 6.8 to 10.9%) of the total recovered radioactivity. Systemic metabolite exposure is unlikely to be of clinical relevance since none of the metabolites identified in the mass balance study accounted for >10% of parent drug exposure.

The applicant provided an estimation of the quantitative contribution of the different elimination pathways based on the amount of dose excreted per the EMA Drug Interaction Guidance (CPMP/EWP/560/95/Rev.1Corr.2**. To account for unabsorbed berotralstat in feces, due to unknown bioavailability in humans, percent of parent drug (17.2%) was subtracted from total amount of radioactivity quantified (60%). This resulted in 42.8% of remaining radioactivity quantified in feces was derived from metabolism.

It is acknowledged that overall estimation of contribution might not be entirely accurate as metabolites can be formed by several separate pathways (e.g. metabolites M5 and M6) and there is no information on rate of conversion from one metabolite to another one.

Overall, no single elimination pathway that would contribute to >25% of berotralstat elimination was identified that would require further evaluation.

Pharmacokinetics in the target population

In the exploratory Study BCX7353-109, through the 24 hours after a single dose of BCX7353 750 mg, the mean plasma concentration of BCX7353 was higher than the BCX7353 EC50 for kallikrein inhibition, and plasma kallikrein was measurably inhibited.

In Study BCX7353-203, steady-state PK of berotralstat in subjects with HAE were consistent with exposure after multiple-dose administration of the same dosing regimen in healthy subjects.

In Studies 302 and 301, HAE subjects who received berotralstat 150 mg QD consistently achieved higher drug concentrations and a higher proportion of subjects maintained concentrations >4 and >6 × EC50 than subjects who received berotralstat 110 mg QD.

Special populations

- Renal impairment

The applicant conducted a dedicated renal impairment study in subjects with severe renal impairment (CrCL<30 mL/min). Severe renal impairment was shown to have a modest effect on berotralstat Cmax and no effect on AUC. Plasma berotralstat Cmax was approximately 39% higher in subjects with severe renal impairment than in matched healthy subjects.

In severe renal impairment, GM Cmax at steady-state following 150 mg QD dosing was estimated to 220 ng/mL (1.39-fold higher than GM Cmax of 158 ng/mL in subjects with normal renal function), which is slightly below the threshold for concern for QT prolongation (see QT prolongation below). According to the applicant, underestimation of the GM Cmax,ss based on the single dose administration is unlikely, and it could be expected that increases in exposure would be similar at steady state in this population. This is not agreed.

The applicant's predicted Cmax,ss in subjects with severe renal impairment is based on a number of assumptions. One of these was that steady state was reached by Day 14 in these subjects, which has been justified by the applicant. A second assumption, which the applicant has not addressed, is that berotralstat has nonlinear or dose-dependent PK, with greater than proportional increases in exposure with increasing dose. Thus, the assumption that berotralstat exposure would be increased by the same magnitude at steady state as that following a single dose in subjects with severe renal impairment is questioned.

As berotralstat has not been studied in patients with ESRD requiring dialysis, the SmPC (sections 4.2 and 5.2) has been adequately updated to recommend that berotralstat use should be avoided in these patients.

- Hepatic impairment

The applicant conducted a dedicated hepatic impairment study in subjects with varying degrees of hepatic impairment.

Plasma exposures of berotralstat in mild hepatic impaired subjects were similar to those in matched healthy subjects. Plasma berotralstat Cmax and AUC0-inf were approximately 77% and 78% higher in subjects with moderate hepatic impairment, whilst Cmax was approximately 27% higher and AUC0-inf was similar in subjects with severe hepatic impairment, compared to matched healthy subjects. The increase in plasma berotralstat Cmax and AUC0-inf were approximately 50% and 38%, respectively, for the combined group (moderate and severe hepatic impairment). The applicant estimates the Cmax,ss to be 240 ng/mL in subjects with moderate or severe hepatic impairment, which is slightly above the threshold for concern for QT prolongation (see QT prolongation below).

It is also important to note that the calculation of Cmax,ss assumes that the unbound (pharmacologically active) fraction of berotralstat in subjects with moderate/severe hepatic impairment and severe renal impairment is the same as in healthy subjects, which is not the case for hepatic impairment. The median unbound fractions were 1.5-1.7% and 2.35-2.4% in subjects with moderate and severe hepatic impairment, respectively, vs 0.9-1.2% in healthy subjects. Therefore, the risk of QT prolongation would be higher in subjects with moderate/severe hepatic impairment if the assessment was based on unbound berotralstat concentrations.

- Gender and race

It is agreed that no dose adjustments are warranted based on gender or race.

- Weight

In the population PK analysis, body weight was shown to have a significant effect on BCX7353 exposure, with AUC predicted to vary approximately 1.4-fold across the weight range of 40 to 120 kg. However, there appears to be no meaningful difference in efficacy and safety between the different body weight groups. The applicant presented the results of simulations and adequately justified that patients with high body weight can be expected to achieve berotralstat concentrations sufficient for clinical efficacy. In addition, the applicant justified that model-predicted exposures in patients of low body weight are reasonably accurate. Therefore, it is agreed that dose adjustments in terms of weight are not required in subjects weighing 40 kg or more. The information is adequately reflected in the SmPC>.

- Age

A limited number of elderly and adolescent subjects were included in the clinical studies with berotralstat. 19 subjects (2.6%) ≥ 66 years of age were included in the Pop PK dataset, which did not identify age ≥ 65 years to have a clinically important impact on berotralstat exposure.

A particular concern is that older age is a risk factor for QT prolongation. As such, Section 4.4 of the SmPC has been appropriately updated to include advancing age in the list of risk factors for QT prolongation. In addition, the SmPC has been updated to reflect that berotralstat has not been studied in patients >75 years.

16 adolescent subjects (12-17 years) were included in the population PK analysis. The simulated GM Cmax,ss in adolescent subjects (≥40 kg) of 153 ng/mL is sufficiently below the threshold of concern for QT prolongation (see QT prolongation below). Berotralstat has not been studied in adolescents with a body weight <40 kg.

Interactions

Study BCX7353-102

The magnitude of the change in exposure of each probe substrate following co-administration with BCX7353 indicates significant inhibition of CYP2D6 enzyme activity (dextromethorphan), CYP2C9 enzyme activity (tolbutamide), CYP2C19 enzyme activity (omeprazole), and CYP3A4 enzyme activity (IV and oral midazolam). At a daily dose of 350 mg [SN], BCX7353 would be classified as a strong CYP2D6 inhibitor, a moderate inhibitor of CYP3A4 (intestinal and hepatic), CYP2C9, and CYP2C19, and a weak inhibitor of hepatic CYP3A4.

Study BCX7353-112

This DDI study aimed to evaluate the degree to which BCX7353 inhibits metabolism of medications commonly co-administered in HAE patients at the proposed dose that will be administered prophylactically, 150 mg QD.

Concomitant administration of danazol (CYP3A and CYP2D6 substrate) with daily BCX7353 150 mg reduced danazol exposure (Cmax and AUC) by approximately 20% to 25% compared to administration of danazol alone. The reduction in danazol exposure with concomitant use of berotralstat is unlikely to be clinically meaningful. Thus, from a PK perspective, no updates to the SmPC in terms of a DDI are required.

BCX7353 at a daily dose of 150 mg was a mild inhibitor of amlodipine metabolism, increasing exposure by <2-fold. As stated in the SmPC for concomitant medicines that are predominantly metabolised by CYP3A4, particularly those with a narrow therapeutic index (e.g. cyclosporine, fentanyl). Appropriate monitoring and ose adjustments of these medicines may be required (see section 5.2).

BCX7353 at a daily dose of 150 mg was a mild/moderate inhibitor of desipramine metabolism, increasing exposure by around 2-fold. As stated in the SmPC, berotralstat is a moderate inhibitor of CYP2D6, increasing the C_{max} and AUC of dextromethorphan by 196% and 177%, respectively, and the C_{max} and AUC of desipramine by 64% and 87%, respectively. Concomitant administration may increase exposure of other medicines that are CYP2D6 substrates. Refer to the SmPC for concomitant medicines that are predominantly metabolised by CYP2D6, particularly those with a narrow therapeutic index (e.g. thioridazine, pimozide) or whose prescribing information recommends therapeutic monitoring (e.g. tricyclic antidepressants). Dose adjustments of these medicines may be required (see section 5.2).

Study BCX7353-115

Study BCX7353-115 was a follow-up study to Study BCX7353-102 to definitively inform the drug interaction liability of berotralstat on CYP2D6, CYP2C9, CYP2C19, and CYP3A4 at the clinically relevant dose of 150 mg QD.

The magnitude of the change in exposure (AUC0-last) of each probe substrate following co-administration with berotralstat indicates that berotralstat at 150 mg daily is a moderate inhibitor of CYP3A4 activity as measured by midazolam metabolism (GLSM ratio of 2.2), a weak inhibitor of CYP2C9 activity as measured by tolbutamide metabolism (GLSM ratio < 2), a moderate inhibitor of CYP2D6 activity as measured by dextromethorphan metabolism (GLSM ratio of 2.8) and not an inhibitor of CYP2C19.

Study BCX7353-105

The results of this study showed that berotralstat was a mild inhibitor of P-gp. However, given digoxin's narrow therapeutic range, the magnitude of the increase in exposure of digoxin seen with concomitant berotralstat dosing (~50%) is clinically important. Therefore, adequate monitoring of digoxin levels is advisable if used concomitantly with berotralstat. This is adequately reflected in the SmPC including also other concomitantly administered medicines that are P-gp substrates.

Cyclosporine increased exposure of a single dose of berotralstat on Day 14 compared to Day 1, with Cmax, AUC0-last, and AUC0-inf GM ratios of 1.25 (1.05, 1.48), 1.55 (1.40, 1.72), and 1.69 (1.50, 1.91), respectively. The SmPC includes appropriate wording that close monitoring for adverse events is needed if berotralstat is used concomitantly with P-gp and BCRP inhibitors.

Berotralstat exposure may be reduced if used concomitantly with P-gp and BCRP inducers. The SmPC advises that cyclosporine, a P-gp and BCRP inhibitor, increased the steady state maximum concentration (C_{max}) of berotralstat by 25% and the AUC of berotralstat by 55%. Berotralstat exposure may be increased with concomitant administration of P-gp and BCRP inhibitors, but no dose adjustment is necessary. Close monitoring for adverse events is recommended for concomitant use with P-gp and BCRP inhibitors.

Cyclosporine, a P-gp and BCRP inhibitor, increased the steady state maximum concentration (C_{max}) of berotralstat by 25% and the AUC of berotralstat by 55%. Berotralstat exposure may be increased with concomitant administration of P-gp and BCRP inhibitors, but no dose adjustment is necessary. Close monitoring for adverse events is recommended for concomitant use with P-gp and BCRP inhibitors.

The applicant does not anticipate these increases in exposure to be a safety concern at the proposed dose of 150 mg daily since single doses of berotralstat with an interacting drug and multiple doses of berotralstat of 350 mg for up to 28 days were generally well tolerated and cover the exposure of the proposed 150 mg daily dose with the degree of interaction observed in this study.

Pharmacodynamics

In study 203, a dose dependent inhibition of kallikrein inhibition was observed with berotralstat treatment over the dose range 62.5 to 350 mg QD. C1-INH and C4 levels were generally stable over time and no clinically meaningful differences were observed between dose groups.

Exposure-response analyses demonstrated a high correlation between ex-vivo kallikrein inhibition activity and plasma concentrations of berotralstat. A sigmoidal Emax model described the berotralstat concentration and kallikrein inhibition relationship in subjects with HAE reasonably well. Although there was no apparent correlation between confirmed attack rate and berotralstat plasma exposure, steady-state BCX7353 AUCtau and Ctau appeared to be moderately correlated with the confirmed attack rate in the lower dose range of 62.5 to 125 mg. In addition, the results suggested that maintaining a threshold concentration of ≥ 4 × EC50 (36 ng/mL) will result in a reduction in attacks.

Simulations predicted that a dose of 175 mg [SN] (equivalent to 150 mg free base) berotralstat QD would provide trough concentrations above 4 × EC50 in approximately 93% of patients. Therefore, selection of 150 mg as a second, higher active dose level in Study 302 is considered appropriate.

In studies 302 and 301, an apparent concentration-related inhibition of kallikrein inhibition was observed in subjects treated with berotralstat, with more subjects achieving sustained maximal levels (>80%) in the 150 mg treatment group compared to the 110 mg treatment group.

Thorough QT Study 106

In the exposure-response analysis, there was a statistically significant positive relationship between ΔΔQTcF and berotralstat concentration ($p<0.001$). At the therapeutic dose of berotralstat 150 mg QD

× 14 days, the estimated mean ΔΔQTcF was 3.4 msec (2-sided 90% UB 6.8 msec). For the supratherapeutic dose, at the GM Cmax of 577 ng/mL for 450 mg QD × 14 days, the estimated ΔΔQTcF was 21.9 msec (2-sided 90% UB 29.4 msec).

The applicant estimated the highest clinically relevant exposure to be 240 ng/mL, based on the Day 14 (steady state) GM Cmax for berotralstat 150 mg QD from the current study of 160 ng/mL multiplied by an average 1.5-fold increase in Cmax seen in a combined group of subjects with moderate and severe hepatic impairment following administration of a single dose of berotralstat 150 mg (Study 108). At the anticipated highest clinically relevant exposure (240 ng/mL), the estimated mean ΔΔQTcF was 7.0 msec and the upper bound of the 90% CI was 10.9, which is above the 10 msec threshold. Appropriate warnings have been included in the SmPC.

The applicant's predicted GM Cmax,ss in severe renal impairment was 220 ng/mL. However, this predicted Cmax,ss is based on a number of assumptions. The possibility of underprediction of GM Cmax,ss (220 ng/mL) cannot be excluded and this is of particular concern because this value is so close to the threshold for concern for QT prolongation (222 ng/mL). At the predicted GM Cmax,ss, the upper bound of the 2-sided 90% CI is 9.9 msec; just 0.1 msec below the threshold that would prompt additional warnings in the SmPC. Overall, as the true value of Cmax,ss in subjects with severe renal impairment is not known, and possibly under-predicted, it is considered appropriate to be cautious. Therefore, the applicant's conclusion that subjects with severe renal impairment treated with 150 mg QD berotralstat are not at increased risk of QT prolongation due to berotralstat exposure is not supported. Upon request of CHMP, the applicant included a warning in the SmPC in relation to the risk of QT prolongation in subjects with severe renal impairment and that it is preferable to avoid the use of berotralstat in these patients. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered.

The simulated GM Cmax,ss in adolescent and low body weight (40 kg) subjects (153 ng/mL and 183 ng/mL, respectively) are sufficiently below the threshold of concern for QT prolongation. As berotralstat use is restricted to subjects weighing 40 kg or more, it is agreed that there is a low risk of QT prolongation in adolescents and patients with low body weight.

There are no data for individuals with risk factors for drug-induced TdP. The SmPC recommendations read as follows:

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

2.4.5. Conclusions on clinical pharmacology

All clinical pharmacology issues have been sufficiently addressed and are considered resolved. The SmPC adequately reflects the clinical pharmacology of berotralstat.

2.5. Clinical efficacy

In support of the application the applicant has submitted five clinical efficacy studies of which four are relevant to the proposed indication i.e. the routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. Of these one is considered a dose finding study (BCX7 353-203), one a pivotal study (BCX7 353-302), and two supportive studies (BCX7 353-204) and (BCX7 353-301). An exploratory study investigating the efficacy of Berotralstat in the acute treatment of HAE attacks was also submitted. The primary objective of the study was "To evaluate the efficacy of

single oral doses of BCX7353 in treating acute attacks in subjects with hereditary angioedema (HAE)".This study is not further discussed in this report. Details of the studies are included in the following Table.

Table 18

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
BCX7353-202 Phase 2		Randomized double blind, placebo controlled	BCX7353 powder and matching placebo powder for reconstitution as oral solutions. 750mg, 500mg, 250 mg 3 separate attacks were treated; 2 with active drug and 1 with placebo	To evaluate the efficacy of single oral doses of BCX7353 in treating acute attacks in subjects with hereditary angioedema (HAE)	63 subjects were randomized 58 received at least 1 dose of study drug/active			Type 1 or Type 2 HAE	
BCX7353-203	24 study centres in Europe and Australia Phase 2	A randomized, double blind, placebo controlled, dose ranging, parallel group study	Part 1: 350mg [SN] berotralstat or placebo orally QD (18) Part 2: 250mg [SN] berotralstat, 125mg [SN] berotralstat or placebo orally QD (13) Part 3: 250mg [SN] berotralstat, 125mg [SN] berotralstat, 62.5 mg [SN] berotralstat or	to evaluate the efficacy of once-daily prophylactic berotralstat up to 5 dose levels, as measured by the number of attacks of HAE observed in subjects with HAE enrolled in each treatment group	Part 1 36 Part 2 15 Part 3 24	28 days dosing duration	M/F 38.7% v 61.3% Median age 45 years	Type 1 or Type 2 HAE	The primary efficacy endpoint was the number of confirmed HAE attacks in the FAS and PP populations.

		placebo orally QD (22						
BCX7 353-204 Phase 2	2-arm, open-label uncontrolled non-randomized study	BCX7353 110 mg QD and 150 mg QD	Secondary To assess the effectiveness (ie, HAE attack frequency, severity, and disease activity over time) of BCX7353 during long-term administration	110 mg n = 100 150 mg n = 127	Ongoing	M/F 38.8% v 61.2% Median age = 41 years	Type 1 or Type 2 HAE	Efficacy was secondary endpoint
BCX7 353-301 Phase 3	Randomized double blind, Placebo controlled, Parallel group study	Berotralstat capsule 55mg x 2 daily Berotralstat capsule 75mg x 2 daily	To determine the efficacy of prophylactic berotralstat (BCX7353) 110 and 150 mg administered once daily (QD) for 24 weeks compared to placebo in subjects with hereditary angioedema (HAE)	N = 19 B 110mg n = 6 B 150mg n = 7 Placebo n = 6	24 weeks	M/F 15.8% v 84.2% Median age 39 years	Type 1 or Type 2 HAE	The rate of expert-confirmed angioedema events during dosing in the entire 24-week treatment period (Days 1 to 168)
BCX7 353-302 Phase 3	Randomized, double blind, Placebo controlled, Parallel group, 3-part study in subjects with Type I or II HAE.	Two capsules of berotralstat at 55 mg (41) or 75 mg (40) were administered orally QD for 24 weeks in Part 1	Part 1 Primary Objective • To determine the efficacy of prophylactic berotralstat 110 mg and 150 mg	121 subjects were randomized (stratified by baseline attack rate, < 2 vs. ≥ 2 per 28 days), and 120 randomized subjects	24 weeks	M/F 33.9% v 66.1£. Median age = 40 years	Type 1 or Type 2 HAE	The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to time of the first dose of

administered QD for 24 weeks compared to placebo	(99%) were treated. Berotralstat 110mg n= 41, Berotralstat 150mg n = 40, placebo n = 40	study drug in Part 2)

2.5.1. Dose response study

The applicant has submitted one phase 2 study (Study BCX7353-203).

Study BCX7353-203. A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema.

This was a Phase 2, randomized, double-blind, placebo-controlled, 4-part, parallel-group, dose-response study to evaluate the safety, tolerability, PK, PD, and efficacy of berotralstat in subjects with HAE (Type 1 or 2). The study was conducted at 24 sites in Europe between 11 August 2016 and 8 August 2017.

Subjects were required to have a clinical diagnosis of HAE Type 1 or 2 as documented at any time in the medical records or at the screening visit by a low C1 esterase inhibitor (C1-INH) functional level (Type 2) or a low C1-INH antigenic level (Type 1) as well as a documented HAE attack rate of at least 2 HAE attacks per month for 3 consecutive months (defined as 93 days) within the 6 months prior to the screening visit as documented in acceptable source records.

The primary objective of the study was to evaluate the efficacy of once-daily prophylactic treatment with berotralstat at up to 5 dose levels (62.5mg, 125mg, 250mg, and 350mg daily) as measured by the number of attacks of HAE observed in subjects with HAE enrolled in each treatment group over a 28 day treatment duration.

The study had potentially 4 parts but only 3 parts were concluded. In Part 1 (n = 36) the 350mg dose was evaluated against placebo and subjects were randomised in a 1:1 proportion. In Part 2 there were 3 treatment groups (n = 15): Berotralstat 125mg QD, Berotralstat 250mg QD and placebo randomised in 1:3:3 proportion (placebo:active:active). In part 3 there were 4 treatment groups (n = 24): Berotralstat 125mg QD; Berotralstat 250mg QD and Berotralstat 62.5mg QD which were randomised in 1:3:3:3 proportions (placebo:active:active:active:active).

Results (efficacy)

A total of 86 patients were screened (adults aged under 65 years), 77 were randomized, and 75 (97.4%) were randomized and treated. Of the 11 patients who were not enrolled in the study, 9 subjects did not meet inclusion or met exclusion criteria. Completion rates for 28 days of dosing were lowest for the 350 mg dose (77.8%), compared to 250mg (93.3%), 125 mg (100%), 62.5 mg (100%) and placebo (95.7%).

Efficacy was assessed in the full analysis population (all those who were randomised and received at least 1 capsule of study drug). The primary efficacy endpoint was the number of confirmed (adjudicated) HAE attacks in the FAS and PP populations. The primary analysis of treatment-effect was performed using an ANCOVA model with the adjusted qualifying attack rate as the covariate.

In the FAS for the entire dosing period, the LSM attack rate for placebo was 0.913 per week. LSM differences (active − placebo) in the confirmed rate of attacks per week by berotralstat dose group were: −0.387 (−42.4%, p = 0.006), −0.446 (−48.9%, p = 0.003), −0.642 (−70.3%, p < 0.001) and −0.046 (−5.0%, p = 0.811) in the berotralstat 350, 250, 125, and 62.5 mg treatment groups, respectively (Table 24). Similar results were observed for the PP population over the entire and effective dosing periods as well as for the FAS population over the effective dosing period.

Table 19: BCX7353-203: Summary of the Rate of Confirmed Attacks During the Entire Dosing Period (FAS Population)

	Berotralstat 350 mg (N = 18)	Berotralstat 250 mg (N = 14)	Berotralstat 125 mg (N = 14)	Berotralstat 62.5 mg (N = 7)	Placebo (N = 22)	Berotralstat Total (N = 53)
Weekly attack rate Mean (SD)	0.498 (0.506)	0.468 (0.425)	0.286 (0.275)	0.929 (0.494)	0.898 (0.565)	0.491 (0.462)
Difference from qualifying attack rate Mean (95% CI)	-0.404 (-0.705, -0.103)	-0.490 (-0.725, -0.255)	-0.703 (-1.048, -0.358)	-0.217 (-0.708, 0.274)	-0.097 (-0.366, 0.172)	-0.481 (-0.634, -0.328)

Table 20: BCX7353-203: Statistical Analysis of the Rate of Overall Confirmed Attacks During the Entire Dosing Period (FAS Population)

Treatment	N	LSM (SE)	Diff v placebo (95% CI)	% diff v placebo	p-value for Treatment Difference
Berotralstat 350 mg	18	0.525 (0.103)	-0.387 (0.663, -0.112)	-42.446	0.006
Berotralstat 250 mg	14	0.467 (0.117)	-0.446 (-0.742, -0.150)	-48.865	0.003
Berotralstat 125 mg	14	0.271 (0.117)	-0.642 (-0.938, -0.346)	-70.327	< 0.001
Berotralstat 62.5 mg	7	0.867 (0.166)	-0.046 (-0.423, 0.332)	-5.001	0.811
All berotalstat	53	0.488 (0.06)	-0.425 (-0.645, -0.205)	-46.561	< 0.001
Placebo	22	0.913 (0.093)			

Confirmed attacks were adjudicated and confirmed by the independent CEAP.

ANCOVA model includes terms of treatment and adjusted qualifying attack rate. The entire dosing interval is the date of first dose to the last dose on day 28+24 hours, or 24 hours post last dose of the study drug, whichever is earlier.

The rate of confirmed attacks requiring treatment was a secondary endpoint. In the FAS for the entire dosing period LSM rates were lowest in the berotralstat 125mg group. The LSM rates per week requiring treatment for placebo was 0.776 per week. LSM differences (active – placebo) in the confirmed rate of attacks per week by berotralstat dose group were: −0.293 (−37.8%, p = 0.047), −0.327 (−42.1%, p = 0.040), −0.558 (−71.9%, p < 0.001) and +0.057 (7.4%, p = 0.775) in the berotralstat 350mg, 250mg, 125mg, and 62.5mg treatment groups, respectively (see Table 26).

Table 21: BCX7353-203: Statistical Analysis of Rate of Confirmed Attacks Requiring Treatment during the Entire Dosing Period (FAS Population)

Treatment	N	LSM	Standard Error	Difference vs Placebo	% Difference vs Placebo	95% CI for Treatment Difference	p-value for Treatment Difference
Berotralstat 350 mg	18	0.483	0.109	-0.293	-37.780	-0.582, -0.004	0.047
Berotralstat 250 mg	14	0.449	0.123	-0.327	-42.141	-0.638, -0.016	0.040
Berotralstat 125 mg	14	0.218	0.123	-0.558	-71.935	-0.870, -0.247	< 0.001
Berotralstat 62.5 mg	7	0.833	0.174	0.057	7.409	-0.339, 0.454	0.775
All berotralstat	53	0.450	0.063	-0.326	-41.986	-0.557, -0.095	0.006
Placebo	22	0.776	0.098				

Abbreviations: ANCOVA = analysis of covariance; CEAP = Clinical Endpoint Adjudication Panel; CI = confidence interval; FAS = full analysis set; LSM = least squares mean.

Confirmed attacks were adjudicated and confirmed by the independent CEAP.

Difference in adjusted least square means are shown (Active treatment minus Placebo).

Percent Difference was calculated as Difference/Placebo*100.

ANCOVA Model included terms of treatment and adjusted qualifying attack rate.

The entire dosing period was from the date of first dose to the last dose on Day 28 + 24 hours, or 24 hours after the last dose of the study drug, whichever was earlier.

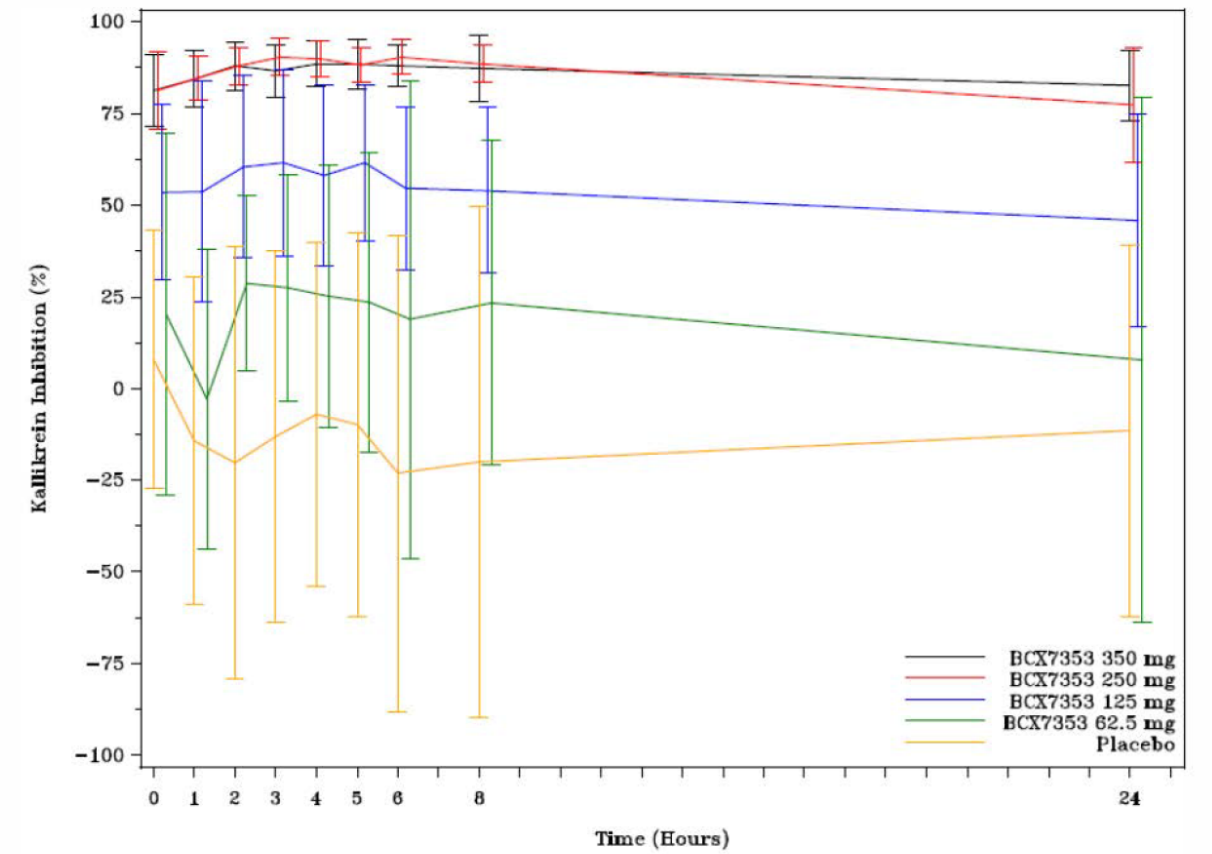
Pharmacodynamic (PD) evaluations

There were 3 PD populations, 1 for each PD assessment (plasma kallikrein inhibition, C1-INH functional levels or complement component 4 (C4) levels, and BMP).

The plasma kallikrein inhibition PD population included all subjects for whom at least 1 pre-dose and post dose plasma kallikrein inhibition result could be estimated. This population was used for all analyses of plasma kallikrein inhibition.

Each of the other PD populations included all subjects with a baseline and at least 1 post dose value and was the primary population for the relevant PD analyses. At doses of 250 or 350 mg berotralstat, plasma kallikrein inhibition was maintained over the dosing interval, with maximal mean inhibition of approximately 90% around the median Tmax, which was sustained above the mean inhibition of 75% over the 24-hour dosing period Maximum mean kallikrein inhibition with 125 mg berotralstat was approximately 62%, with mean inhibition of 46% at 24 hours, whereas at 62.5 mg berotralstat, maximum mean kallikrein inhibition was only about 29%, with mean inhibition of 8% at 24 hours. During placebo treatment, kallikrein inhibition remained relatively stable with no significant change from pre-dose activity further substantiating the robustness of the assay to detect a difference.

Figure 8: BCX7353-203: Mean (± SD) Kallikrein Inhibition-Time Profiles following Administration of Multiple Doses of Berotralstat (Kallikrein PD Population)



Abbreviations: PD = pharmacodynamic; SD = standard deviation.
Source: Section 14.2, Figure 14.2.3.1

None of the berotralstat steady-state PK parameters (Cmax, AUCtau, and Ctau) appeared to have been correlated with the confirmed attack rate. In addition, there was no correlation between the percent of plasma berotralstat Ctau above 4 ×and 8 ×kallikrein inhibition EC50 and confirmed attack rate. However, berotralstat concentrations at all dose groups were well above the measured EC50 for kallikrein inhibition. The results suggest that maintaining a threshold concentration of ≥ 4 × EC50 or 35.8 ng/mL will result in clinically meaningful reductions in attacks. A 125-mg dose provided a mean Ctau of 4.7-fold EC50, with a corresponding reduction in attacks of 70% ($p < 0.001$) compared with placebo and a 62.5-mg dose provided a mean Ctau of 1.5-fold EC50, with no change in attack rate vs. placebo ($p = 0.811$).

Overall, all doses above 125mg had a statistically significant positive effect on the attack rate, with the greatest effect seen with the 125 mg dose. This is surprising given the result of PD studies which showed greater kallikrein inhibition for the 250mg and 350mg doses with a mean inhibition over 24 hours of approximately 75% for the two highest doses and approximately 46% for the 125 mg dose. A 125-mg dose provided a mean Ctau of 4.7-fold EC50, with a corresponding reduction in attacks of 70% ($p < 0.001$) compared with placebo and a 62.5-mg dose provided a mean Ctau of 1.5-fold EC50, with no change in attack rate vs. placebo ($p = 0.811$). Evidence from modelling and the results from this Phase 2 study suggest that maintaining a threshold concentration of ≥ 4 × EC50 or 35.8 ng/mL will result in clinically meaningful reductions in attacks.

2.5.2. Main study

The main study is BCX7353 302 which was conducted in a North American and European population.

Study BCX7353-302: A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema.

Methods

The study had a run-in period which could last up to 56 days to establish the baseline HAE attack rates (i.e. the attack rate over the period from screening to first dose of study drug) and which largely coincided with the screening period. Randomisation occurred at D 1 at the end of the screening period and was required to be ≤ 10 weeks from start of the screening period. The study was further divided into three parts: Part 1 from Day 1 to end of Week 24 (placebo controlled, blinded evaluation of efficacy and safety); Part 2 from the end of Week 24 to week 48 (blinded safety evaluation of berotralstat) and Part 3 from Week 48 to Week 96+ (evaluation of safety of open-label berotralstat).

Efficacy was evaluated in Part 1 and the applicant is only presenting results from Part 1 as the rest of the study is ongoing and will be provided post approval.

Study Participants

The main inclusion criteria were:

- Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (sub-study in North America only), with a clinical diagnosis of hereditary angioedema Type 1 or Type 2
- Patients must have been medically suited for on-demand treatment as the sole medical management for their HAE during the study and should have access to and ability to use 1 or more SOC-Rx approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived or recombinant C1-INH, or ecallantide).
- The subject must have had ≥ 2 HAE attacks that met all of the requirements below during the run-in period of a maximum of 56 days from the screening visit: (a) The attacks were unique, which was defined as an attack that did not begin within 48 hours of the end of a previous attack; (b) the attacks must have either been treated, required medical attention, or been documented to cause functional impairment based on subject entry in the e-diary. Functional impairment was defined as the subject being unable to perform daily activities without restriction (i.e. subjects recorded that they were at least slightly restricted in their daily activities during their HAE attack); (c) the attacks included symptoms of swelling. Symptoms of swelling, in addition to visible swelling, may also have included symptoms in the oropharyngeal or abdominal regions that were indicative of internal swelling;

Treatments

There were three treatment groups Berotralstat 15mg QD; Berotralstat 110mg QD and placebo all randomised in a 1:1:1 fashion. dose was to be taken orally QD at approximately the same time each day with whichever meal was typically the largest meal of the day, or up to 30 minutes after consuming that meal. All patients could avail of rescue treatment for HAE attacks that required treatment.

Objectives

The primary objective of the study was to determine the efficacy of prophylactic BCX7353 110 mg and 150 mg administered QD for 24 weeks compared to placebo in subjects with HAE. Secondary objectives relevant to efficacy included: to assess the effects of berotralstat on HAE disease activity and HAE attack characteristics; to evaluate the effects of berotralstat on QoL; to characterize the PD effects of berotralstat.

Outcomes/endpoints

The primary efficacy endpoint of the study was: the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to time of the first dose of study drug in Part 2). Secondary endpoints included the following: change from baseline in Angioedema Quality of Life questionnaire (AE-QoL) at Week 24 (total score); number and proportion of days with angioedema symptoms through 24 weeks; rate of investigator-confirmed HAE attacks during dosing in the effective treatment period (beginning on Day 8 through to the first dose of study drug in Part 2.

Sample size

The final sample size was to have been the maximum of either the original planned sample size (32 per group) or the re-estimated sample size. No statistical adjustment for the final analysis was planned.

Randomisation and blinding (masking)

Subjects were randomised on a 1:1:1 basis by means of an interactive voice response system (IXRS). Enrolment into treatment groups was stratified by the HAE attack rate over the period from screening to randomization (≥ 2 attacks per month vs. < 2 attacks per month).

This was a double-blind study throughout Part 1. As such, study drug assignment was blinded to the investigator, study staff, study subjects, and clinical research organization staff. During Part 1, sponsor employee(s) were also blinded to the treatment allocation of individual subjects, with the exception of sponsor staff responsible for managing clinical supplies. Employees who were not blinded to drug assignment had no access to any other subject-level information for the duration of the study.

statistical methods

Statistical Analysis Plan

SAP v1.0 is dated 29 January 2019 and is based on Protocol Version 2.0 dated 11 October 2018. The database was locked to conduct the Part 1 analysis on 9 May 2019.

The applicant highlighted a number of changes in the planned analyses in the Part 1 Interim CSR.

Changes from protocol-specified analyses included the following:

- For Part 1 analyses, the protocol stated that efficacy displays were generally to be performed over the entire dosing period beginning on Day 1 and effective treatment period beginning on Day 8. In the SAP, a reduced number of displays were selected for analysis over the effective treatment period.
- In the protocol, the PP population was originally defined as a subset of the ITT population. It was redefined in the SAP as a subset of the safety population.
- Due to an error in the IXRS equation, the baseline attack rate for screening for purposes of stratification was slightly larger than it should have been because the denominator did not

include the “+1”; ie, the number of days in screening was underestimated by 1 day. For analysis purposes, the baseline attack rate was recalculated using the intended equation for baseline attack rate as shown in the SAP.

- Clarified that Part 1 ends at the time of the first dose for Part 2.
- The sample size per group was increased from 32 to 40 subjects to account for potential dropouts. Initial sample size estimates did not allow for any subject dropout.
- Due to rapid enrolment that exceeded the planned total sample size before the planned timing of sample size re-estimation was reached, i.e. when 50% of subjects reached Week 24, the planned sample size re-estimation was not conducted.

Changes from the SAP to the Part 1 analysis included:

- The equation for WPAI work productivity loss in the SAP Section 6.7.6.3 was corrected (“Q10” was changed to “10”).
- The equation for the attack rate reduction compared to placebo as specified in Section 8.6.1 of the SAP was multiplied by 100% and reported as a percentage reduction rather than as a proportion.
- Analysis of PD data excluded hemolyzed samples as specified in the PD data transfer agreement.
- Treatment compliance calculations were changed to add a calculation of compliance by visit as well as for Part 1 overall.
- A definition of laryngeal attacks was added and the number of laryngeal events occurring during Part 1 were summarized. Laryngeal attacks were defined as attacks which have visible swelling in the mouth/tongue/lips or any of the following internal swelling symptoms: lump in throat (tightness), difficulty swallowing, change in voice, or difficulty breathing.
- For the PP population definition, a requirement was added that a subject needed to have > 85% overall treatment compliance based upon capsule counts to be included.

A large number of post-hoc analyses were also performed.

Analysis Populations

Subjects who gave informed written consent but were not randomized to study treatment were noted as screen failures in the eCRF and were considered screen failures. Reasons for screen failures were summarized using this population.

The ITT population included all randomized subjects, regardless of whether study treatment was administered. This population was the primary population for the analysis of the efficacy and health outcomes data. Data were analysed according to randomized treatment.

The safety population included all subjects who received ≥ 1 capsule of study drug. This population was used in the assessment and reporting of accountability, demographic information, berotralstat drug concentrations, and safety data. Data were analysed according to the actual treatment received at first dose.

The per protocol (PP) population included subjects in the safety population who completed Part 1. For study 302 subjects included in the PP population had ≥ 85% treatment compliance without any major protocol deviations that could impact efficacy measures. A decision was made prior to database lock on which subjects (if any) were excluded from the PP population based upon major protocol deviations. In

the PP analysis, subjects were assessed based on the actual treatment received on Day 1. The PP population was used as a secondary population for efficacy analyses.

The subset of subjects in the ITT population who completed Part 1 of the study comprised the completers population. The completers population was used for a sensitivity analysis of the primary efficacy analysis for Part 1 only. Data were analysed according to randomized treatment.

The PD population included all subjects for whom ≥ 1 pre-dose and 1 post dose plasma kallikrein inhibition result could be estimated. Data were analysed according to the actual treatment received. This population was used for all analyses of plasma kallikrein inhibition.

The PK/PD population included all subjects for whom ≥ 1 pre-dose and 1 post-dose plasma kallikrein inhibition result could be estimated with a corresponding plasma berotralstat concentration (placebo samples not analysed were assumed to have a 0 concentration). This population was used for plots comparing plasma kallikrein inhibition and plasma berotralstat concentrations.

Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint for Part 1 of the study is the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period during Part 1 (Day 1 to first dose of Part 2). The first dose in Part 2 is expected on Day 169. The primary efficacy analysis was to conducted using the ITT population. The primary analysis was to be based on data from subjects who were on study treatment and this analysis was not to include data post treatment discontinuation.

The attack rate and the treatment comparisons between each BCX7353 dose and placebo in the

rate of investigator-confirmed HAE attacks during the Part 1 dosing period was to be analysed using a Poisson regression model. The number of investigator-confirmed attacks was to be included as the dependent variable, the treatment will be included as a fixed effect, the stratification variable (baseline attack rate) was to be included as a covariate and the logarithm of duration on treatment was to be included as an offset variable. The estimated rate of attack for each treatment group, the treatment differences expressed as the attack rate ratio (BCX7353 over placebo rate ratio) and their associated 95% confidence intervals (CIs) were to be provided from the Poisson regression model.

The percentage reduction from placebo was to be calculated for each dose as:

$$\text{Rate Reduction} = 1 - \text{attack rate ratio} = 1 - R_A/R_P$$

where R_P is the estimated attack rate for placebo treatment and R_A is the estimated attack rate for active treatment.

As a sensitivity analysis to examine the appropriateness of the Poisson model, a negative binomial model was to be used in place of the Poisson regression model. If the results of the model obtained using the negative binomial distribution were similar to that of the model that assumes the Poisson distribution and a statistical test of the dispersion parameter did not show that it is significantly greater than zero, the Poisson model would remain as the primary model for analysis.

<u>Sensitivity Analyses of the Primary Efficacy Results – Supplementary estimands and missing data</u>

Sensitivity analyses for the primary endpoint based on the PP and Completers populations were to be conducted. A second analysis using the ITT population with subject-reported rather than investigator-confirmed attacks was also be conducted.

In addition, there were to be 3 sensitivity analyses to examine the effect of missing data:

1. Using observed post-treatment discontinuation data where available without imputation for missing data. For this analysis, the attack rate was to be computed through the last date of

observed data up to the Part 2 treatment start date/time, including data collected after treatment discontinuation.

2. Observed post-treatment discontinuation data were to be used in combination with an imputed attack rate for the time period, post-treatment discontinuation, where data were not observed. An imputed rate for the entire 24-week period will be a weighted average of the observed rate up to the last day of diary collection (including days post treatment discontinuation) and the imputed rate for the time after treatment discontinuation during which data were not observed, with weighting based on the fraction of days with observed vs. unobserved data.

   For this rate, actual diary data collected after discontinuation of study treatment will be included in the observed rate where it is available by extending the time period in the denominator of the attack rate calculation to the last day that diary data were collected, even if past study treatment discontinuation. The only exception to this is if the subject started other prophylactic treatment after discontinuation of study treatment. In that case, actual diary data will be used up until the time of start of other prophylactic treatment.

   For subjects for whom no diary data is missing post study treatment discontinuation, no imputation is necessary. An observed confirmed attack rate will be computed to include data post study treatment discontinuation as applicable, as long as the subject did not start other prophylactic therapy.

   For subjects with missing data post study treatment discontinuation, missing data will be imputed as follows:

$$f = Fraction\ of\ Non\text{-}missing\ Data$$

$$= \frac{\text{Date of Last Day of Diary Collection Prior to Any Other Prophylactic Treatment} - \text{Date of First Dose} + 1}{169}$$

$$r_{observed}$$

$$= Observed\ \ Monthly\ Attack\ Rate\ Regardless\ of\ Study\ Treatment\ Discontinuation$$

$$= \frac{\text{Number of Attacks} * 28}{\text{Date of Last Day of Diary Collection Prior to Any Other Prophylactic Treatment} - \text{Date of First Dose} + 1}$$

$$r_{imputed} = Imputed\ Monthly\ Attack\ Rate\ for\ the\ Unobserved\ Period$$

$$= \begin{cases} \text{if missing at random, impute from complete cases in same treatment group} \\ \text{if not missing at random, median value of highest (worst) quartile rate in same treatment group or subject observed rate, if worse} \end{cases}$$

$$r_{analyzed} = f * r_{observerd} + (1 - f) * r_{imputed}$$

   As shown above, if a subject discontinues study treatment or withdraws from the study, the imputation of $r_{imputed}$ will differ depending on whether the data are considered missing at random or not missing at random based on the reason for study treatment discontinuation or study withdrawal as shown in the table below. Data missing at random will be imputed using multiple imputation with 10 separate rounds of imputations, randomly selecting from observed confirmed attack rates of other subjects in the treatment group who completed the treatment for Part 1. Data not missing at random will be imputed using the median attack rate of subjects in the worst quartile of performance (ie, highest attack rate quartile) with regard to the primary endpoint for the given treatment group or the subject's observed rate over the time period of available data, if worse.

Missing Data Considered Missing at Random	Missing Data Considered Not Missing at Random
Subsequent determination that inclusion/exclusion criteria were not met	Laboratory abnormality or adverse event
Intercurrent illness or emergence of new illness/medical condition/pregnancy	Discontinuation due to QT prolongation
Subject noncompliance with study drug or procedures	Discontinuation due to rash
Subject withdrew consent	Perceived lack of efficacy
Other [a]	Other [a]
Sponsor discontinuation [a]	Sponsor discontinuation [a]
Investigator judgment [a]	Investigator judgment [a]

[a] A review of discontinuations for Sponsor discontinuation, Investigator judgment, or other reason will be completed prior to unblinding of Part 1 data for determination of missing at random or not missing at random.

3. A tipping point analysis was to be conducted using the observed data post treatment discontinuation combined with imputed data for missing time periods. However, for tipping point analysis, $r_{imputed}$ will be multiplied by a factor, δ, for the active treatment group in the determination of the analysed rate, as shown below. For the placebo group, there will be no such multiplicative factor.

   The tipping point is the value of δ that leads to a reversal of a significant p-value. It shows how much larger than expected the attack rate would need to be for the time period of missing data for the active group in order to "tip" the significance level to non-significant. For tipping point analysis, the analysed rate for the active treatment group is:

$$r_{analyzed} = f * r_{observed} + (1-f) * \delta * r_{imputed}$$

   For the placebo group, the analysed rate would remain as:

$$r_{analyzed} = f * r_{observed} + (1-f) * r_{imputed}$$

Analysis of the Secondary Efficacy Endpoints

Angioedema Quality of Life (Total and Domain Scores)

Change from baseline in AE-QoL questionnaire at Week 24 (total score) was a secondary endpoint for Part 1. For Part 1, changes from baseline in AE-QoL were to be assessed with a MMRM model with fixed effects for treatment, baseline attack rate, baseline AE-QoL, visit, and a visit by treatment interaction and a random effect for subject. An unstructured covariance structure was to be used. The estimated treatment difference comparing each active treatment to placebo at each post-baseline visit (Weeks 4, 6, 12, 18, and 24) was to be displayed together with the 95% CI and the associated p-value. Least squares means (LSM) for each visit were also to be presented with the standard error and the number of subjects contributing to the LSM.

A summary and analysis of the number and percent of subjects with at least a 6-point decrease (Minimum Clinically Important Difference [MCID]) in total AE-QoL score will be performed by visit for Part 1. The analysis for Part 1 will be based on a logistic model with response of achievement of the MCID (yes/no), baseline attack rate and baseline AE-QoL total score as covariates and a fixed effect for treatment.

Number and Proportion of Days with Angioedema Symptoms

The number of proportion of days with angioedema symptoms through 24 weeks was a secondary endpoint for Part 1. For Part 1, the proportion of days with angioedema symptoms through Week 24 was to be analysed using an ANCOVA model with baseline attack rate as a covariate and treatment included as a fixed effect. The estimated treatment difference comparing each active treatment to placebo was to be displayed together with the 95% CI and the associated p-value. LSMs were to be presented with the standard error and the number of subjects contributing to the LSM. A similar analysis was to be conducted based on the effective dosing period, beginning on Day 8 and continuing through Week 24.

Rate of Investigator/Expert-Confirmed HAE Attacks during Dosing in the Effective Treatment Period

The rate of investigator/expert-confirmed HAE attacks during dosing in the effective treatment period is a secondary endpoint for Part 1.

Summaries and analysis of the investigator-confirmed attack rate using the ITT population for the effective treatment period (Day 8 through Week 24, inclusive) will be conducted using Poisson regression, similar to what is done for the primary efficacy endpoint analysis.

Subgroup analyses

Subgroup analyses for the primary endpoint of investigator-confirmed attack rate during the entire 24-week dosing period and the secondary endpoint of Week 24 change from baseline AEQoL (total score) were to be provided by:

1. Region (North America vs. Europe)
2. Sex
3. Race (white vs. other)
4. Baseline attack rate (≥ 2 attacks/month vs. < 2 attacks/month)
5. Age group (< 18, 18 to 65, > 65 years)

Forest plots showing the original results and the results by subgroups were to be provided.

A summary of TEAEs by age group was also to be provided.

Type I error control

There are 4 endpoints being tested. For each endpoint, there are 2 potential doses to be tested against placebo. The 4 endpoints were to be tested in a hierarchical fashion, with the 2 doses being tested using the Hochberg step-up procedure at each level of the hierarchy.

The testing hierarchy for study 302 was as follows:

1. The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to Day 168)
2. Change from baseline in AE-QoL at Week 24 (total score)
3. Number and proportion of days with angioedema symptoms through 24 weeks
4. Rate of investigator-confirmed HAE attacks during dosing in the effective treatment period (beginning on Day 8 through 24 weeks)

Multicentre Study

There were no adjustments made based on multiple centres.

Interim analyses

The protocol and SAP allowed for a blinded interim analysis to have been performed to estimate the standard deviation (SD) from the pooled treatment groups after 50% of the subjects had completed 24 weeks. The sample size may have been re-estimated based on the variability from the pooled data. The final sample size was to have been the maximum of either the original planned sample size (32 per group) or the re-estimated sample size. No statistical adjustment for the final analysis was planned.

Due to rapid enrolment that exceeded the planned total sample size before the planned timing of sample size re-estimation was reached, i.e. when 50% of subjects reached Week 24, the planned sample size re-estimation was not conducted.

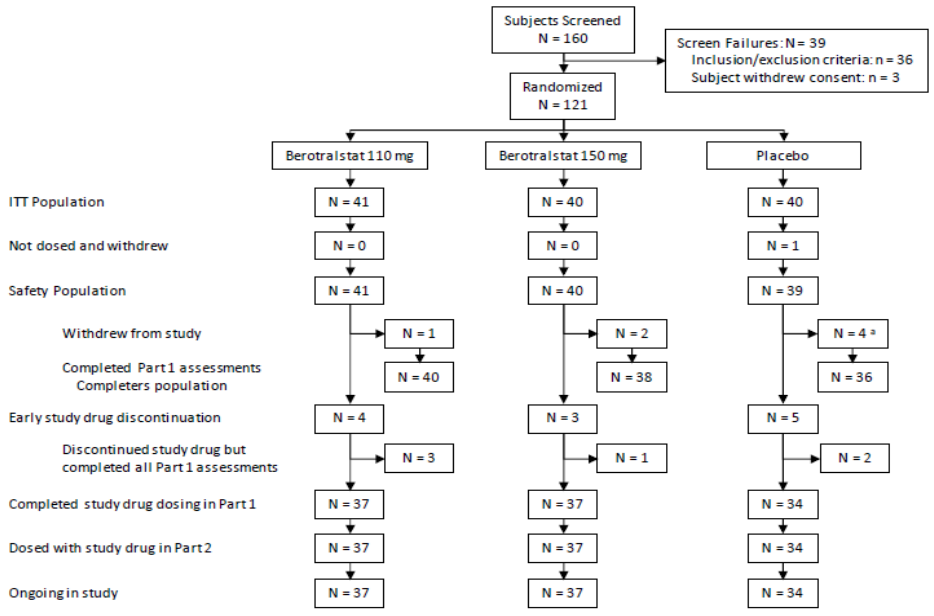
Results

Participant flow

A total of 160 patients were screened, of whom 121 were randomized. Of the 39 screen failures 36 did not meet all of the inclusion criteria or met an exclusion criterion. Three withdrew consent. One subject was randomized to placebo but did not receive study drug and was not included in the safety population.

Participant flow

Figure 9: BCX7353-302 Part: Disposition of Subjects



Abbreviations: eCRF = electronic case report form; ITT = intent to treat; N/n = number of subjects.
[a] Includes the subject not dosed and not included in the safety population.
Notes:
A subject was considered to have completed study drug dosing in Part 1 if he/she had been randomized to Part 2 or had completed ≥ 168 days of dosing.
A subject was considered a Part 1 completer if he/she completed the Week 24 visit in the eCRF.

Baseline data

A majority of patients were recruited at North American sites, 71.9% overall, with 28.1% from European sites. Almost all study patients were White (93.4%) in total. Ninety-five percent of study participants (n =115/121) were adults of whom 9 (7.4%) were aged over 65 years. Only 6 adolescent patients were enrolled in the study, 2 in each treatment group. Adolescent participants could only enrol at North American study sites. There were no participants aged over 75.

A majority of study participants were female ranging from 73.2% in the Berotralstat 110mg group to 57.5% in the Berotralstat 150mg group (See Table 12).

All 121 subjects randomized met the required diagnostic criteria prior to study entry. The majority of subjects (88%) had C4 values < LLN with C1-INH functional levels < 50%. C1-INH functional levels (C1-INH-f) were measured at screening and C1-INH antigen (C1-INH-Ag) levels at baseline. Two subjects had levels C1-INH-f levels > 50% at screening but less than the LLN (74%). Both subjects had C1-INH-Ag levels that were < 10% at baseline.

The mean subject age at the first onset of HAE symptoms was 10.7 years (range 0.5 to 55 years). Fifty-two percent of subjects experienced their first HAE symptoms before the age of 12 years, and 33% of subjects had their first HAE symptoms during adolescence (defined as ages of 12 to 17 years). Subjects had HAE symptoms for a mean of almost 10 years before receiving a diagnosis of HAE. Overall, the mean age at the time of diagnosis of HAE was approximately 20 years (range 0.5 to 67 years). In a few subjects, the diagnosis was made prior to the onset of symptoms when subjects were screened due to family member diagnosis. Eighty-four percent of subjects had a family history of HAE with 89% of these having a parent with a confirmed diagnosis of HAE.

The 3 most common anatomic regions reported where swelling occurred during HAE attacks over the year prior to screening were stomach and abdomen (97%), hands and arms (93%), and feet and legs (88%). Most subjects reported having had a laryngeal attack (74%) in the past, and the mean (SD) number of lifetime laryngeal attacks they reported was 9.8 (± 15.6) attacks. Thirty percent of subjects reported having had a laryngeal attack in the year prior to screening. This varied from 24.4% for Berotralstat 110mg, 22.5% for Berotralstat 150mg and 42.5% for placebo.

Table 22: Baseline demographic and disease characteristics by treatment group

	Berotralstat 110 mg (N = 41)	Berotralstat 150 mg (N = 40)	Placebo (N = 40)
Region			
Europe	9 (22%)	13 (32.5%)	12 (30%)
North America	32 (78%)	27 (67.5%)	28 (70%)
Sex			
Female	30 (73.2%)	23 (57.5%)	27 (67.5%)
Male	11 (26.8%)	17 (42.5%)	13 (32.5%)
Mean age (SD) at consent	40.4 (17.51)	40 (13.98)	44.5 (14.12)
Age distribution			
12 – 17 years	2 (4.9%)	2 (5%)	2 (5%)
18 - 64 years	34 (82.9%)	37 (92.5%)	35 (87.5%)
65 – 74 years	5 (12.2%)	1 (2.5%)	3 (7.5%)
Age at onset first symptoms (years)			
Mean (SD)	9.8 (7.16)	11.2 (5.93)	11 (8.89)
Age at diagnosis (years)			
Mean (SD)	19.2 (15.18)	18.6 (12.63)	22.1 (12.93)

Baseline investigator confirmed attack rate ≥ 2 attacks/month < 2 attacks/month	28 (68.3%) 13 (31.7%)	30 (75%) 10 (25%)	27 (67.5%) 13 (30%)
Baseline investigator confirmed attack rate (attacks/month measured from start of screening to first dose of study drug)[a] Mean (SD) Median (range)	2.97 (1.36) 2.9 (0.86, 6.09)	3.06 (1.56) 2.7 (0.86, 6.67)	2.91 (1.12) 3 (1.27, 6.22)
Laryngeal attack ever Subject has had a laryngeal attack past year Estimated number of laryngeal attacks past year Mean (SD)	30 (73.2%) 10 (24.4%) 2 (1.49)	26 (65%) 9 (22.5%) 2.2 (2.39)	34 (85%) 17 (42.5%) 2.4 (1.73)
Commonest symptoms of HAE attacks Abdominal pain Substantial fatigue Nausea	39 (97.5%) 30 (75%) 32 (80%)	39 (97.5%) 34 (85%) 31 (77.5%)	38 (95%) 32 (80%) 32 (80%)
Any past prophylactic treatment for HAE	32 (78%)	30 (75%)	29 (72.5%)
Prior androgen use Yes No	19 (46.3%) 22 (53.7%)	22 (55%) 18 (45%)	25 (62.5%) 14 (35%)

a. Baseline attack HAE attack rate was calculated from the e-diary data over the period from screening to first dose of study drug and was expressed as attacks per month where 1 month = *28 days as follows*

Numbers analysed

The intent to treat (ITT) population included all randomized subjects, regardless of whether study treatment was administered (see Table 28). This population was the primary population for the analysis of the efficacy and health outcomes data. Data were analysed according to randomized treatment.

Table 23: BCX7353-302 Part 1: Summary of Analysis Populations (ITT Population)

Population	Berotralstat			Placebo	Total
	110 mg (N = 41) n (%)	150 mg (N = 40) n (%)	All Active (N = 81) n (%)	(N = 40) n (%)	(N = 121) n (%)
ITT	41 (100.0%)	40 (100.0%)	81 (100.0%)	40 (100.0%)	121 (100.0%)
Safety	41 (100.0%)	40 (100.0%)	81 (100.0%)	39 (97.5%)	120 (99.2%)
PP	38 (92.7%)	37 (92.5%)	75 (92.6%)	33 (82.5%)	108 (89.3%)
Completers	40 (97.6%)	38 (95.0%)	78 (96.3%)	36 (90.0%)	114 (94.2%)
PD	41 (100.0%)	38 (95.0%)	79 (97.5%)	39 (97.5%)	118 (97.5%)
PK-PD	41 (100.0%)	38 (95.0%)	79 (97.5%)	39 (97.5%)	118 (97.5%)

Abbreviations: ITT = intent to treat; N = number of subjects; n = number of subjects who experienced the event; PD = pharmacodynamic; PK = pharmacokinetic; PP = per protocol.
Source: Table 14.1.2.1.

Outcomes and estimation

Descriptive statistics

There were 492, 402, and 601 subject-reported attacks in the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. Almost all subjects reported an attack (40/41 in the Berotralstat 110mg arm, 37/40 in the Berotralstat 150mg treatment arm and 39/41 in the placebo arm). Of the subject-reported attacks, approximately 90% were also investigator-confirmed attacks: 443, 357, and 508 investigator-confirmed attacks in the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The percentage of investigator confirmed attacks that were treated were slightly lower for those treated with Berotralstat 150 mg (80%) compared to Berotralstat 110mg (86.9%) and placebo (88.4%). Descriptive statistics are shown in the following Table for subject reported and investigator confirmed attack rates.

Table 24: HAE attack summary by treatment group (subject reported and investigator confirmed) showing number of subjects with an attack, number of attacks, and number of treated attacks by treatment group.

	Berotralstat 110mg N = 41	Berotralstat 150mg N = 40	Placebo N = 40
Subject reported attacks No. subjects with ≥ 1 attack, n (%)	40 (97.6%)	37 (92.5%)	39 (97.5%)
No. of attacks	492	402	601
Total no. of treated attacks (% of total subject-reported attacks)	413 (83.9%)	336 (83.6%)	531 (88.4%)
Investigator-confirmed attacks No.subjects with ≥ 1 attack, n (%)	40 (97.6%)	37 (92.5%)	38 (95%)

No. of attacks	443	357	508
Total no. of treated attacks (% of total subject-reported attacks)	385 (86.9%)	311 (80%)	449 (88.4%)

Concomitant SOC-Rx used to treat HAE attacks during Part 1 are summarized in Table 30. A similar proportion of attacks were treated with SOC-Rx for all the treatment groups, in the ITT population (around 87%) treating 87% of all investigator-confirmed attacks with any SOC-Rx. Both Berotralstat groups used 'Any C1-INH' more frequently to treat an HAE attack than the placebo group (48.5% Berotralstat 110mg, Berotralstat 150mg 54.9% and placebo 36.4% of attacks). The most commonly used SOC-Rx were Firazyr (icatibant) and Berinert (C1-INH) in the berotralstat 110 mg '(41% and 29% of attacks, respectively) and placebo (59% and 18% of attacks, respectively) treatment groups. The subjects in the berotralstat 150 mg treatment group used Berinert (42% of attacks) most commonly and more frequently and used Firazyr (38% of attacks) less frequently compared with the other 2 treatment groups.

Table 25: BCX7353-302 Part 1: Concomitant Medications Taken for HAE Attacks (ITT Population)

Concomitant Medications for HAE Attacks	Berotralstat		Placebo (N = 40) n (%)	Total (N = 121) n (%)
	110 mg (N = 41) n (%)	150 mg (N = 40) n (%)		
Number of investigator-confirmed attacks	443	357	508	1308
Any SOC-Rx concomitant treatment for HAE [b]	385 (86.9%)	310 (86.8%)	446 (87.8%)	1141 (87.2%)
Berinert	127 (28.7%)	150 (42.0%)	91 (17.9%)	368 (28.1%)
Cinryze	44 (9.9%)	27 (7.6%)	69 (13.6%)	140 (10.7%)
Firazyr	183 (41.3%)	135 (37.8%)	299 (58.9%)	617 (47.2%)
Kalbitor	1 (0.2%)	0	0	1 (< 0.1%)
Ruconest	49 (11.1%)	20 (5.6%)	26 (5.1%)	95 (7.3%)
Any C1-INH [c]	215 (48.5%)	196 (54.9%)	185 (36.4%)	596 (45.6%)
Any non-targeted medication for HAE	2 (0.5%)	6 (1.7%)	5 (1.0%)	13 (1.0%)
Pain medication	2 (0.5%)	6 (1.7%)	4 (0.8%)	12 (0.9%)
Other	0	0	1 (0.2%)	1 (< 0.1%)

Abbreviations: C1-INH = complement 1 esterase inhibitor; e-diary = electronic diary; HAE = hereditary angioedema; ITT = intent to treat; N = number of subjects; n = number of subjects experiencing the event.
a Medications were as recorded in the e-diary for each attack. The percentages provided were based on the number of investigator-confirmed attacks.
b Medications displayed were those HAE medications recorded on the e-diary that were taken concomitantly with study drug for an investigator-confirmed attack in Part 1. If a medication was used more than once for a given investigator-confirmed attack, a single occurrence was summarized.
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. Subjects may have more than 1 medication that they use for HAE.

Primary endpoint

The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to first dose in Part 2). Investigator-confirmed attack rates for the ITT population are summarized in Table 31. The primary efficacy endpoint was assessed after the last subject completed Part 1 (had taken the first dose in Part 2). The negative binomial analysis estimated attack rates per 28 days were 1.65 for berotralstat 110 mg subjects, 1.31 for berotralstat 150 mg subjects, and 2.35 for placebo subjects over the 24-week Part 1 dosing period. The study met its primary endpoint for both dose levels, with the 110 and 150 mg berotralstat doses reducing the HAE attack rate by 30% (p = 0.024) and 44% (p < 0.001), respectively, compared with placebo.

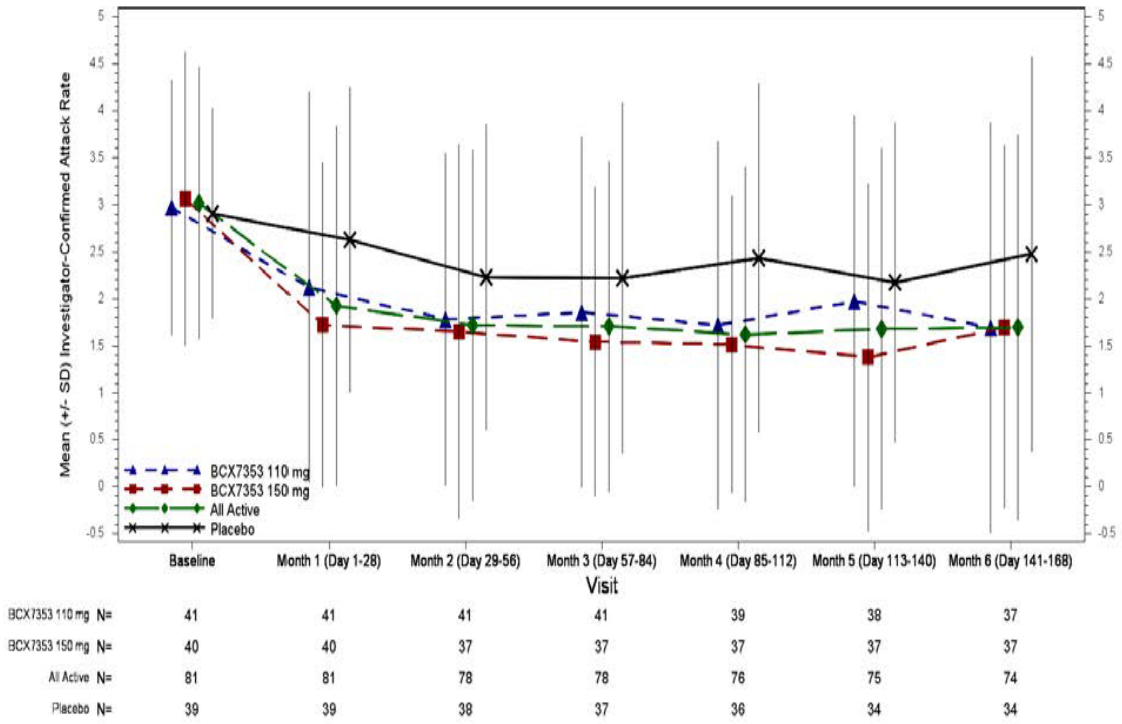
Table 26: BCX7353-302 Part 1: Summary of Investigator-confirmed Attack Rates (Entire Dosing Period) (ITT Population)

	Berotralstat						Placebo n = 40
	110 mg; N = 41			150 mg; N = 40			
Primary Endpoint	Rate per 28 days[b]	Rate reduction % from placebo (95% CI)	P-value	Rate per 28 days[b]	Rate reduction % from placebo (95% CI) ji	P-value	Rate per 28 days[b]
Investigator confirmed attack rate[a]	1.65	-30.0% (-48.7, -4.6)	0.024	1.31	-44.2% (-59.5, -23.0)	< 0.001	2.35

Abbreviations: CI = confidence interval; HAE = hereditary angioedema; ITT = intent to treat; N = number of subjects.
a Investigator-confirmed attack rate was defined as (total number of investigator-confirmed HAE attacks experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time of dose in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or date of last dose in Part 1] - date of first dose in Part 1 + 1).
b Statistical analysis was based on a negative binomial regression model. The number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline investigator-confirmed attack rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

The investigator-confirmed attack rate by month is shown in Figure 10 and table 32. After an initial decrease upon starting study drug, attack rates remained consistently lower for study drug vs. placebo across the 24-week dosing period.

Figure 10: BCX7353-302 Part 1: Plot of Mean Investigator-confirmed Attack Rate by Month (ITT Population)



Abbreviations: BCX7353 = berotralstat; ITT = intent to treat; N = number of subjects; SD = standard deviation.
Source: Figure 14.2.2.3.

Table 27: BCX7353-302 Part 1: Summary of Rate of Investigator-confirmed Attacks by Month During Part 1 (ITT Population)

		Observed			Change from baseline		
		Berotralstat 110mg n = 41	Berotralstat 150mg n = 40	Placebo n = 40	Berotralstat 110mg n = 41	Berotralstat 150mg n = 40	Placebo n = 40
Baseline attack rate N		41	40	39			
Mean (SD)		2.97 (1.36)	3.06 (1.56)	2.91 (1.12)			
M 1 attack rate N		41	40	39	41	40	39
Mean (SD)		2.12 (2.08)	1.72 (1.73)	2.63 (1.62)	-0.85 (1.84)	-1.34 (1.74)	-0.28 (1.54)
M 2 attack rate N		41	37	38	41	37	38

Mean (SD)		1.78 (1.77)	1.65 (1.99)	2.23 (1.62)	-1.19 (1.57	-1.52 (1.86)	-0.68 (1.46)
M 3 attack rate N		41	37	37	41	37	37
Mean (SD)		1.86 (1.86)	1.54 (1.64)	2.22 (1.86)	-1.12 (1.48)	-1.63 (1.64)	-0.66 (1.67)
M 4 attack rate N		39	37	36	39	37	36
Mean (SD)		1.72 (1.96)	1.51 (1.57)	2.43 (1.85)	-1.24 (1.77)	-1.65 (1.36)	-0.47 (1.67)
M 5 attack rate N		38	37	34	38	37	34
Mean (SD)		1.97 (1.97)	1.38 (1.85)	2.18 (1.70)	-0.96 (1.43)	-1.79 (1.75)	-0.67 (1.48)
M 6 attack rate N		37	37	34	37	37	34
Mean (SD)		1.69 (2.18)	1.70 (1.93)	2.48 (2.10)	-1.29 (1.93)	-1.47 (1.75)	-0.37 (1.75)

Sensitivity analyses

Two sensitivity analyses of the primary endpoint using the PP and completer populations were performed as well as analysis using subject reported attacks. In addition, three sensitivity analyses were performed in the ITT population as follows:

1. A missing data sensitivity analysis was conducted in which observed data post study drug discontinuation were included in attack rate determination.
2. A missing data sensitivity analysis was conducted in which observed data post study drug discontinuation were used in combination with imputed data for subjects who discontinued study treatment prior to the end of Part 1 and did not continue to record HAE attacks.
3. A tipping point analysis was conducted in which observed data post study drug discontinuation were combined with imputed data for subjects who discontinued study treatment prior to the end of Part 1 and did not continue to record HAE attacks.

All 6 sensitivity analyses of treatment with both doses of berotralstat were supportive of the primary analysis outcomes (results for 150 mg presented in Figure 11; ad-hoc figure).

Sensitivity Analysis Including Observed Data Post-treatment Discontinuation

This sensitivity analysis was supportive of the primary endpoint for both dose levels, with the 110 and 150 mg doses reducing HAE attacks by 31% (95% CI: 5.7, 49.0; p = 0.020) and 42% (95% CI: 20.3, 57.8; p < 0.001), respectively, vs. placebo. The negative binomial analysis estimated attack rates per

28 days were 1.60 for berotralstat 110 mg, 1.34 for berotralstat 150 mg, and 2.31 for placebo over the 24-week Part 1 dosing period.

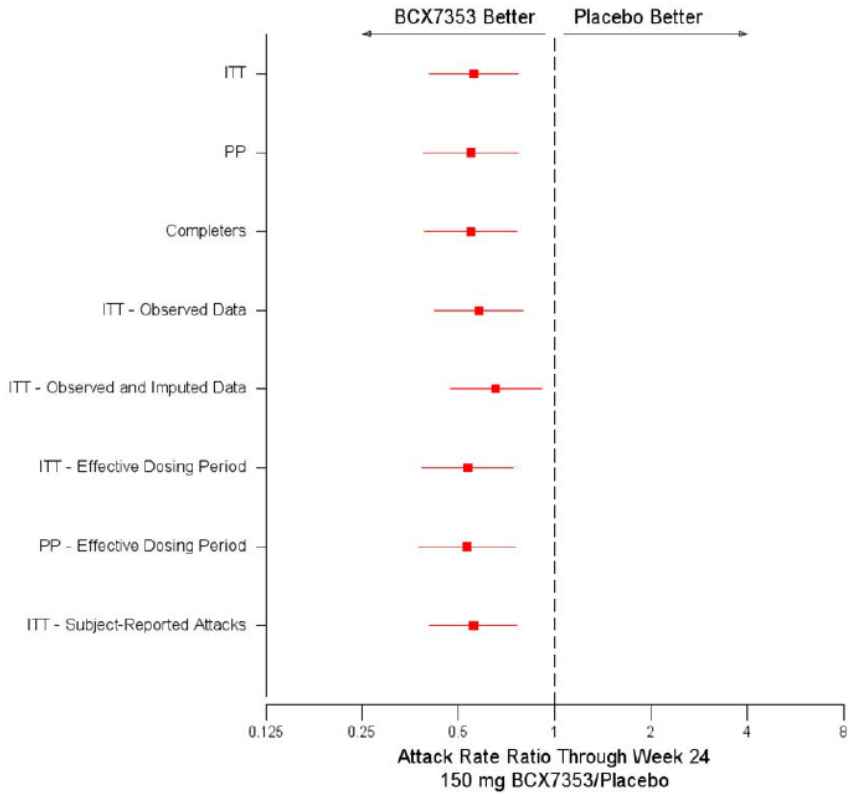
Sensitivity Analysis Including Observed Data Post-treatment Discontinuation and Imputing Missing Data Post-treatment Discontinuation

This sensitivity analysis was supportive of the primary endpoint for both dose levels, with the 110 and 150 mg doses reducing HAE attacks by 31% (95% CI: 4.9, 50.0; p = 0.023) and 35% (95% CI: 9.2, 52.9; p = 0.011), respectively, vs. placebo. The negative binomial analysis estimated attack rates per 28 days were 1.64 for berotralstat 110 mg subjects, 1.55 for berotralstat 150 mg subjects, and 2.37 for placebo subjects over the 24-week Part 1 dosing period.

Missing Data Sensitivity Analysis: Tipping Point Analysis on the Rate of Investigator-confirmed Attacks

In this analysis observed data post-treatment discontinuation were combined with imputed data for subjects who discontinued study treatment prior to the end of Part 1 and did not continue to provide attack information. However, for this analysis the imputed attack rates were multiplied by a factor, δ, for subjects on active treatment. No such factor was used for imputation of missing data for subjects on placebo treatment. The tipping point was estimated as the value of δ that tips the analysis to non-significant. It shows how much greater than expected the attack rate on active treatment would need to be for the missing data to alter the result of the analysis. The 110 and 150 mg doses require a δ of 3 and 2, respectively, to alter the results of the primary analysis.

Figure 11: BCX7353-302 Part 1: Forest Plot of Results of Sensitivity Analyses of Investigator-confirmed Attack Rate for Entire Dosing Period and Effective Dosing Period, 150 mg Berotralstat (ITT, PP, and Completers Populations; Ad-hoc Figure)



Abbreviations: BCX7353 = berotralstat; HAE = hereditary angioedema; ITT = intent to treat; PP = per protocol.
Notes: The investigator-confirmed attack rate was defined as the total number of investigator-confirmed HAE attacks experienced in the period of interest adjusted for the length of a month (defined as 28 days) and the number of days during that period. The subject-reported attack rate was defined similarly for subject-reported HAE attacks.

Secondary endpoints

Change from Baseline in Angioedema Quality of Life Questionnaire Total Score at Week 24

The AE-QoL scores range from 0 to 100, and a decrease (change with a negative value) in AE-QoL questionnaire scores indicates an improvement in the subject's QoL. The MCID for the AE-QoL questionnaire is -6 (total score). All treatment groups had an average QoL improvement that exceed the MCID. The LSM differences from placebo in AE-QoL total scores were -2.8 (95% CI: -10.1, 4.5; p = 0.453) and -4.9 (95% CI: -12.2, 2.4; p = 0.188) for the berotralstat 110 and 150 mg treatment groups, respectively. The differences from placebo were not statistically significant. A hierarchical approach was used for statistical testing. As the secondary endpoint for change from baseline in Angioedema Quality of Life Questionnaire Total Score at week 24 was not met p values for the remaining secondary endpoints are nominal and no inference can be drawn.

Table 28: BCX7353-302 Part 1 AE QoL scores at Week 24

	Change from baseline		
Week 24 visit	Berotralstat 110mg N = 41	Berotralstat 150mg N = 40	Placebo n = 40
n	40	38	36
AE-QoL total score LSM (SE)	-12.46 (2.53)	-14.59 (2.592)	-9.69 (2.643)
LSM difference from placebo (95% CI)	-2.77 (-10.08, 4.53)	-4.9 (-12.23, 2.43)	
P value	0.453	0.188	

Number and Proportion of Days with Angioedema Symptoms Through 24 Weeks

As the first secondary endpoint did not meet statistical significance, the p values for subsequent efficacy endpoints can only be reported as nominal. The mean (SD) number of days subjects had angioedema symptoms from investigator-confirmed attacks was 20.8 (± 19.22), 19.4 (± 21.50), and 29.2 (± 24.29) days in the 24-week treatment period for the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The LSM (SE) proportion of days subjects had angioedema symptoms from investigator-confirmed attacks were 0.134 (0.0191), 0.119 (0.0194), and 0.197 (0.0196) days over the 24-week treatment period for the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The differences from the placebo treatment in the LSM proportion of the 169 days of treatment with angioedema symptoms were -0.062 (95% CI: -0.117, -0.008; nominal p = 0.025; approximately 10 more symptom-free days over the 6 months of Part 1) and -0.078 (95% CI: -0.133, -0.023; nominal p = 0.006; approximately 13 more symptom-free days over the 6 months of Part 1) for the berotralstat 110 mg and 150 mg groups, respectively.

Rate of Investigator-confirmed HAE Attacks During Dosing in the Effective Treatment Period

The rate of investigator confirmed attacks for the effective treatment period gives an analysis of the efficacy of active treatment after berotralstat had reached steady-state concentrations in subjects given the effective half-life of 150 mg berotralstat in Study BCX7353-106 of 89 hours. The reductions in attack rate relative to the placebo treatment group were 30% (95% CI: 4.3, 49.3; nominal p = 0.026) and 47% (95% CI: 25.6, 61.5; nominal p < 0.001) for the berotralstat 110 and 150 mg treatment groups, respectively (Table 34). Similar results were observed for the PP population. The treatment effects observed with berotralstat in this analysis were similar to those determined for the entire dosing period.

Table 29: BCX7353-302 Part 1: Rate of Investigator-confirmed Attacks During Effective Treatment Period (ITT Population)

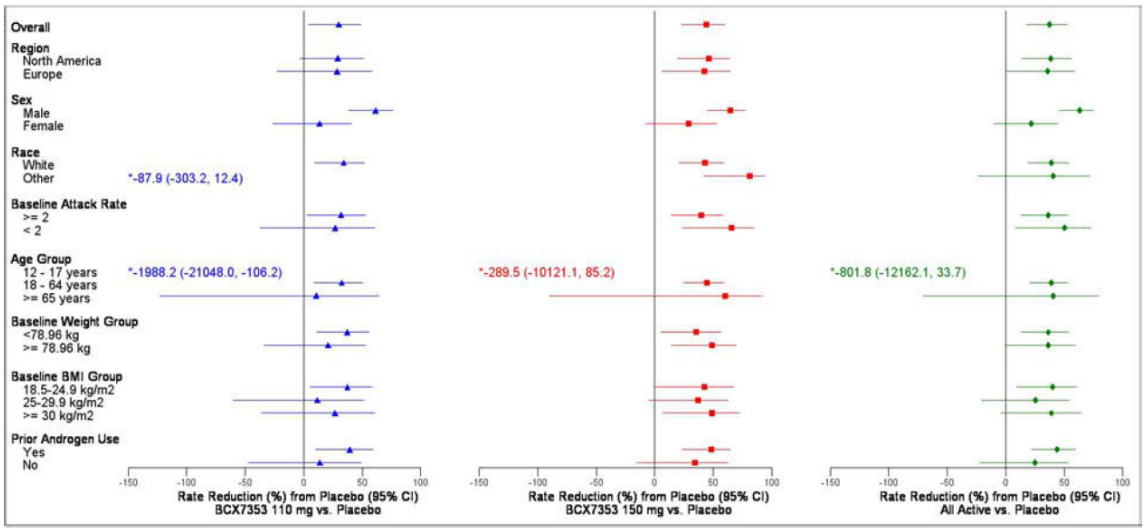
Attack Rate During Effective Treatment Period	Berotralstat		Placebo (N = 40)
	110 mg (N = 41)	150 mg (N = 40)	
Investigator-confirmed attack rate [a]			
N	41	40	39
Mean (SD)	1.918 (1.7345)	1.552 (1.6390)	2.490 (1.6135)
Median	1.383	1.037	2.420
Range	0 to 7.78	0 to 7.43	0 to 7.43
Negative binomial regression analysis [b]			
Estimated rate	1.65	1.27	2.38
Attack rate ratio (relative to placebo)	0.70	0.54	-
P-Value	0.026	< 0.001	-
Rate reduction from placebo	30.4%	46.5%	-
95% CI about rate reduction	4.3, 49.3	25.6, 61.5	-

Abbreviations: CI = confidence interval; HAE = hereditary angioedema; ITT = intent to treat; N = number of subjects; SD = standard deviation.
a Investigator-confirmed attack rate during the effective treatment period was defined as (total number of investigator-confirmed HAE attacks experienced in the period between Study Day 8 in Part 1 and the first dose date/time in Part 2 [or the last dose date/time in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or last dose date in Part 1] – date of Study Day 8 in Part 1 + 1).
b Statistical analysis was based on a negative binomial regression model. The number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline investigator confirmed attack rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

Ancillary analyses

Prespecified subgroup analyses of the primary efficacy endpoint were performed for region, sex, race, baseline attack rate, and age group. Ad-hoc exploratory subgroup analyses included prior androgen use, baseline weight, and baseline BMI. The study was not designed or powered to make definitive statements about efficacy by subgroup. Results of the sub-group analyses are presented with a Forest plot (Figure 12)

Figure 12: BCX7353-302 Part 1: Forest Plot of Results of Subgroup Analyses of Investigator-confirmed Attack Rate for Entire Dosing Period, Percent Rate Reduction from Placebo (ITT Population; Included Ad-hoc Subgroups)



Abbreviations: BCX7353 = berotralstat; BMI = body mass index; CI = confidence interval; eCRF = electronic case report form; HAE = hereditary angioedema; ITT = intent to treat; SAP = Statistical Analysis Plan.

A subgroup analysis by age group is uninterpretable given the small number of adolescents and older persons recruited to the study and the large placebo effect for adolescents (Table 35).

Table 30: BCX7353-302 Part 1: Summary of Investigator-confirmed Attack Rates by Subgroups (ITT Population; With Ad-hoc Subgroups) Age-group

Subgroup Investigator confirmed attack rate a	Berotralstat								Placebo	
	110 mg; N = 41				150 mg; N = 40				N = 40	
	N	Rate per 28 days b	Active vs. Placebo %	P-value	N	Rate per 28 days b	Active vs. Placebo %	P-value	N	Rate per 28 days b
Overall	41	1.65	-30.0%	0.024	40	1.31	-44.2%	<0.001	40	2.35
12 – 17 yrs	2	0.6	1988.2%	0.010	2	0.11	289.5%	0.415	2	0.03
18 – 64 yrs	34	1.74	-32.5%	0.011	37	1.44	-44.4%	<0.001	35	2.59
⩾ 65 years	5	1.39	-10.7%	0.809	1	0.62	-60.2%	0.248	3	1.56

In the sub-group analysis by sex males experienced a larger reduction in HAE attack rate than females. Males in the berotralstat 110 and 150 mg treatment groups had a 61% ($p < 0.001$) and 65% ($p < 0.001$) attack rate reduction compared with males in the placebo group (Table 32b). Females in the berotralstat 110 and 150 mg treatment groups had a 13% ($p = 0.454$) and 29% ($p = 0.102$) attack rate reduction compared with females in the placebo group (Table 36). This was the only subgroup analysis with a consistent difference between subgroups v placebo for both doses of active treatment compared to placebo.

Table 31: BCX7353-302 Part 1: Summary of Investigator-confirmed Attack Rates by Subgroups (ITT Population; With Ad-hoc Subgroups)

Subgroup Investigator confirmed attack rate a	Berotralstat								Placebo	
	110 mg; N = 41				150 mg; N = 40				N = 40	
	N	Rate per 28 days b	Active vs. Placebo %	P-value	N	Rate per 28 days b	Active vs. Placebo %	P-value	N	Rate per 28 days b
Overall	41	1.65	-30.0%	0.024	40	1.31	-44.2%	<0.001	40	2.35
Male	11	0.99	-61.4%	<0.001	17	0.91	-64.6%	<0.001	13	2.56
Female	30	1.92	-13.4%	0.454	23	1.58	-28.8%	0.102	26	2.21

Table 37, containing an analysis of baseline and on-study investigator-confirmed attack rates by subgroup, shows that male subjects in the placebo group had a minor change from a baseline investigator-confirmed mean (SD) attack rate of 2.86 attacks per month (± 0.93) to 2.70 attacks per month (± 1.03) during placebo treatment in Part 1. Female subjects in the placebo group had a larger change from baseline of 2.93 attacks per month (± 1.22) to 2.35 attacks per month (± 1.83) during placebo treatment. An ad-hoc multiple regression analysis looking at the relationship of sex, among other potential covariates, to the on-study attack rate found that sex was not a significant predictor of the on-study attack rate. This same regression analysis identified that the baseline attack rate was a significant predictor of the on-study attack rate, and females in the berotralstat 150 mg treatment group had a higher mean (SD) baseline attack rate of 3.4 (± 1.6) attacks per month relative to the total group (3.0 [± 1.4] attacks per month) while the baseline attack rate for males in the berotralstat 150 mg treatment group (2.7 [± 1.4] attacks per month) was lower.

Table 32: BCX7353-302 Part 1: Baseline Investigator-confirmed Attack Rates and Post-treatment Investigator-confirmed Attack Rates in Males and Females (ITT Population, Ad-hoc Analysis)

	Berotralstat 110mg n = 41		Berotralstat 150mg n = 40		Placebo n = 40	
Baseline investigator-confirmed attack rate per month a,b	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Males	11	3.03 (1.28)	17	2.67 (1.44)	13	2.86 (0.93)
Females	30	2.95 (1.4)	23	3.35 (1.6)	26	2.93 (1.22)
Investigator-confirmed attack rate per month c						
Males	11	1.31 (1.08)	17	1.31 (1.55)	13	2.7 (1.03)
Females	30	2.12 (1.85)	23	1.87 (1.74)	26	2.35 (1.83)

a Ad-hoc analysis.
b Baseline investigator-confirmed attack rate was defined as (total number of investigator-confirmed HAE attacks experienced in the period between screening and first date/time of study drug) × 28/(date of first dose - date of screening + 1).
c Investigator-confirmed attack rate was defined as (total number of investigator-confirmed HAE attacks experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or last dose date in Part 1] - date of first dose in Part 1 + 1).

Summary of main efficacy results

Table 33: Summary of efficacy for Study BCX7353-302

<table>
<tr><td colspan="3">Title: A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema</td></tr>
<tr><td>Study identifier</td><td colspan="2">BCX7353-302</td></tr>
<tr><td rowspan="4">Design</td><td colspan="2">BCX7353-302 was designed as a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of berotralstat administered at doses of 110 mg or 150 mg QD to reduce the frequency of attacks in subjects with Type 1 or 2 HAE over 24 weeks (Part 1). Following week 24, subjects continued study drug: placebo subjects were re-randomized to active treatment (110 mg or 150 mg berotralstat); subjects initially randomized to active drug continued on their assigned dose through 48 weeks.</td></tr>
<tr><td>Duration of main phase:</td><td>24 weeks</td></tr>
<tr><td>Duration of Run-in phase:</td><td>14 to 56 days</td></tr>
<tr><td>Duration of Extension phase:</td><td>24 weeks (total 48 weeks)</td></tr>
<tr><td>Hypothesis</td><td colspan="2">The primary study hypothesis was that the treatment effect in reduction of HAE attacks during 24 weeks of prophylactic berotralstat will be superior to placebo.</td></tr>
<tr><td rowspan="3">Treatments groups</td><td>Berotralstat 110 mg</td><td>Berotralstat 110 mg administered orally QD for 24 weeks, N = 41</td></tr>
<tr><td>Berotralstat 150 mg</td><td>Berotralstat 150 mg administered orally QD for 24 weeks, N = 40</td></tr>
<tr><td>Placebo</td><td>Placebo administered orally QD for 24 weeks, N = 40</td></tr>
</table>

Table 33: Summary of efficacy for Study BCX7353-302 (Continued)

Endpoints and definitions	Primary endpoint	Primary - Rate Reduction	The rate of investigator-confirmed HAE attacks during dosing in the entire 24 week treatment period of Part 1.	
	Secondary endpoint	First Secondary – AE-QoL	Change from baseline in AE-QoL at Week 24 (total score)	
	Secondary endpoint	Second Secondary – Symptom Days	Number and proportion of days with angioedema symptoms through 24 weeks	
	Secondary endpoint	Third Secondary – Attack Rate – After Steady State	Rate of investigator-confirmed HAE attacks during dosing in the effective treatment period	
Database lock	09 May 2019			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Intent to treat population at 24 weeks			
Descriptive statistics and estimate variability	Treatment group	Berotralstat 110 mg	Berotralstat 150 mg	Placebo
	Number of subjects	41	40	40
	Mean investigator-confirmed attacks per 28 days	1.90	1.63	2.47
	SD	1.71	1.66	1.60

Table 33: Summary of efficacy for Study BCX7353-302 (Continued)

Effect estimate per comparison	Primary endpoint	Comparison groups	Berotralstat 110 mg	Berotralstat 150 mg
		Attack rate reduction from placebo over first 24 weeks	30.0%	44.2%
		95% CI	4.6, 48.7	23.0, 59.5
		P-value	0.024	< 0.001
	First Secondary – AE-QoL	Comparison groups	Berotralstat 110 mg	Berotralstat 150 mg
		AE-QoL total score change from baseline to Week 24 difference from placebo	-2.77	-4.90
		95% CI	-10.08, 4.53	-12.23, 2.43
		P-value	0.453	0.188
	Second Secondary – Symptom Days	Comparison groups	Berotralstat 110 mg	Berotralstat 150 mg
		Proportion of days with angioedema symptoms during first 24 weeks difference from placebo	-0.062	-0.078
		95% CI	-0.117, -0.008	-0.133, -0.023
		P-value	0.025	0.006
	Third Secondary – Attack Rate – After Steady State	Comparison groups	Berotralstat 110 mg	Berotralstat 150 mg
		Attack rate reduction from placebo during effective dosing period (Day 8 to Week 24)	30.4%	46.5%
		95% CI	4.3, 49.3	25.6, 61.5
		P-value	0.026	< 0.001

Table 33: Summary of efficacy for Study BCX7353-302 (Continued)

Notes	Secondary endpoints were analysed using hierarchical testing. Although the primary efficacy endpoint of the study was met, results for the first secondary endpoint, AE-QoL, were not statistically significant vs. placebo for either treatment group; therefore, formal statistical testing for significance was not performed on the descending secondary efficacy endpoints. Days without angioedema symptoms and the attack rate during the effective treatment period were both reduced in the berotralstat 150 mg group compared with the placebo group and are reported using nominal p-values
Analysis description	Primary and Secondary
	For the investigator-confirmed attack rate endpoints, entire dosing period in Part 1 and effective treatment period in Part 1, the rate reduction from placebo was estimated from a negative binomial regression model where the number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline investigator-confirmed attack rate was included as a covariate and the logarithm of duration on treatment was included as an offset variable. For the change from baseline in AE-QoL total score at Week 24, the difference was the LSM difference from a mixed-model repeated measures analysis with investigator-confirmed baseline attack rate, baseline AE-QoL, treatment group, visit and visit × treatment group interaction included as fixed effects, and subject included as a random effect. For the proportion of days with angioedema symptoms, the difference was the LSM difference from an ANCOVA model with baseline investigator-confirmed attack rate as a covariate and treatment included as a fixed effect. The 95% CI was the 95% CI for the rate reduction or difference as generated from the models noted

Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; ANCOVA = analysis of covariates; BCX7353 = berotralstat; CI = confidence interval; HAE = hereditary angioedema; LSM = least squares mean; QD = once daily; SD = standard deviation.

Supportive study

BCX7353-301 A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dose Levels of BCX7353 as an Oral Treatment for the Suppression of Events in Subjects with Hereditary Angioedema

Study BCX7353-301 is a small randomised double blind placebo controlled trial conducted in Japanese patients with a similar design, inclusion and exclusion criteria, treatment arms, and primary endpoint to Study BCX7353-302. Study BCX7353-204 is an ongoing uncontrolled phase 2, open label study to evaluate long-term safety, in which effectiveness is evaluated as a secondary endpoint.

The study was conducted at 10 sites in Japan and has a similar design to Study BCX7353-302 but with a smaller population enrolled. The applicant has presented results for Part 1 of the Study which concluded at 24 weeks. Part 2 of the study is ongoing.

Study participants

Inclusion and exclusion criteria were similar to those for Study BCX7353-302.

Treatments

The treatment arms were the same as those for Study BCX7353-302.

Objectives

The primary objective of Part 1 the study was to determine the efficacy of berotralstat 110 and 150 mg QD administered for 24 weeks compared to placebo in the suppression of angioedema events in subjects with HAE.

The efficacy related secondary objectives were to: assess the effects of berotralstat on HAE disease activity and angioedema event characteristics; and evaluate the effects of berotralstat on QoL.

Outcomes/endpoints

The primary efficacy endpoint of the study was: the rate of expert-confirmed angioedema events during dosing in the entire 24-week treatment period (Days 1 to 168). Secondary efficacy endpoints were as follows: number and proportion of days with angioedema symptoms through 24 weeks; rate of expert-confirmed angioedema events during dosing in the effective treatment period (beginning on Day 8 through to the first dose of study drug in Part 2; change from baseline (CFB) in Angioedema Quality of Life questionnaire (AE-QoL) at Week 24 (total score).

Randomisation and blinding

Subjects were randomized via the interactive (web or voice) response system (IXRS) in a 1:1:1 (active: active: placebo) ratio, with enrolment stratified by the baseline angioedema event rate over the period from screening to randomization (≥ 2 events per month vs. < 2 events per month (similar to Study 302).

This was a double-blind study throughout Part 1. As such, study drug assignment was blinded to the investigator, study staff, study subjects, and clinical research organization staff. Sponsor employees were also blinded to the treatment allocation of individual subjects, with the exception of sponsor staff responsible for managing clinical supplies. Employees who were not blinded to drug assignment had no access to any other subject-level information for the duration of the study.

Statistical methods

Statistical Analysis Plan

The study 301 SAP was almost identical to that for study 302. The SAP also detailed pre-specified pooled analyses of the part 1 301 and 302 study data. The pooled analyses used identical methods as for study 301, unless otherwise stated.

SAP v1.0 is dated 04 November 2019 and is based on Protocol Version 5.0 dated 29 August 2019. The database was locked to conduct the Part 1 analysis on 6 December 2019.

The applicant highlighted a number of changes in the planned analyses in the Part 1 Interim CSR.

Changes from protocol-specified analyses included the following:

- The definition of the screen failure population has changed from subjects not dispensed treatment to those who are not randomized and are reported as screen failures in the eCRF.
- The definition of the PP population has been altered to include ≥ 85% treatment compliance as an inclusion requirement.
- Part 1 is defined as Day 1 to first dose of Part 2 rather than Day 1 through Day 168.
- The entire dosing period for Part 1 is defined as Day 1 to first dose of Part 2 rather than Day 1 through Day 168 and Day 1 through Day 168 + 24 hours.

A number of post-hoc analyses were also performed.

Analysis Populations

As for study 302.

Analysis of the Primary Efficacy Endpoint

As for study 302, except a negative binomial regression model rather than a Poisson regression model was to be used for the primary analysis.

Expert confirmed angioedema events from Study 301 and investigator-confirmed HAE attacks from Study 302 were considered equivalent for the pooled analysis and were collectively referred to as “confirmed HAE events” in this CSR.

Analysis of the Secondary Efficacy Endpoints

As for study 302.

Type I error control

As for study 302 4 endpoints were included in the confirmatory testing strategy. For each endpoint, 2 potential doses were to be tested against placebo. The 4 endpoints were to be tested in a hierarchical fashion, with the 2 doses being tested using the Hochberg step-up procedure at each level of the hierarchy.

The testing hierarchy for study 301 was as follows:

1. The rate of expert-confirmed HAE events during dosing in the entire 24-week treatment period (Day 1 to Day 168)
2. Number and proportion of days with angioedema symptoms through 24 weeks
3. Rate of expert-confirmed HAE events during dosing in the effective dosing period (beginning on Day 8 through 24 weeks)
4. Change from baseline in AE-QoL at Week 24 (total score)

Multicentre Studies

There were no adjustments made based on multiple centres.

Interim analyses

No interim analyses for efficacy were planned during part 1 of the study.

Subgroup analyses – 301

No subgroup analyses were planned due to the small sample size.

Subgroup analyses – Combined study 301 & 302

Subgroup analyses for the primary and secondary endpoints for the combined study 301 and 302 data were to be provided by:

1. Sex
2. Race (white vs. other)
3. Baseline event rate (≥ 2 events/month vs. < 2 events/month)
4. Age group (12 - 17, 18 to 64, ≥ 65 years)
5. Region (North America vs. Japan vs. rest of world)

6. Weight (< median vs. ≥ median)
7. BMI (18.5 to 24.9 kg/m2 vs. 25 to 29.9 kg/m2 vs. ≥ 30 kg/m2)
8. Prior androgen use (yes vs. no)

A summary of TEAEs by age group was also to be provided.

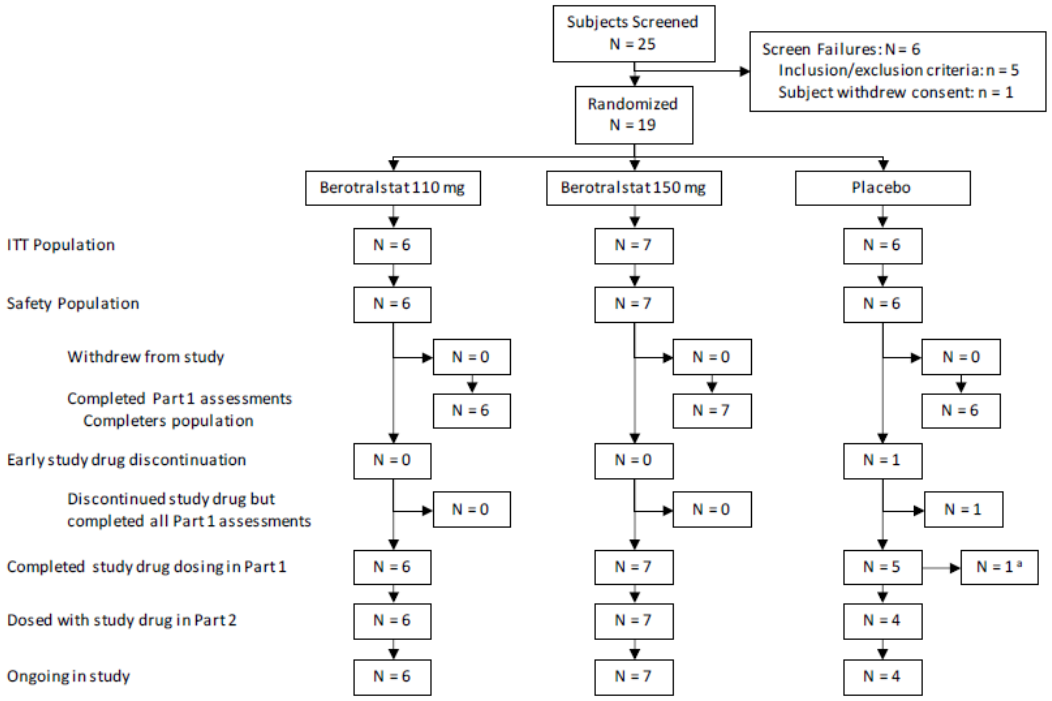
Results

Participant flow

Overall, a total of 25 subjects were screened, 19 subjects were randomized (ITT population), and all 19 subjects (100%) were treated (safety population): 6, 7, and 6 subjects in the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. Of the 6 screen failures who were not enrolled in the study, 5 subjects did not meet ≥ 1 IC and/or met ≥ 1 EC and 1 subject withdrew consent

A total of 18 subjects (95%) completed study drug dosing in Part 1: 6 berotralstat 110 mg subjects (100%), 7 berotralstat 150 mg subjects (100%), and 5 placebo subjects (83%). No subjects in the 110 and 150 mg berotralstat treatment groups discontinued study drug.

Figure 13: BCX7353-301 Part 1: Disposition of Subjects



Abbreviations: ITT = intent to treat; N/n = number of subjects.
[a] One subject withdrew consent after the completion of Part 1 but prior to the initiation of dosing in Part 2.

Six patients had a major protocol deviation (Berotralstat 110 mg n = 1, berotralstat 150mg n = 3 and placebo n = 2)). It was determined that none of the major protocol deviations resulted in inappropriate subject selection or affected the overall quality or interpretation of the study data.

Baseline data

Overall, 84% of subjects were female (Table 39). The majority (95%) of subjects were adults aged 18 to 64 years and one was aged between 65 and 74 years. The mean age was 42.1 years (range 21 to 69 years). Most subjects were Asian (95%), with 1 subject with race unknown but of Hispanic or Latino ethnicity (5.3%) enrolled (in the 150 mg dose group).

Table 34: Baseline demographic and disease characteristics by treatment group Study BCX7353-301

	Berotralstat 110 mg (N = 6)	Berotralstat 150 mg (N = 7)	Placebo N = 6
Sex Female Male	 5 (83.3%) 1 (16.7%)	 6 (85.7%) 1 (14.3%)	 5 (83.3%) 1 (16.7%)
Mean age (SD) at consent	47.3 (15.03)	37.3 (9.05)	42.3 (13.52)
Age at onset first symptoms (years) Mean (SD) Age at diagnosis (years) Mean (SD)	 10.83 (8.377) 34.17 (19.031)	 19.57 (7.161) 28.86 (7.734)	 20.00 (15.786) 30.17 (16.940)
Baseline investigator confirmed attack rate ≥ 2 attacks/month < 2 attacks/month	 2 (33.3%) 4 (66.7%)	 4 (57.1%) 3 (42.9%)	 3 (50.0%) 3 (50.0%)
Baseline expert confirmed angioedema event rate (attacks/month measured from start of screening to first dose of study drug) Mean (SD) Median (range)	 2.42 (1.29) 1.85 (1.31, 4.52))	 1.97 (1.07) 2.19 (0.82, 3.94)	 2.5 (1.5) 2.17 (0.89, 5.31)
Subject has had a laryngeal attack past year Estimated number of laryngeal attacks past year Mean (SD)	3 (50%) 1 (0.00)	0 0	3 (50.0%) 2.7 (1.53)
Any past prophylactic treatment for HAE	5 (83.3%)	6 (85.7%)	4 (66.7%)
Prior androgen use Yes	 0	 2 (28.6%)	 1 (16.7%)

Numbers analysed

The ITT population included all randomized subjects, regardless of whether study treatment was administered. This population was the primary population for the analysis of the efficacy and health outcomes data. Data were analysed according to randomized treatment. The ITT population was the same as the randomised population.

Outcomes and estimation

All subjects reported at least 1 attack and all had at least 1 investigator confirmed attack. The number of investigator confirmed attacks was highest in the placebo arm (n = 94) followed by the berotralstat 110mg treatment arm (n = 71) and the berotralstat 150mg treatment arm (n = 46) respectively (Table 40).

Table 35: HAE attack summary by treatment group (subject reported and investigator confirmed) Study BCX7353-301

	Berotralstat 110mg N = 6	Berotralstat 150mg N = 7	Placebo N = 6
Subject reported attacks No.subjects with ≥ 1 attack, n (%)	6 (100%)	7 (100.0%)	6 (100.0%)
No. of attacks	81	53	107
Total no. of treated attacks (% of total subject-reported attacks)	67 (82.7%)	37 (69.8%)	90 (84.1%)
Investigator-confirmed attacks No.subjects with ≥ 1 attack, n (%)	6 (100%)	7 (100.0%)	6 (100.0%)
No. of attacks	71	46	94
Total no. of treated attacks (% of total subject-reported attacks)	63 (88.7%)	34 (73.9%)	83 (88.3%)

The primary efficacy endpoint was the rate of expert-confirmed angioedema events during dosing in the entire 24-week treatment period (Day 1 to first dose in Part 2). The primary efficacy endpoint was assessed after the last subject completed Part 1. Expert-confirmed angioedema event rates for the ITT population are summarized in Table 41. The study met its primary endpoint for the 150 mg dose level, and there was a clear dose response, with the 110 and 150 mg berotralstat doses reducing the rate of angioedema events by 25% (p = 0.181) and 49% (p = 0.003), respectively, compared with placebo. The negative binomial analysis estimated event rates per 28 days were 1.64 for berotralstat 110 mg subjects, 1.11 for berotralstat 150 mg subjects, and 2.18 for placebo subjects over the 24-week Part 1 dosing period.

Table 36: BCX7353-301 Part 1: Summary of Expert-confirmed Angioedema Event Rates (Entire Dosing Period) (ITT Population)

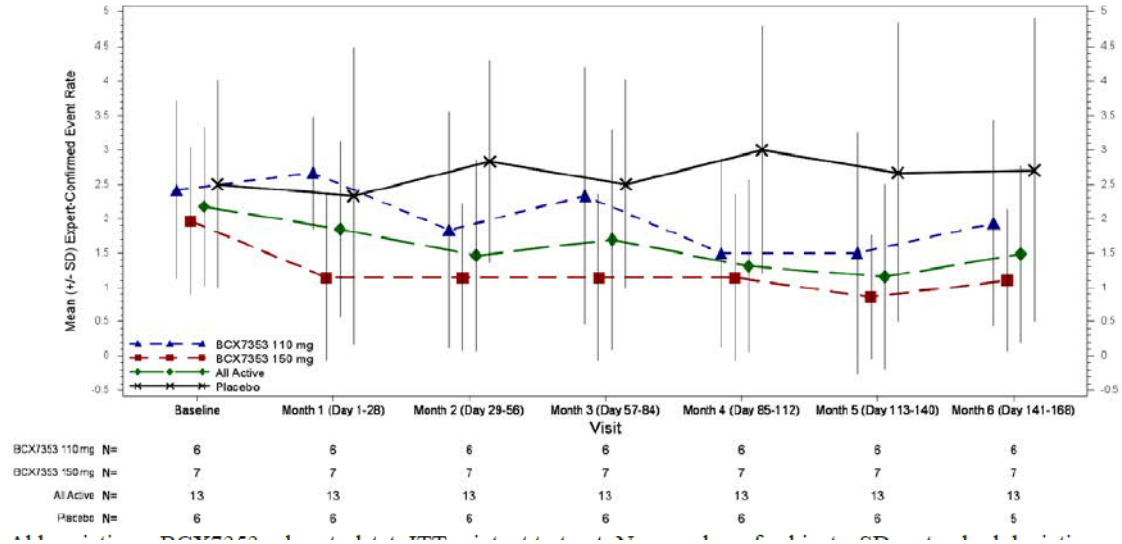
Primary Endpoint	Berotralstat 110 mg; N = 6			Berotralstat 150 mg; N = 7			Placebo N = 6
	Rate per 28 days [b]	Active vs. Placebo % (95% CI)	P-value	Rate per 28 days [b]	Active vs. Placebo % (95% CI)	P-value	Rate per 28 days [b]
Expert-confirmed angioedema event rate [a]	1.64	-24.6% (-50.1, 14.0)	0.181	1.11	-49.1% (-67.5, -20.4)	0.003	2.18

Abbreviations: CI = confidence interval; HAE = hereditary angioedema; ITT = intent to treat; N = number of subjects

Expert-confirmed angioedema event rate was defined as (total number of expert-confirmed angioedema events experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time of dose in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or date of last dose in Part 1] - date of first dose in Part 1 + 1). b Statistical analysis was based on a negative binomial regression model. The number of expert-confirmed angioedema events was included as the dependent variable, the treatment was included as a fixed effect, baseline expert-confirmed event rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

One subject discontinued study drug prior to the end of Part 1 but remained on study and continued to provide event data post-treatment discontinuation. This sensitivity analysis was supportive of the primary endpoint for both dose levels, with the 110 and 150 mg doses reducing angioedema events by 25% (95% CI: -12.9, 49.6; p = 0.171) and 49% (95% CI: 21.1, 67.2; p = 0.003), respectively, vs. placebo. The negative binomial analysis estimated event rates per 28 days were 1.64 for berotralstat 110 mg subjects, 1.11 for berotralstat 150 mg subjects, and 2.18 for placebo subjects over the 24-week Part 1 dosing period.

Figure 14: BCX7353-301 Part 1: Plot of Mean Expert-confirmed Angioedema Event Rates by Month (ITT Population)



Secondary endpoints were analysed using hierarchical testing as shown in Table 42. The primary efficacy endpoint of the study was met for the 150 mg dose level, allowing testing of the first secondary endpoint of proportion of days with angioedema symptoms during Part 1 at the 150 mg dose level only; the results for the first secondary endpoint were not statistically significant vs. placebo for the berotralstat 150 mg treatment group; therefore, formal statistical testing for significance was not performed on the descending secondary efficacy endpoints. The angioedema event rate during the effective treatment period and the AE-QoL total score at Week 24 were both improved in both

berotralstat treatment groups compared with the placebo group and are reported using nominal p-values.

Table 37: BCX7353-301 Part 1: Summary of Hierarchical Testing for Efficacy Endpoints (ITT Population)

Endpoint Type Efficacy Variable	Treatment Group	Rate Reduction/ Difference from Placebo [a]	95% CI [b]	Unadjusted P-value	Hochberg Adjusted α Level	Statistical Significan
Primary endpoint						
Expert-confirmed event rate (entire dosing period in Part 1)	Berotralstat 110 mg (N = 6)	24.6%	-14.0, 50.1	0.181	0.050	No
	Berotralstat 150 mg (N = 7)	49.1%	20.4, 67.5	0.003	0.025	Yes
Secondary endpoints						
Proportion of days with angioedema symptoms in Part 1	Berotralstat 110 mg (N = 6)	0.018	-0.143, 0.179	0.814	NA	NA
	Berotralstat 150 mg (N = 7)	-0.122	-0.280, 0.036	0.120	0.025	No
Expert-confirmed event rate (effective treatment period in Part 1)	Berotralstat 110 mg (N = 6)	24.5%	-14.7, 50.3	0.188	NA	NA
	Berotralstat 150 mg (N = 7)	47.6%	17.7, 66.6	0.005	NA	NA
AE-QoL total score - CFB to Week 24	Berotralstat 110 mg (N = 6)	-12.65	-33.33, 8.03	0.213	NA	NA
	Berotralstat 150 mg (N = 7)	-19.00	-39.00, 0.99	0.061	NA	NA

Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; ITT = intent to treat; LSM= least squares mean; NA = n applicable

a. For the expert-confirmed angioedema event rate endpoints, entire dosing period in Part 1 and effective treatment period in Part 1, the rate reduction from placebo was estimated from a negative binomial regression model where the number of expert-confirmed angioedema events was included as the dependent variable, the treatment was included as a fixed effect, baseline expert-confirmed event rate was included as a covariate and the logarithm of duration on treatment was included as an offset variable. For the CFB in AE-QoL total score at Week 24, the difference was the LSM difference from a mixed-model repeated measures analysis with expert-confirmed baseline event rate, baseline AE-QoL, treatment group, visit and visit × treatment group interaction included as fixed effects, and subject included as a random effect. For the proportion of days with angioedema symptoms, the difference was the LSM difference from an ANCOVA model with baseline expert-confirmed event rate as a covariate and treatment included as a fixed effect.
b. The 95% CI was for the rate reduction or difference as generated from the models noted in footnote a.
c. A comparison was considered statistically significant if the unadjusted p-value was less than the corresponding Hochberg adjusted α level.

Ancillary analysis

No subgroup analyses were conducted.

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant pooled results from Study 302 and 301.This pooling would appear to have been done to fulfil requirements for the Japanese regulatory authority.

A prespecified statistical analysis was conducted using combined data from Study 301 and BCX7353-302 (Study 302), the pivotal Phase 3 efficacy and safety study, in the evaluation of efficacy. Expert-confirmed HAE events from Study 301 and investigator-confirmed HAE attacks from Study 302 were considered equivalent for the combined analysis and are collectively referred to as “confirmed HAE events”.

The study design was similar for both studies with some slight difference in the secondary endpoints. Differences between recruited populations have been discussed in the assessment of Study 301.

Combined subject disposition

Overall, a total of 185 subjects were screened, 140 subjects were randomized (ITT population), and 139 of these subjects (99%) were treated (safety population). A total of 126 subjects (90%) completed study drug dosing in Part 1: 43 berotralstat 110 mg subjects (92%), 44 berotralstat 150 mg subjects (94%), and 39 placebo subjects (85%). Among the subjects in the 110 and 150 mg berotralstat treatment groups, 3 (6.4%) and 1 (2.1%) subjects, respectively, discontinued study drug due to a laboratory abnormality or AE, 1 (2.1%) and 1 (2.1%) subjects, respectively, discontinued study drug due to perceived lack of efficacy, and 0 and 1 (2.1%) subject, respectively, withdrew consent. Among the placebo-treated subjects, 1 subject (2.2%) discontinued study drug due to a laboratory abnormality or AE, 2 subjects (4.3%) discontinued study drug due to perceived lack of efficacy, 1 subject (2.2%) withdrew consent, and 1 subject (2.2%) discontinued for other (subject’s choice) reasons. One subject in the placebo treatment group discontinued at the end of Part 1. A total of 125 of 126 subjects who completed study drug dosing in Part 1 continued into Part 2 of the studies.

Baseline characteristics

The baseline event rate is shown in Table 29 and is similar for all treatment groups. The percentage with 2 or more baseline attacks/months was highest in those treated with berotralstat 150mg (72.3%) compared to berotralstat 110mg (63.8%) and placebo (65.2%).

Primary Efficacy Endpoint

The primary efficacy endpoint was the rate of confirmed HAE events during dosing in the entire 24-week treatment period (Day 1 to first dose in Part 2). The primary efficacy endpoint was assessed after the last subject completed Part 1 (had taken the first dose in Part 2).

The combined analysis met the primary endpoint for both dose levels, with the 110 and 150 mg berotralstat doses reducing HAE events by 30% ($p = 0.013$) and 46% ($p < 0.001$), respectively, compared with placebo. The negative binomial analysis estimated event rates per 28 days were 1.65 for berotralstat 110 mg subjects, 1.27 for berotralstat 150 mg subjects, and 2.34 for placebo subjects over the 24-week Part 1 dosing period.

Table 38: Combined BCX7353-301 and BCX7353-302 Part 1: Summary of Confirmed HAE Event Rates (Entire Dosing Period) (Combined ITT Population)

Primary Endpoint	Berotralstat 110 mg; N = 47			Berotralstat 150 mg; N = 47			Placebo N = 46
	Rate per 28 days [b]	Active vs. Placebo % (95% CI)	P-value	Rate per 28 days [b]	Active vs. Placebo % (95% CI)	P-value	Rate per 28 days [b]
Confirmed HAE event rate [a]	1.65	-29.5% (-46.6, -7.1)	0.013	1.27	-45.6% (-59.1, -27.7)	< 0.001	2.34

Abbreviations: CI = confidence interval; HAE = hereditary angioedema; ITT = intent to treat; N = number of subjects.

[a] Confirmed HAE event rate was defined as (total number of confirmed HAE events experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time of dose in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or date of last dose in Part 1] - date of first dose in Part 1 + 1).

[b] Statistical analysis was based on a negative binomial regression model. The number of confirmed HAE events was included as the dependent variable, the treatment was included as a fixed effect, baseline confirmed HAE event rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

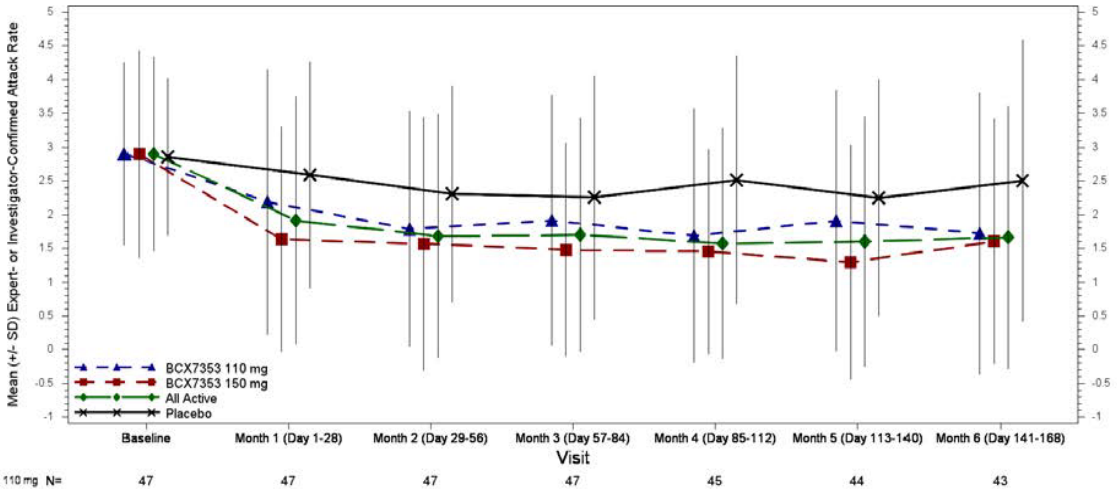
Source: Table 14.2.1.4.1.C.

A number of sensitivity analyses were conducted using similar methods to those for Study 302 and Study 301. All sensitivity analyses were supportive. However, the sensitivity analysis using observed data post-treatment discontinuation and imputing missing data post-treatment discontinuation showed a reduction in effect size. for Berotralstat 150mg. The 110 and 150 mg doses reduced HAE events by 31% (95% CI: 7.6, 47.8; p = 0.012) and 39% (95% CI: 18.0, 54.4; p = 0.001), respectively, vs. placebo. The negative binomial analysis estimated event rates per 28 days were 1.64 for berotralstat 110 mg subjects, 1.44 for berotralstat 150 mg subjects, and 2.36 for placebo subjects over the 24-week Part 1 dosing period.

Confirmed HAE Events Over Time

The confirmed HAE event rate by month is shown in Figure 15 and table 44 for the combined ITT population. After an initial decrease upon starting study drug, event rates remained consistently lower for berotralstat vs. placebo across the 24-week dosing period.

Figure 15: Combined BCX7353-301 and BCX7353-302 Part 1: Plot of Mean Confirmed HAE Event Rates by Month (Combined ITT Population)



BCX7353 110 mg	N=	47	47	47	47	45	44	43
BCX7353 150 mg	N=	47	47	44	44	44	44	44
All Active	N=	94	94	91	91	89	88	87
Placebo	N=	45	45	44	43	42	40	39

Abbreviations: BCX7353 = berotralstat; HAE = hereditary angioedema; ITT = intent to treat; N = number of subjects; SD = standard deviation.
Source: Figure 14.2.2.3.C.

In the combined ITT population, the effects of berotralstat in reducing event rate were evident in Month 1 and stable over the 6-month duration of Part 1 (Table 44). The berotralstat 150 mg treatment group had a mean event rate of 2.9 events per month at baseline that decreased to 1.64 events per month by the end of Month 1 and held relatively steady through Month 6 with mean event rates of 1.57, 1.48, 1.46, 1.3, and 1.6 events per month at the ends of Months 2, 3, 4, 5, and 6, respectively (Table 63). There was a slight increase at Month 6 similar to the pattern seen in Study 302 and is probably driven by the larger Study 302 population. It is unclear whether the increase in event rate at 6 months is the start of a trend or due to random variation.

Table 39: Combined BCX7353-301 and BCX7353-302 Part 1: Summary of Rate of Confirmed HAE Events by Month During Part 1 (Combined ITT Population)

Visit event rate	Observed			Change from baseline		
	Berotralstat 110mg	Berotralstat 150mg	Placebo	Berotralstat 110mg	Berotralstat 150mg	Placebo
Baseline event rate [a]						
N	47	47	45			
Mean (SD)	2.9 (1.35)	2.9 (1.54)	2.85 (1.16)			
Median (range)	2.55 (0,86, 6.09)	2.47 (0.82, 6.67)	2.9 (0.89, 6.22)			
Month 1 event rate [b]						
N	47	47	45	47	47	45
Mean (SD)	2.19 (1.96)	1.64 (1.66)	2.59 (1.68)	-0.71 (1.77)	-1.26 (1.63)	-0.27 (1.48)
Median (range)	2 (0, 8.0)	1 (0, 7.0)	2 (0, 6.0)	-0.86 (-4.0, 4.0)	-1.10 (-6.59, 2.22)	-0.24 (-4.42, 2.42)
Month 2 event rate [b]						
N	47	44	44	47	44	44
Mean (SD)	1.79 (1.74)	1.57 (1.87)	2.31 (1.60)	-1.11 (1.52)	-1.41 (1.73)	-0.54 (1.41)
Median (range)	1 (0.0, 8.0)	1 (0.0, 8.0)	2.0 (0, 6.0)	-1.08 (-4.94', 4.0)	-1.29 (-5.59, 2.1)	-0.28 (-4.67, 2.27)
Month 3 event rate [b]						
N	47	44	43	47	44	43
Mean (SD)	1.92 (1.85)	1.48 (1.58)	2.26 (1.80)	-0.99 (1.46)	-1.50 (1.54)	-0.57 (1.57)
Median (range)	1 (0.0, 7.0)	1 (0.0, 7.0)	2.0 (0.0, 8.0)	-0.86 (-4.94, 1.53)	-1.30 (-5.6, 1.2)	-0.53 (-4.42, 3.16)
Month 4 event rate [b]						
N	45	44	42	45	44	42
Mean (SD)	1.69 (1.88)	1.46 (1.52)	2.51 (1.83)	-1.19 (1.72)	-1.52 (1.29)	-0.33 (1.61)
Median (range)	1 (0, 9.0)	1 (0, 7.0)	2 (0, 8.0)	-1.52 (-3.94, 5.0)	-1.29 (-5.59, 0.44)	-0.08 (-4.42, 2.89)
Month 5 event rate [b]						
N	44	44	40	44	44	40
Mean (SD)	1.91 (1.93)	1.30 (1.73)	2.25 (1.75)	-0.95 (1.37)	-1.68 (1.67)	-0.54 (1.51)

Median (range)	1 (0.0, 8.0)	1 (0.0, 8.0)	2 (0, 8.0)	-1.28 (-3.11, 4.0)	-1.29 (-6.59,1.33)	-0.6 (-4.42, 2.27)
Month 6 event rate [b]						
N	43	44	39	43	44	39
Mean (SD)	1.73 (2.08)	1.60 (1.82)	2.50 (2.09)	-1.17 (1.84)	-1.37 (1.69)	-0.29 (1.68)
Median (range)	0.97 (0.0, 8.69)	0.97 (0.0, 7.72)	1.93 (0.0, 8.69)	-1.52 (-4.73, 4.69)	-1.06 (-5.62, 1.85)	-0.34 (-4.67, 2.68)

Article I. Baseline confirmed HAE event rate was defined as the total number of confirmed HAE events experienced in the period between screening and first dose of study drug adjusted for the length of a month (defined as 2 days) and the number of days during that period (ie, Date of first dose - date of screening visit + 1).
Article II. Monthly event rate was defined as the total number of confirmed HAE events experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month.

Ancillary analyses

Subgroup analysis

A similar range of subgroup analysis were conducted in the combined population as in Study 302. Results for the subgroup analysis by sex and baseline event rate are presented below. The results of all the subgroup analyses are shown in the Forest plot (Figure 16). As expected for the pooled analysis (with only 1 additional male patient in each treatment arm) and similar to Study 302 an apparently poorer response is noted for females compared to males. For both berotralstat doses. In addition, a larger rate reduction percentage from placebo for berotralstat 150mg is seen in those with a lower baseline event rate compared to those with a higher baseline event rate.

HAE Event Rates by Subgroups (Combined ITT Population)

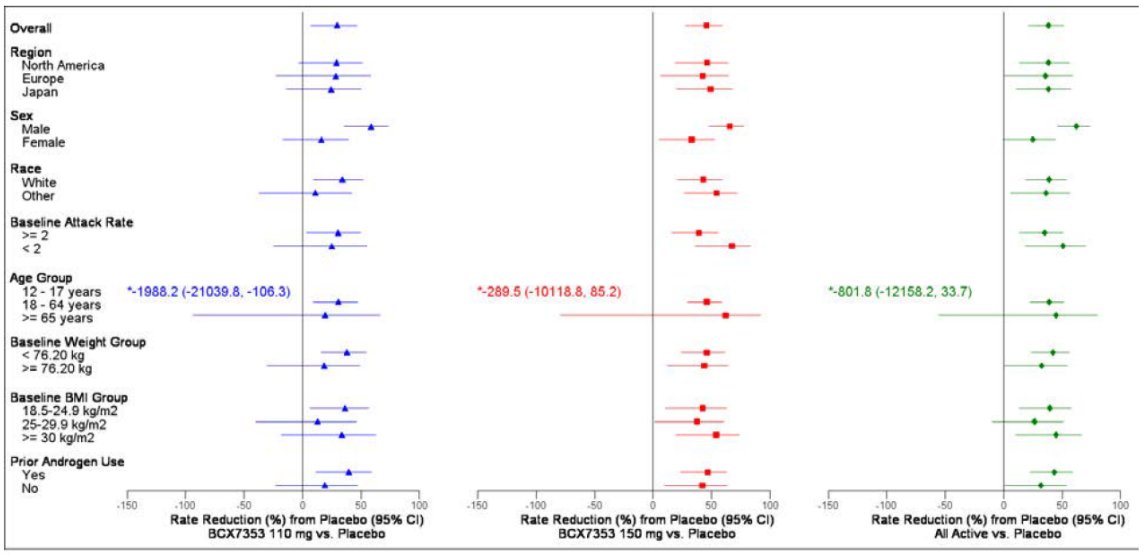
Table 40: Combined BCX7353-301 and BCX7353-302 Part 1: Summary of Confirmed

Subgroup	Berotralstat 110mg n = 47				Berotralstat 150 mg n = 47				Placebo n = 46	
Confirmed event rate a	N	Rate per 28 days b	Rate reduction (%) from placebo	P-value	N	Rate per 28 days b	Rate reduction (%) from placebo	P-value	N	Rate per 28 days b
Overall										
Sex										
Male	12	1.03	-58.6%	<0.001	18	0.85	-65.6%	<0.001	14	2.48
Female	35	1.89	-16.0%	0.296	29	1.51	-33.0%	0.024	31	2.25
Baseline event rate										
≥ 2/mnth	30	2.04	-30.4%	0.030	34	1.79	-39%	0.002	30	2.94
< 2 mnth	17	1.08	-25.1%	0.265	13	0.47	-67.4%	0.001	15	1.44

Confirmed event rate was defined as (total number of confirmed HAE events experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time of dose in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or date of last dose in Part 1] - date of first dose in Part 1 + 1).

b Model fit was questionable.

Figure 16: Combined BCX7353-301 and BCX7353-302 Part 1: Forest Plot of Results of Subgroup Analyses of Confirmed HAE Event Rate for Entire Dosing Period, Percent Rate Reduction from Placebo (Combined ITT Population)



Abbreviations: BCX7353 = berotralstat; BMI = body mass index; CI = confidence interval; eCRF = electronic case report form; HAE = hereditary angioedema; ITT = intent to treat.

Notes:
The confirmed HAE event rate was defined as the total number of confirmed HAE events experienced in the period of interest adjusted for the length of a month (defined as 28 days) and the number of days during that period.
* indicates a CI was too wide to display. Numbers given are the rate reduction (%) from placebo (95% CI).
Prior androgens were as noted on the HAE Medical and Medication History – Part 1 and Part 2 eCRFs. These medications included any of the following: androgens (unspecified), oxandrolone, methyl-testosterone, danazol (brand name = Danocrine), and stanozolol.

Secondary endpoints

Secondary endpoints were analysed using hierarchical testing as shown in Table 46. Statistical significance for the primary efficacy endpoint, first secondary endpoint (days with angioedema symptoms), and second secondary endpoint (event rate in effective dosing period) of the combined analysis were met; however, results for the final secondary endpoint, AE-QoL, were not statistically significant vs. placebo for either treatment group (Table 46).

The mean (SD) number of days subjects had angioedema symptoms from confirmed HAE events was 23.9 (± 22.68), 19.0 (± 20.64), and 30.8 (± 24.64) days in the 24-week treatment period for the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The LSM (SE) proportion of days subjects had angioedema symptoms from confirmed HAE events were 0.150 (0.0185), 0.118 (0.0185), and 0.203 (0.0189) days over the 24-week treatment period for the berotralstat 110 mg, berotralstat 150 mg, and placebo treatment groups, respectively. The differences from the placebo treatment in the LSM proportion of the 169 days of treatment with angioedema symptoms were -0.053 (95% CI: -0.105, 0.000; p = 0.048; approximately 9 more symptom-free days over the 6 months of Part 1) and -0.085 (95% CI: -0.138, -0.033; p = 0.002; approximately 14 more symptom-free days over the 6 months of Part 1) for the berotralstat 110 and 150 mg groups, respectively.

The rate of confirmed HAE events for the effective treatment period gives an analysis of the efficacy of active treatment after berotralstat had reached steady-state concentrations in subjects given the effective half-life of 150 mg berotralstat in Study 106 of 89 hours. The reductions in event rate relative

to the placebo treatment group were 30% (95% CI: 6.9, 47.1; p = 0.014) and 47% (95% CI: 29.3, 60.5; p < 0.001) for the berotralstat 110 and 150 mg treatment groups, respectively.

Table 41: Combined BCX7353-301 and BCX7353-302 Part 1: Summary of Hierarchical Testing for Efficacy Endpoints (Combined ITT Population)

Endpoint Type Efficacy Variable	Treatment Group	Rate Reduction/ Difference from Placebo [a]	95% CI [b]	Unadjusted P-value	Hochberg Adjusted α Level	Statistically Significant [c]
Primary endpoint						
Confirmed HAE event rate (entire dosing period in Part 1)	Berotralstat 110 mg (N = 47)	29.5%	7.1, 46.6	0.013	0.050	Yes
	Berotralstat 150 mg (N = 47)	45.6%	27.7, 59.1	< 0.001	0.050	Yes
Secondary endpoints						
Proportion of days with angioedema symptoms in Part 1	Berotralstat 110 mg (N = 47)	-0.053	-0.105, 0.000	0.048	0.050	Yes
	Berotralstat 150 mg (N = 47)	-0.085	-0.138, -0.033	0.002	0.050	Yes
Confirmed HAE event rate (effective treatment period in Part 1)	Berotralstat 110 mg (N = 47)	29.8%	6.9, 47.1	0.014	0.050	Yes
	Berotralstat 150 mg (N = 47)	47.2%	29.3, 60.5	< 0.001	0.050	Yes
AE-QoL total score - CFB to Week 24	Berotralstat 110 mg (N = 47)	-4.15	-11.05, 2.75	0.237	0.050	No
	Berotralstat 150 mg (N = 47)	-7.44	-14.31, -0.57	0.034	0.025	No

Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; HAE = hereditary angioedema; ITT = intent to treat; LSM= least squares mean.

[a] For the confirmed HAE event rate endpoints, entire dosing period in Part 1 and effective treatment period in Part 1, the rate reduction from placebo was estimated from a negative binomial regression model where the number of confirmed HAE events was included as the dependent variable, the treatment was included as a fixed effect, baseline confirmed HAE event rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable. For the CFB in AE-QoL total score at Week 24, the difference was the LSM difference from a mixed-model repeated measures analysis with confirmed baseline event rate, baseline AE-QoL, treatment group, visit and visit × treatment group interaction included as fixed effects, and subject included as a random effect. For the proportion of days with angioedema symptoms, the difference was the LSM difference from an ANCOVA model with baseline confirmed HAE event rate as a covariate and treatment included as a fixed effect.

[b] The 95% CI was for the rate reduction or difference as generated from the models noted in footnote a.

[c] A comparison was considered statistically significant if the unadjusted p-value was less than the corresponding Hochberg adjusted α level.

Clinical studies in special populations

Six adolescents were included in the Study 302 and 22in Study 204. No children less than 12 years old were included in any study. No patients aged over 75 appear to have been included in any study and only a small number aged 65-74.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	9/368	0/368	0/368
Non Controlled trials	18/526	0/526	0/526

BCX7353-204

Study BCX7353-204 is an ongoing uncontrolled phase 2, open label study to evaluate long-term safety, in which effectiveness is evaluated as a secondary endpoint. The study was conducted at multiple sites. The applicant has presented data from an interim analysis of a total of 227 study participants treated with either berotralstat 110mg (n =100) or berotralstat 150mg (n = 127). Apart from in South Korea patients were not allocated to the 110mg and 150mg doses by randomisation.

Study BCX7353-204 underwent a number of protocol changes and patients were recruited under different versions of the protocol. Initially only the 150mg dose, with the 110mg dose added under a later version of the protocol. In addition, the potential duration of the study is 96 weeks in the US and 240 weeks outside of the US.

Inclusion criteria also changed over the course of the study. All participants had Type 1 or 2 HAE and were either recruited from previous berotralstat studies or were new patients that it was thought could benefit from berotralstat treatment. Of note no baseline attack rate was calculated primarily as this was a safety study and no minimum baseline attack rate was required for inclusion in the study. In addition: 1) not all subjects entering the study had baseline measures collected as some subjects were enrolling from a previous berotralstat study; 2) some subjects were on prophylactic HAE medications at study entry; and 3) some subjects had recently discontinued androgens used as HAE prophylaxis, precluding an adequate attack rate collection period.

The spectrum of prohibited medications was narrowed during the conduct of the study based on safety information and DDI study data. In the most recent protocols, only drugs which worsened the underlying disease, those with narrow therapeutic indices with lack of drug level monitoring, those with known QT prolongation, and those whose efficacy may be significantly diminished by CYP inhibition are prohibited However, for version 6 of the protocol subjects who had switched from another prophylaxis were required to discontinue androgens at least 28 days prior to starting treatment with berotralstat; discontinue tranexamic acid and C1-INH dosing 14 days after berotralstat initiation; and the final dose of lanadelumab could be given with the first dose of berotralstat.

The secondary efficacy endpoints of the study according to version 7 of the protocol were:

- Number and rate of HAE attacks (described in the study report as adjusted HAE attacks*)
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms

- Patient-reported outcomes (HAE disease-specific AE-QoL questionnaire scores and TSQM Global Satisfaction scores)
- Number of attacks requiring attack medication
- Discontinuations due to lack of efficacy (through Week 48 only)
- Severity of attacks

Attacks were identified from paper diaries completed by study participants.

*Adjusted attacks must have included at least 1 symptom of swelling, have a response of 'no' to the diary question, 'In retrospect, could there be an alternative explanation for your symptoms other than an HAE attack (i.e. allergic reaction, viral cold etc.)?', and be unique (attack began > 24 hours from the end of the prior attack). Any attack that began within 24 hours from the end of a prior attack was combined with the prior attack. If the entire adjusted attack was untreated, it must have had a duration > 24 hours. (broadly similar to investigator confirmed attacks in Study 302 but with 48 hours rather than 24 hours).

Treatment administered participants were either treated with Berotralstat 110mg or berotralstat 150mg PO daily. Specific regions and/or countries initiated the study under different versions of the protocol, and consequently treatment allocation was based on the version of the protocol the sites were initiated under. Initially, the study was a single-arm study and all subjects received treatment with berotralstat 150 mg. (Protocol Version 1). Protocol Versions 2.0 through 5.0, subjects were initially allocated to 1 of 2 treatment groups:

Group 1: berotralstat 110 mg administered orally QD

Group 2: berotralstat 150 mg administered orally QD

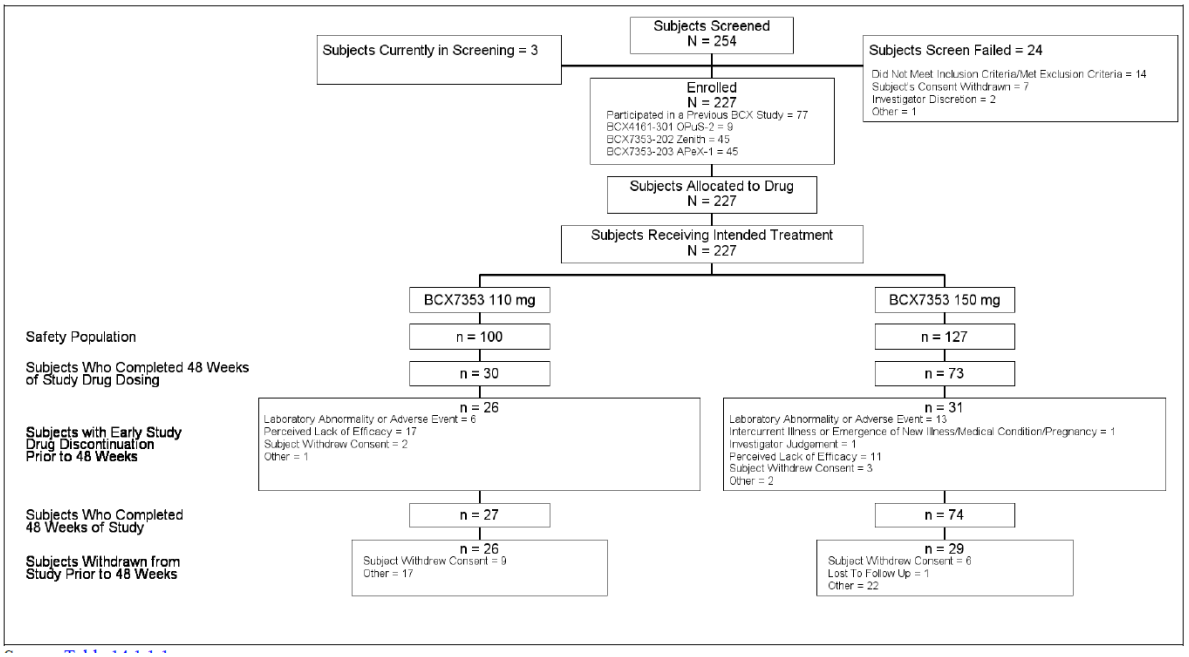
Subject disposition

As of the data cut off of 20 August 2019, a total of 168 subjects (74.0%) are ongoing in the study. Of the 227 subjects allocated and treated with study drug, 103 subjects (45.4%) have completed the Week 48 visit on study drug and an additional 67 subjects (29.5%) are continuing on berotralstat but have not yet reached 48 weeks of dosing.

Overall 59 study participants prematurely discontinued study drug, 26 (26%) in the Berotralstat 110mg treatment arm and 33 (26%) in the Berotralstat 150mg arm. The most common reason for discontinuation was perceived lack of efficacy.

A total of 28 subjects (12.3%), 17 of 100 subjects (17.0%) in the berotralstat 110-mg dose group and 11 of 126 subjects (8.7%) in the berotralstat 150-mg dose group, discontinued the study drug due to perceived lack of efficacy Twenty of the 28 subjects who discontinued study drug due to a perceived lack of efficacy discontinued prior to Week 12.

Figure 17: BCX7353-204: CONSORT Diagram



Demographics and baseline characteristics

227 study participants with a diagnosis of Type 1 or 2 HAE are included in the study report, 100 in the Berotralstat 110mg group and 127 in Berotralstat 150mg group.

Fifteen (15%) of those treated with Berotralstat 110mg had participated in a previous Berotralstat study and 61 (48%) of the Berotralstat 150mg treatment arm had previously participated in a Berotralstat study.

Overall, 10 adolescent subjects (4.4%) aged 12 to 17 years of age and 5 elderly subjects (2.2%) ≥ 65 years of age were enrolled in the study. The remainder were aged 18 to 64 years... Overall 61.2% of participants were female, with similar proportions in each treatment arm.

At screening, 81% of subjects reported that they had used prophylactic treatments for HAE in the past. Past prophylactic treatment included use of androgens (62.6% of subjects), tranexamic acid (33.9% of subjects), and any C1-INH (23.8% of subjects). A total of 26 subjects (11.5%) were taking medications for HAE prophylaxis at screening. By Day 169 (24 weeks) and Day 337 (Week 48), 13 (50%) and 8 (31%) of these subjects, respectively, remained on concomitant HAE prophylactic medications. Twenty eight percent had experienced laryngeal attacks in the year preceding the study.

Number and rate of HAE attacks

Baseline attack rates were not calculated for this study for the following reasons: (1) not all subjects entering the study had baseline measures collected as some subjects were rolling over from previous studies; (2) some subjects were on other prophylactic HAE medications; and (3) some subjects were discontinuing androgens that were used as HAE prophylaxis.

For the 150-mg dose group, the mean (SD) attack rate through week 48 was 1.36 (1.51) attacks per month and the median attack rate was 0.93 attacks per month. For the 110mg dose the mean (SD) attack rate was 1.161 (1.320) and median attack rate was 0.796 (See following Table)

Table 42: BCX7353-204: Summary of Adjusted HAE Attack Rates, Through Week 48 of Treatment (Safety Population)

Adjusted attacks per month: overall (attacks per month) a	Berotralstat 110mg N = 100	Berotralstat 150mg N = 127
Mean (SD)	1.161 (1.1320)	1.361 (1.5073)
Median (min, max)	0.796 (0, 4.67)	0.931 (0, 7.59)

a Monthly attack rate was defined as the total number of adjusted HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month.

Adjusted HAE Attack Rates Over Time

After the first month of treatment with berotralstat 150 mg, the mean (SD) attack rate was 1.64 (1.83) attacks per month. This rate was 1.38 (1.73) and 0.77 (1.00) attacks per month at Months 6 and 12, respectively. These rates include subjects who continued on study to the month of interest and could therefore have been affected by discontinuations due to perceived lack of efficacy (See Table 48).

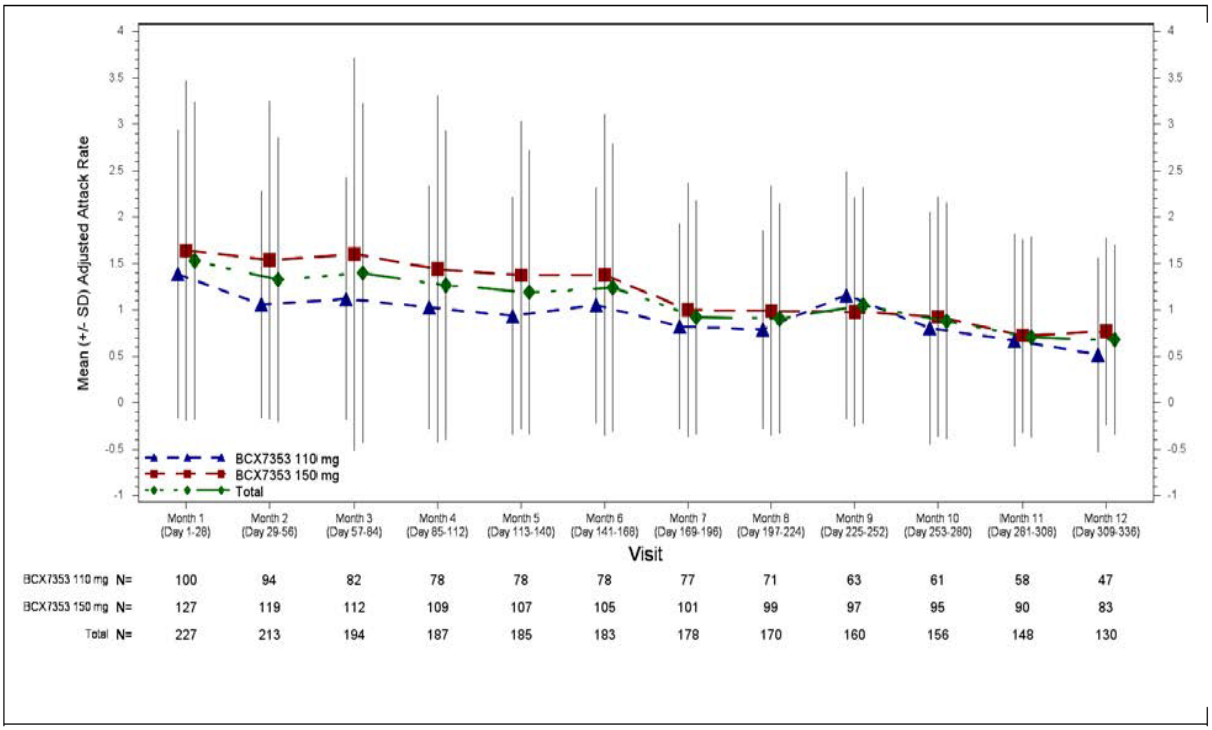
Table 43: Summary of response by month, adjusted attack rate

	Berotralstat 110mg n = 100	Berotralstat 500mg n = 127
Month 1 (D 1 to 28) N	100	127
Mean (SD)	1.387 (1.5536)	1.639 (1.8291)
Month 2 (D 29 to 56) N	94	119
Mean (SD)	1.059 (1.2249)	1.538 (1.7088)
Month 3 (D57 to 84) N	82	112
Mean (SD)	1.118 (1.3042)	1.601 (2.1101)
Month 4 (D85 to 112) N	78	109
Mean (SD)	1.026 (1.3091)	1.44 (1.863)
Month 5 (Day 113 to 140) N	78	107
Mean (SD)	0.936 (1.2826)	1.374 (1.6627)
Month 6 (Day 141 to 168) N	78	105
Mean (SD)	1.053 (1.2696)	1.377 (1.7281)
Month 7 (Day 169 to 196) N	77	101
Mean (SD)	0.822 (1.1052)	1 (1.3638)
Month 8 (Day 197 to 224) N	71	99
Mean (SD)	0.789 (1.0679)	0.99 (1.3439)
Month 9 (Day 225 to 252) N	63	97
Mean (SD)	1.159 (1.3345)	0.979 (1.2330)
Month 10 (Day 253 to 280) N	61	95
Mean (SD)	0.803 (1.2493)	0.926 (1.2902)

Month 11 (Day 281 to 308) N	58	90
Mean (SD)	0.672 (1.1454)	0.724 (1.0411)
Month 12 (Day 309 to 336) N	47	83
Mean (SD)	0.518 (1.0444)	0.768 (1.0039)

Monthly attack rate was defined as the total number of adjusted HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month.
Note: Paper diaries and corresponding attack data were returned at each study visit for the time period leading up to the visit and therefore lag a subject's progress through the study by up to 12 weeks. The attack rate was determined based on reported attacks up to the time of data cut with no distinction between diaries remaining with subjects until their next visit and diaries with no attacks. Therefore, attack rates reported at later study timepoints may underestimate the number of attacks. Diary data for Months 1 to 6 are very complete: the 110-mg dose group returned all diaries; the 150-mg dose group has 3 of 673 months of diary data remaining with the subjects. Estimates of the diary data remaining with subjects for Months 7 to 12 are approximately 6% of diaries for the 150-mg dose group and approximately 20% of diaries for 110 mg dose group.

Figure 18: BCX7353-204: Plot of Mean Adjusted Attack Rate by Month Through Month 12 (Safety Population)



Abbreviations: BCX7353 = berotralstat; HAE = hereditary angioedema; SD = standard deviation.
Note: Monthly attack rate was defined as the total number of adjusted HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month.
Source: Figure 14.2.1.10.1.

Number and proportion of days with angioedema symptoms

Total days with angioedema symptoms were generally similar between treatment groups and declined over time: during Month 1 the median days (median percentage of days) with symptoms was 2.0 (7.1%) and 2.0 (7.1%) days for the 110- and 150-mg dose groups, respectively; by Month 6 the median days was 1.0 (3.6%) and 1.0 (3.6%) days respectively; and Month 12 the median days was 0.0 (0.0%) and 0.0 (0.0%) days respectively. Note that the decline in number of days with angioedema symptoms over time might be related to study discontinuation.

2.5.3. Discussion on clinical efficacy

In support of the application the applicant submitted a phase 2 randomised double blind placebo-controlled dose finding and proof of concept study (BCX7353-203), a phase 3 randomised double blind placebo controlled trial conducted in North American and European populations (BCX7353-302), a smaller study with the same design conducted in a Japanese population (BCX7353-301) and an open label uncontrolled phase 2 study (BCX7353-204). The applicant has also provided a pre-specified pooled analysis of data from Studies BCX7353 302 and 301.

Design and conduct of clinical studies

Three of the four submitted studies were randomised double blind, placebo-controlled trials. The one uncontrolled study was primarily a safety and tolerability study with efficacy as a secondary endpoint. Studies BCX7353 302 and 301 can be regarded as pivotal studies. Study 301 is a smaller study conducted in a Japanese population and has a similar design to Study 302. Both studies are still ongoing. Efficacy was evaluated at the end of Part 1 in both studies i.e. after 24 weeks treatment.

Inclusion and exclusion criteria

The patient population in all submitted efficacy studies were required to have a diagnosis of either Type 1 or Type 2 HAE. Only adult patients were eligible for recruitment to the dose finding study. Adolescents were eligible to participate in both Study BCX7353-302 and 301 studies. However, only 6 adolescent patients (2 per study arm) were recruited to Study BCX7353-302 and all 6 were at North American sites. Study BCX7353-203 subjects were required to have had a documented attack rate of at least 2 HAE attacks per month for 3 consecutive months within 6 months prior to screening. Whereas for Studies BCX7353-302 and 301 subjects were required to have had ≥ 2 HAE attacks during a 56-day run-in period. This suggests that the patients in the dose finding/proof of concept study may have been a more severely affected population than those in the pivotal studies. Any use of prophylaxis medication was prohibited within 7 days prior to screening or during the study in Study BCX7353 203 and for 14 days prior to screening and during the study for BCX7353 302 and 301.

The inclusion criteria regarding the diagnosis of Type 1 or 2 HAE and characteristics of a HAE attack were defined in greater detail for the pivotal studies compared to the dose finding study. There was a clear definition of an attack with a requirement that the attacks included symptoms of swelling, have either been treated, required medical attention or been documented to cause functional impairment and be unique i.e. did not begin within 48 hours of a previous attack.

Use of a C1-INH therapy for treatment of acute attacks was not excluded at any time, nor was C1-INH for pre-procedure prophylaxis for an unplanned/unforeseen procedure. In general, the list of prohibited medications was similar in the dose finding study and pivotal studies.

All of the randomised controlled studies were placebo controlled. This is considered acceptable. An additional treatment arm with an active comparator would have been preferable but it is acknowledged that this could have presented challenges in terms of blinding as the alternatives are not administered orally. However, given the rarity of the condition the lack of an active comparator may have presented recruitment challenges.

Primary endpoint

The primary endpoint for the dose finding/proof of concept study was the investigator confirmed attack rate, i.e. the total number of (count) confirmed attacks during the treatment period and standardized to an appropriate denominator (e.g. 7 days for a weekly attack rate) reported in the full analysis set population (all subjects who were randomized, received at least 1 dose of study drug, and had post-baseline HAE diary data recorded. Subjects were analysed according to the randomized treatment).

The primary analysis of treatment-effect was performed using an ANCOVA with the adjusted qualifying attack rate as the covariate. Data on symptoms was recorded by the patient in a paper diary.

For both phase 3 studies the primary endpoint was the rate of confirmed HAE attacks during the entire 24-week dosing period of Part 1 evaluated in the ITT population, defined as the total number of investigator-confirmed HAE attacks experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time of dose in Part 1 + 24 hours for subjects who discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or date of last dose in Part 1] - date of first dose in Part 1 + 1). Statistical analysis was based on a negative binomial regression model. Data on symptoms was recorded by the patient in an electronic diary to which the investigators had real time access.

The primary endpoints used in the phase 2 and 3 studies are considered acceptable given the proposed indication for berotralstat in the prophylaxis of HAE. Similar endpoints have been accepted for previous applications with a similar indication (e.g. lanadelumab).

In Study 302 subjects were stratified by a single factor, baseline attack rate. There was an error in the IXRS equation, which, resulted in the baseline attack rate for screening for purposes of stratification being slightly larger than it should have been because the denominator did not include the "+1"; ie, the number of days in screening was underestimated by 1 day. For analysis purposes, the baseline attack rate was recalculated using the intended equation for baseline attack rate. This may have resulted in some patients being assigned to the incorrect baseline attack rate category (>2 attacks per month; <2 attacks per month) in the randomization procedure. Baseline imbalances in the proportion of males and females across treatment arms could also be attributable to this calculation error. Apart from the stratification error the study appears to have been conducted appropriately.

Efficacy data and additional analyses

In Study BCX7353-302 there was an imbalance by sex across treatment arms, with the proportion of females varying from 73.2% in the berotralstat 110mg arm to 57.5% in the berotralstat 150mg arm and 66% in the placebo arm. In addition, there was an imbalance with regard to laryngeal attacks in the year preceding the study with higher rates in the placebo arm 42.5%, compared to berotralstat 110mg and 150mg, 24.4% and 22.5% respectively.

Study BCX7353-302 met its primary endpoint for both berotralstat doses with a greater rate reduction (%) from placebo for berotralstat 150mg (-44.2% with 95% CI from -59.5 to -23%, p-value <0.001) compared to berotralstat 110mg (-30% with 95% CI from -48.7, -4.6%, p-value=0.024). Investigator attack rates over the dosing period were 1.65/28 days for berotralstat 110mg, from a baseline of 2.97/28 days; 1.31/28 days for berotralstat 150mg from a baseline of 3.06/28 days; and 2.35/28 days for placebo, from a baseline of 2.91/28 days.

A missing data sensitivity analysis conducted on the primary endpoint in which observed data post study drug discontinuation was used in combination with imputed data for subjects who discontinued study treatment prior to the end of Part 1 and did not continue to record HAE attacks showed an attenuation in the effect size for berotralstat 150mg but not for berotralstat 110mg, with a rate reduction % from placebo of -35% (95% CI -9.2, -52.9%) as compared to -44.2% in the original analysis. As the method for imputing data for subjects with no data on HAE attacks post discontinuation was not described in sufficient detail, the applicant was asked to provide clarification on the method used and further analysis. Further sensitivity analyses provided by the applicant at request of CHMP has demonstrated a lesser attenuation of effect for the 150 mg dose from 44% to 39% (using all observed data and imputing remaining missing data under a Jump to Reference

assumption) and from 44% to 40% (imputing all data post-discontinuation of study drug under a Jump to Reference assumption).

The clinical relevance of the effect seen in the primary endpoint was questioned. Effects on quality of life were evaluated using change from baseline in AE-QoL at Week 24. There was a decrease in score (an improvement) in all treatment arms which were numerically greater than placebo in both berotralstat treatment arms. These differences were not statistically significant. This suggests that though attack rates were reduced in both active treatment arms, this had a minimal impact on quality of life, which could question the clinical importance of the reduction in attack rates. However, the mean improvement comparing subjects' on-study to Baseline AE-QoL total scores was more than twice the MCID at Week 24 in Study 302, consistent with the improvement in QoL total scores observed in Study 301 and Study 204.

The number of days with angioedema symptoms over 24 weeks was similar for both active treatment arms (19 and 20 days) and lower than placebo (29 days). There were uncertainties regarding efficacy at different attack sites, e.g. abdominal, laryngeal and peripheral etc. and for varying degrees of severity. Evaluation of efficacy by attack site was an exploratory endpoint only and though numerically there was a reduction in attack rate for abdominal, peripheral and laryngeal attacks in the berotralstat treatment arms compared to placebo, these were not nominally significant. Further data provided by the applicant has demonstrated that berotralstat 150mg produced a reduction in moderate to severe attacks, a reduction in acute attack medication usage and in the rate of laryngeal attacks.

A pre-planned subgroup analysis in Study 302 showed a greater rate reduction (%) from placebo in males in both berotralstat treatment arms compared to females. This was explained by the applicant as possibly being due to a larger placebo effect and a higher baseline attack for females compared with males in the berotralstat 150mg treatment arms. Additional analyses provided by the applicant suggested that the magnitude of the treatment effect on HAE attack rate could be smaller in females than males but a definitive conclusion could not be made on the basis of the available data. Additionally, there was an imbalance in the proportion of females across treatment arms with 73.2% in the berotralstat 110mg arm, 57.5% in the berotralstat 150mg arm and 66% in the placebo arm. Given the greater response seen for males, it is possible that the higher rate reduction (%) from placebo seen in berotralstat 150mg may have been driven by the larger proportion of males in that treatment group (42.5%) compared to that of berotralstat 110mg (26.8%). Additional analyses provided by the applicant were not considered to fully exclude this possibility. The CHMP considered that no definite conclusion could be drawn from the current data therefore no information is warranted in the SmPC.

BCX7353-204

The efficacy results from this study are difficult to interpret given that it is uncontrolled and study participants have been recruited under many different protocol versions. The definition of an attack also differs somewhat from that used in the pivotal study with a requirement that the attack have begun more than 24 hours after the end of a prior attack, whereas in the pivotal study this time interval was 48 hours. Subjects recorded attacks in paper diaries. It is unclear how complete these diaries were, albeit that attacks were adjudicated upon by the investigators.

Baseline attack rates were not calculated according to the applicant because not all subjects entering the study had baseline measures collected as some subjects were rolling over from previous studies; (2) some subjects were on other prophylactic HAE medications; and (3) some subjects were discontinuing androgens that were used as HAE prophylaxis.

It would appear that the attack rate decreased gradually over time as did the mean proportion of days with angioedema symptoms. However, this could be due to discontinuation from the study of

participants who were not demonstrating any benefit and the absence of complete data in the later months of the follow up period.

Quality of life data is difficult to interpret as baseline AE-QoL total score was only available for 84 /100 in the 110mg group and 118/127 (93%) in the 150mg group. The number of study participants with available scores continued to diminish over time with 23/100 and 73/127 (57.5%) at Week 48.

Maintenance of effect

Maintenance of effect appears to be maintained for both doses across the time period with a small reduction seen at month 6. Additional data provided by the applicant did not demonstrate a decrease in effect over time. Given the small sample size and possible individual subjects' data influence, the interpretation of durability of response is not straightforward. However, an effect on HAE attack rate seems sustained over time for both 110 mg and 150 mg berotralstat doses. Relevant information on maintenance of effect has been mentioned in the SmPC.

Indication

The applicant's proposal for a broad indication in HAE was not initially supported as the clinical development programme recruited only patients with Types 1 and 2 HAE. Two subtypes of HAE patients with normal C1INH are also recognised (FXII-HAE) and (U-HAE) in the literature. Upon CHMP request, the applicant justified further the extrapolation of efficacy to allow the use also in these 2 subtypes. From a mechanism of action view point, and also the pathophysiology, classification of HAE and role of bradykinin in HAE it can be accepted that therapies targeting the contact system (eg, C1-INH replacement, BK receptor blockers, and kallikrein inhibitors) have been successful in HAE-C1-INH, supporting the concept that angioedema is mediated via BK production. Therefore, the indication will not be restricted to types 1 and 2 HAE patients.

Paediatric data

There was limited exposure in the development programme to berotralstat in adolescent subjects, with only 4 subjects aged from 12 to 17 and weighting ≥40Kg exposed to berotralstat in a randomised controlled trial. Sub-group analysis by age-group was uninformative. There are very limited data on efficacy in adolescents. However, considering similarity of disease and mechanism of action between both populations and existing scientific and therapeutic knowledge, the use in adolescent patients was considered justified despite the very limited data available. The proposed posology for adolescents is the same as that for adults. However, as body weight had a significant effect on berotralstat exposure in a Population PK analysis, the CHMP recommended that berotralstat should not be used in patients weighing less than 40 Kgs and under 12 years of age.

2.5.4. Conclusions on the clinical efficacy

The pivotal study (Study BCX7353-302) met its primary endpoint and the effect of treatment is considered to be clinically relevant.

The applicant's proposal for a broad indication in HAE was not initially supported as the clinical development programme recruited only patients with Types 1 and 2 HAE. The applicant provided justification for use in these 2 subtypes to which the CHMP agreed, therefore the indication will not be restricted to types 1 and 2.

A difference of effect was observed among gender with a greater rate reduction from placebo in males in both berotralstat treatment arms compared to females. Additionally, there was an imbalance in the proportion of females across treatment arms (73.2% in the berotralstat 110mg arm, 57.5% in the berotralstat 150mg arm and 66% in the placebo arm). It could be possible that the difference seen in

the primary endpoint between the two berotralstat doses may have been driven by an imbalance in the allocation of females across treatment arms. Overall, there is a potential for lower efficacy in females than males, however it remains uncertain, and no definite conclusion could be drawn.

2.6. Clinical safety

Patient exposure

The clinical development program for berotralstat is comprised of 14 Phase 1 studies and 5 Phase 2/3 studies. The table below summarizes all clinical studies completed or ongoing in the berotralstat program to date.

A total of 894 subjects have been enrolled in the 19 studies and exposed to at least 1 dose of berotralstat; 397 healthy subjects, 7 subjects with renal impairment, 18 subjects with hepatic impairment, and 472 subjects with HAE. The total number of exposures to berotralstat was 1314 of which 653 exposures were not included in the integrated analyses; 445 exposures in healthy subjects, 25 exposures in special populations, and 183 exposures in HAE subjects.

A total of 395 unique subjects with HAE received berotralstat, primarily in multiple-dose studies.> 100 HAE subjects completed a 48 week visit in Studies 302 and 204 at the proposed marketed dose of 150 mg QD.(73 subjects in Study 204 and 30 subjects in Study 302).

The primary placebo-controlled safety populations consist of subjects in Studies 301 and 302.

Study 302, as the largest randomized, prospective, placebo-controlled trial, was used to determine the most accurate incidence of adverse reactions. Study 301, as a smaller, less diverse study, provided supportive adverse reaction information.

The safety data for 7 studies (5 Studies in healthy subjects [Studies 101, 103, 104, 106, and 113]and 2 studies in HAE subjects [Studies 204 and 302]) were integrated for presentation in this application. The safety data for Study 301 are presented separately and not integrated with the other long-term studies in HAE.

Considering differences in study designs and subject populations, in the studies that were integrated, 3 different subject pools were identified: Phase 1 single-dose studies in healthy subjects; Phase 1 multiple-dose studies in healthy subjects; Phase 2 and 3 (Phase 2/3) prophylactic long-term studies in subjects with Type 1 or 2 HAE (Studies 302 and 204).

Non integrated studies included the phase 3 Study 301 (APeX-J) (pivotal Japanese prophylactic indication) and the Phase 1 studies in healthy subjects or special populations DDI studies, renal and hepatic impairment, exploratory and B/E for acute HAE indication.

Table 44: Total Exposure to Berotralstat Across the Berotralstat Clinical Development Program

Dose	Study	Berotralstat		Not Berotralstat		Overall	
		Number of Subjects	Number of Exposures	Number of Subjects	Number of Exposures	Number of Subjects	Number of Exposures
Integrated single dose							
	Study 101	46	52	16	18	62	70
	Study 103	24	67	0	0	24	67
	Study 104	7	7	0	0	7	7
	Study 113	60	115	0	0	60	115
	Subtotal	137	241	16	18	153	259
Integrated multiple dose							
	Study 101	50	50	10	10	60	60
	Study 106	28	28	12	12	40	40
	Subtotal	78	78	22	22	100	100
Integrated Phase 2/3 long-term prophylactic							
	Study 204	227	227	0	0	227	227
	Study 302	115	115	39	39	120	154
	Subtotal	342	342	39	39	347	381

Dose	Study	Berotralstat		Not Berotralstat		Overall	
		Number of Subjects	Number of Exposures	Number of Subjects	Number of Exposures	Number of Subjects	Number of Exposures
Integrated single dose							
	Study 101	46	52	16	18	62	70
	Study 103	24	67	0	0	24	67
	Study 104	7	7	0	0	7	7
	Study 113	60	115	0	0	60	115
	Subtotal	137	241	16	18	153	259
Integrated multiple dose							
	Study 101	50	50	10	10	60	60
	Study 106	28	28	12	12	40	40
	Subtotal	78	78	22	22	100	100
Integrated Phase 2/3 long-term prophylactic							
	Study 204	227	227	0	0	227	227
	Study 302	115	115	39	39	120	154
	Subtotal	342	342	39	39	347	381

Dose	Study	Berotralstat		Not Berotralstat		Overall	
		Number of Subjects	Number of Exposures	Number of Subjects	Number of Exposures	Number of Subjects	Number of Exposures
Nonintegrated prophylactic Phase 2 and Phase 3							
	Study 301	13	13	6	6	19	19
	Study 203	53	53	22	22	75	75
	Subtotal	66	66	28	28	94	94
Nonintegrated DDI studies							
	Study 102	21	57	21	42	21	99
	Study 105	54	141	36	36	54	177
	Study 112	50	130	52	52	52	182
	Study 115	21	63	21	21	21	84
	Subtotal	146	391	130	151	148	542
Nonintegrated special populations							
	Study 107	14	14	0	0	14	14
	Study 108	24	24	0	0	24	24
	Subtotal	38	38	0	0	38	38
Nonintegrated other							
	Study 109	6	7	0	0	6	7
	Study 110	5	5	7	7	12	12
	Study 114	18	36	0	0	18	36
	Study 202	58	110	53	53	58	163
	Subtotal	87	158	60	60	94	218
	Overall [a]	894	1314	295	318	974	1632
	Unique Subjects [b]	817		291		865	

Post finalization of the SCS statistical analysis plan (SAP), a fourth subject pool was identified for integration and ad hoc analyses of human leukocyte antigen (HLA) data only. Specific HLA alleles have been shown to be associated with adverse drug reactions (ADRs), including rash/hypersensitivity reactions and drug-induced liver injury (DILI). However, this analysis did not demonstrate any pattern of effect.

Adverse events

Study 302

Table 45: BCX7353-302 Part 1: Overall Summary of TEAEs (Safety Population)

TEAE Summary	Berotralstat 110 mg N = 41 n (%)	Berotralstat 150 mg N = 40 n (%)	Berotralstat All Active N = 81 n (%)	Placebo N = 39 n (%)
Number of subjects with:				
Any TEAE	34 (82.9%)	34 (85.0%)	68 (84.0%)	30 (76.9%)
Any drug-related TEAE [a]	17 (41.5%)	15 (37.5%)	32 (39.5%)	13 (33.3%)
Any SAE	1 (2.4%)	0	1 (1.2%)	3 (7.7%)
Any drug-related SAE [a]	0	0	0	0
Any Grade 3 or 4 TEAE	5 (12.2%)	1 (2.5%)	6 (7.4%)	4 (10.3%)
Any drug-related Grade 3 or 4 TEAE [a]	3 (7.3%)	0	3 (3.7%)	0
Any TEAE leading to interruption of study drug [b]	0	0	0	2 (5.1%)
Any TEAE leading to discontinuation of study drug	3 (7.3%)	1 (2.5%)	4 (4.9%)	1 (2.6%)
Any investigator-identified rash [c]	0	1 (2.5%)	1 (1.2%)	0
Any GI abdominal TEAE [d]	17 (41.5%)	20 (50.0%)	37 (45.7%)	14 (35.9%)
Any GI abdominal TEAE leading to discontinuation of study drug	1 (2.4%)	0	1 (1.2%)	0

Abbreviations: AE = adverse event; eCRF = electronic case report form; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects who experienced the event; PT = preferred term; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] A drug-related TEAE was defined as any AE where the investigator defines the relationship to blinded study drug as Possibly Related, Probably Related, or Definitely Related.

[b] An AE leading to interruption of study drug was any AE where the Action Taken on the AE eCRF was marked as 'Drug Interrupted'.

[c] An investigator-identified rash was any AE that the investigator noted as an AE of special interest on the AE eCRF.

[d] GI abdominal AE was any AE with a PT within the MedDRA 19.1 hierarchy under the High-level Group Terms of 1) GI signs and symptoms or 2) GI motility and defaecation conditions.

Note: TEAEs were defined as those events that occurred after initiation of study drug through the initiation of dosing in Part 2 or through the last dose of study drug in Part 1 + 30 days for subjects who did not continue into Part 2.

Source: Table 14.3.1.1.

Overall, 83% of berotralstat 110 mg subjects, 85% of berotralstat 150 mg subjects, and 77% of placebo subjects experienced a TEAE during Part 1. The number of TEAEs considered drug-related by investigators was 42% of berotralstat 110 mg subjects, 38% of berotralstat 150 mg subjects, and 33% of placebo subjects.

No subject in the berotralstat 150 mg treatment group experienced a treatment-emergent SAEs. One subject (2%) in the berotralstat 110 mg group experienced the treatment-emergent SAE of plasma cell myeloma, and 3 placebo-treated subjects (8%) experienced the treatment-emergent SAEs of uterine leiomyoma, diverticulum intestinal haemorrhagic and transient ischemic attack (on different dates), and pneumonia; none of these events were considered study drug related by the investigator.

All study drug related TEAEs were mild to moderate in the placebo arm and in the berotralstat 150 mg group. Although the majority of related TEAEs in the 110 mg group were mild to moderate 3 subjects (7%) were reported as experiencing Grade 3 (severe) drug-related TEAEs on study. The events were the events were abdominal pain (2 subjects and purpura (1 subject). There were no study-drug related Grade 4 TEAEs. Five subjects discontinued study drug due to TEAEs: 3 berotralstat 110 mg subjects (7%), 1 berotralstat 150 mg subject (3%), and 1 placebo subject (3%).

Skin rash was an event of special interest (EOSI) in this study. There were no drug-related EOSIs on study; the single rash identified was an unrelated petechiae due to mechanical irritation. Overall, 42% and 50% of berotralstat 110 and 150 mg subjects, respectively, had GI abdominal TEAEs compared with 36% of placebo subjects. One berotralstat 110 mg subject (2%) discontinued study drug due to GI abdominal TEAEs (Grade 2 dyspepsia, nausea, and vomiting).

Study 204

Table 46: BCX7353-204: Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

Summary	Berotralstat		
	110 mg (N = 100)	150 mg (N = 127)	Total (N = 227)
Number of Subjects with:			
Any TEAE	91 (91.0%)	115 (90.6%)	206 (90.7%)
Any drug-related TEAE [a]	56 (56.0%)	57 (44.9%)	113 (49.8%)
Any TESAE	18 (18.0%)	12 (9.4%)	30 (13.2%)
Any drug-related TESAE [a]	2 (2.0%)	1 (0.8%)	3 (1.3%)
Any G3 or G4 TEAE	14 (14.0%)	20 (15.7%)	34 (15.0%)
Any drug-related G3 or G4 TEAE [a]	6 (6.0%)	8 (6.3%)	14 (6.2%)
Any TEAE leading to interruption of study drug [b]	6 (6.0%)	21 (16.5%)	27 (11.9%)
Any TEAE leading to discontinuation of study drug	6 (6.0%)	13 (10.2%)	19 (8.4%)
Any investigator-identified drug-related rash (EOSI)[c]	5 (5.0%)	3 (2.4%)	8 (3.5%)
Any investigator-identified drug-related rash (EOSI) leading to discontinuation of study drug [c]	1 (1.0%)	1 (0.8%)	2 (0.4%)
Any GI abdominal TEAE [d]	53 (53.0%)	52 (40.9%)	105 (46.3%)
Any GI abdominal TEAE leading to discontinuation of study drug	2 (2.0%)	4 (3.1%)	6 (2.6%)

Abbreviations: EOSI = event of special interest; G = grade; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Reference: Listing 16.2.7.1, 16.2.7.7
Note: TEAEs were defined as those events which occurred after initiation of study drug through 30 days post the last dose of study drug.
[a] A drug-related TEAE was defined as any TEAE where the investigator defined the relationship as possibly related, probably related, or definitely related.
[b] A TEAE leading to interruption of study drug was any TEAE where the action taken on the AE CRF was marked as 'drug interrupted'.
[c] An investigator-identified drug-related rash was any TEAE that the investigator noted as an EOSI that was assessed as possibly related, probably related, or definitely related to study drug on the adverse event case report form.
[d] GI abdominal TEAE was any TEAE with a preferred term within the MedDRA 19.1 hierarchy under the high level group terms (HLGTs) of 1) GI signs and symptoms or 2) GI motility and defaecation conditions. These events were termed GI abdominal-related in the statistical outputs.
Source: Table 14.3.1.1.1 and Table 14.3.1.15.1.

Study 204 showed that berotralstat was safe and generally well tolerated and, there was not a well-defined increase in the frequency of TEAEs with increasing dose. Overall, in the total berotralstat group, 206 of 227 subjects (90.7%) experienced a TEAE, with almost equal % between groups. Nineteen subjects (8.4%) discontinued study drug due to a TEAE. SAEs assessed by the investigator as related to study drug occurred in 3 subjects (1.3%).

Integrated Phase 2/3 Prophylactic Long-term Studies in HAE Subjects

TEAEs that were more frequently reported among berotralstat-treated subjects vs. placebo-treated subjects (ie, > 5% difference) were nasopharyngitis (28.4% vs. 23.1%), headache (14.3% vs. 5.1%), diarrhoea (12.6% vs. 0), abdominal pain (12.3% vs. 5.1%), upper respiratory tract infection (9.9% vs. 2.6%), vomiting (7.9% vs. 2.6%), urinary tract infection (6.4% vs. 0), and gastroesophageal reflux disease (5.3% vs. 0). Likewise, the TEAEs of nausea (17.9% vs. 11.1%), viral gastroenteritis (7.7% vs. 2.0%), pain in extremity (7.7% vs. 1.2%), anxiety (7.7% vs. 2.3%), and irritability (5.1% vs. 0) were more frequently reported among placebo-treated subjects (Table S.58.3.A). Overall, among subjects treated with berotralstat, the most frequent TEAEs were nasopharyngitis (28.4%), headache (14.3%), and diarrhoea (12.6%). The frequency of TEAEs was similar between the berotralstat 110-mg and 150-mg dose groups.

The infections and infestations SOC had the greatest number of subjects with a TEAE; 57.9% and 51.3% of berotralstat- and placebo-treated subjects, respectively. The next most frequently reported

TEAEs were in the GI disorders SOC; 50.0% vs. 41.0% treated with berotralstat and placebo, respectively. Most TEAEs were Grade 1 or Grade 2 in severity.

48.7% and 45.1% of subjects in the berotralstat 110-mg and150-mg dose groups, respectively, experienced a drug-related TEAE. In the GI SOC, 37.1% vs. 28.2% of berotralstat- and placebo-treated subjects experienced a drug-related TEAE. The GI TEAEs of abdominal pain (8.8%), diarrhoea (7.3%), and nausea (7.3%) were the most frequently reported berotralstat-related TEAEs. Other SOCs that had at least 2% of berotralstat-treated subjects experiencing a drug-related TEAE were investigations, nervous system disorders, skin and subcutaneous tissue disorders, and general disorders and administration site conditions.

The investigations and GI SOCs (3.2% and 1.5%, respectively) had the most subjects with a drug-related Grade 3 or Grade 4 TEAE. The most common drug-related Grade 3 or Grade 4 TEAEs reported in berotralstat-treated subjects were ALT increased (1.8%) and abdominal pain (1.2%). The only other drug-related Grade 3 or Grade 4 TEAEs reported in > 1 subject treated with berotralstat was hepatic enzyme increased (0.6%) and LFT abnormal (0.6%).

TEAEs were also evaluated by calculating the rate per 100 patient years of exposure (PYE) to normalize for length of time on study and account for differential observation time bias. The per 100 PYE rates of TEAEs occurring in at least 5% of the total number of berotralstat exposures are outlined below.

Table 47: TEAE Rate Per 100 Person Years of Exposure Occurring in at Least 5% of Berotralstat Exposures (Phase 2/3 Prophylactic Long-term Studies Safety Population)

System Organ Class Preferred Term	Berotralstat 110 mg (N = 158) Events/100 PYE [Events]	Berotralstat 150 mg (N = 184) Events/100 PYE [Events]	Placebo (N = 39) Events/100 PYE [Events]
PYE	98.5	133.6	16.5
Any Event	701.8 [691]	673.0 [899]	750.1 [124]
Infections and infestations	185.9 [183]	221.6 [296]	217.8 [36]
Nasopharyngitis	68.0 [67]	79.3 [106]	90.7 [15]
Upper respiratory tract infection	18.3 [18]	17.2 [23]	6.0 [1]
Urinary tract infection	12.2 [12]	11.2 [15]	0.0 [0]
Gastrointestinal disorders	183.8 [181]	170.7 [228]	181.5 [30]
Abdominal pain	39.6 [39]	26.9 [36]	12.1 [2]
Diarrhoea	21.3 [21]	24.7 [33]	0.0 [0]
Nausea	20.3 [20]	20.2 [27]	48.4 [8]
Vomiting	9.1 [9]	18.7 [25]	12.1 [2]
Abdominal pain upper	14.2 [14]	12.0 [16]	6.0 [1]
Dyspepsia	8.1 [8]	11.2 [15]	36.3 [6]
Gastrooesophageal reflux disease	12.2 [12]	5.2 [7]	0.0 [0]
Flatulence	5.1 [5]	9.7 [13]	6.0 [1]
Nervous system disorders	53.8 [53]	42.7 [57]	30.2 [5]
Headache	42.7 [42]	26.2 [35]	12.1 [2]

Source: Integrated SCS, Table S.19.3.

Integrated Phase 1 Single-Dose Studies in Healthy Subjects (Studies 101, 103, 104 and 113)

241 healthy subjects were treated with a single dose of berotralstat. The highest single berotralstat dose administered was 871 mg (1000 mg [SN]). Other berotralstat doses included in the > 150 mg dose group included 218 mg, 300 mg, and 450 mg.

Subjects in the < 110-mg group and the 150-mg dose groups were younger than subjects in the other 2 berotralstat dose groups (and slightly younger than placebo) and more female subjects were enrolled in the 2 lower berotralstat dose groups compared to the other groups. All subjects were between the ages of 18 and 64 years. Subjects treated with berotralstat were enrolled in North America (47.7%) or Europe (52.3%). The majority of subjects were white 87.1% followed by Black or African American

(6.2%) Asian (5.4%). No subjects in the Phase 1 single-dose healthy subject pool experienced a Grade 3 or Grade 4Grade 4 TEAE.

Table 48: Summary of Treatment-emergent Adverse Events (Phase 1 Single-dose Studies Safety Population)

	Berotralstat					Placebo (N = 18)
	< 110 mg (N = 22)	110 mg (N = 58)	150 mg (N = 57)	> 150 mg (N = 104)	Total (N = 241)	
Number of subjects with						
TEAEs	10 (45.5%)	20 (34.5%)	17 (29.8%)	35 (33.7%)	82 (34.0%)	8 (44.4%)
Drug-related TEAEs[a]	5 (22.7%)	7 (12.1%)	4 (7.0%)	9 (8.7%)	25 (10.4%)	3 (16.7%)
G3 or G4 TEAEs	0	0	0	0	0	0
SAEs	0	0	0	0	0	0
Fatal SAEs (deaths)	0	0	0	0	0	0
TEAEs leading to discontinuation of study drug	0	0	2 (3.5%)	3 (2.9%)	5 (2.1%)	0
Drug-related rash/hypersensitivity TEAE [b]	0		1 (1.8%)	1 91.0%)	2 (0.8%)	0
Hepatic disorders (potentially drug related) TEAE [c]	0	0	0	1 (1.0%)	1 (0.4%)	0
GI Abdominal TEAE [d]	3 (13.6%)	7 (12.1%)	2 (3.5%)	9 (8.7%)	21 (8.7%)	3 (16.7%)

Common Treatment-emergent Adverse Events (Phase 1 Single-dose Studies Safety Population)

Table 49: Treatment-emergent Adverse Events Assessed by the Investigator as Related to Study Drug and Occurring in at Least 2% of Berotralstat-treated Subjects by System Organ Class or Preferred Term (Phase 1 Single-dose Studies Safety Population)

System Organ Class Preferred Term	Berotralstat					Placebo (N = 18) n (%) [events]
	< 110 mg (N = 22) n (%) [events]	110 mg (N = 58) n (%) [events]	150 mg (N = 57) n (%) [events]	> 150 mg (N = 104) n (%) [events]	Total (N = 241) n (%) [events]	
Any drug-related event	5 (22.7%) [12]	7 (12.1%) [10]	4 (7.0%) [8]	9 (8.7%) [12]	25 (10.4%) [42]	3 (16.7%) [4]
Gastrointestinal disorders	2 (9.1%) [6]	4 (6.9%) [5]	1 (1.8%) [3]	5 (4.8%) [8]	12 (5.0%) [22]	2 (11.1%) [2]
Nausea	2 (9.1%) [3]	1 (1.7%) [1]	1 (1.8%) [1]	2 (1.9%) [2]	6 (2.5%) [7]	1 (5.6%) [1]
Diarrhoea	0	2 (3.4%) [2]	0	3 (2.9%) [3]	5 (2.1%) [5]	0
Nervous system disorders	5 (22.7%) [6]	2 (3.4%) [2]	1 (1.8%) [1]	2 (1.9%) [2]	10 (4.1%) [1]	2 (11.1%) [2]
Headache	5 (22.7%) [5]	1 (1.7%) [1]	1 (1.8%) [1]	1 (1.0%) [1]	8 (3.3%) [8]	2 (11.1%) [2]

5 subjects experienced a TEAE that led to permanent study drug discontinuation. Three of the 5 subjects were enrolled in the relative bioavailability study, Study 103; the TEAEs of Grade 2 transaminases increased and Grade 1 eczema were assessed by the investigator as possibly related to study drug and the TEAE of G Grade 2 neutropenia was assessed as not related to study drug. The remaining 2 TEAEs were reported in subjects enrolled in the bioequivalence cross-over Study 113; Grade 2 sinus infection and Grade 1 abdominal discomfort were assessed as unrelated to study drug.

Integrated Phase 1 Multiple-dose Studies in Healthy Subjects (studies 101 and 106)

78 subjects treated with berotralstat, 54 subjects were treated with a daily dose > 150 mg berotralstat, 14 subjects treated with berotralstat 150 mg, and 10 subjects treated with berotralstat 110 mg. Overall, the mean (SD) duration of study drug dosing was 10.1 (3.61) days in subjects who received berotralstat. Just under half of the subjects (47.4%) received > 7 to 28 days of berotralstat

treatment and the mean (SD) daily dose was 273.8 (129.79) mg berotralstat. The highest multiple berotralstat dose administered was 500 mg (SN) or 450 mg.

The majority of subjects treated with berotralstat were male (72.7%), white (75.6%), and 64.1% and 45.5% of berotralstat-treated subjects were enrolled in Europe and North America, respectively.

Table 50: Summary of Treatment-emergent Adverse Events (Phase 1 Multiple-dose Studies Safety Population)

	Berotralstat				Placebo (N = 22)
	110 mg (N = 10)	150 mg (N = 14)	> 150 mg (N = 54)	Total (N = 78)	
Number of subjects with					
TEAEs	2 (20.0%)	11 (78.6%)	39 (72.2%)	52 (66.7%)	15 (68.2%)
Drug-related TEAEs [a]	1 (10.0%)	6 (42.9%)	27 (50.0%)	34 (43.6%)	5 (22.7%)
G3 or G4 TEAEs	0	0	1 (1.9%)	1 (1.3%)	0
SAEs	0	0	0	0	0
Fatal SAEs (Deaths)	0	0	0	0	0
TEAEs leading to discontinuation of study drug	0	0	3 (5.6%)	3 (3.8%)	0
Drug-related Rash/hypersensitivity TEAE [b]	0		3 (5.6%)	3 (3.8%)	0
Hepatic disorders (potentially drug related) TEAE [c]	0	0	0	0	0
GI abdominal TEAE [d]	1 (10.0%)	3 (21.4%)	26 (48.1%)	30 (38.5%)	3 (13.6%)

Most Common Treatment-emergent Adverse Events (assessed as related)

Table 51: Treatment-Emergent Adverse Events Assessed by the Investigator as Related to Study Drug and Occurring in at Least 2% of Berotralstat-treated Subjects by System Organ Class or Preferred Term (Phase 1 Multiple-dose Studies Safety Population)

System Organ Class Preferred Term	Berotralstat 110 mg (N = 10) n (%) [events]	Berotralstat 150 mg (N = 14) n (%) [events]	Berotralstat > 150 mg (N = 54) n (%) [events]	Berotralstat Total (N = 78) n (%) [events]	Placebo (N = 22) n (%) [events]
Any drug-related event	1 (10.0%) [1]	6 (42.9%) [14]	27 (50.0%) [71]	34 (43.6%) [86]	5 (22.7%) [11]
Gastrointestinal disorders	1 (10.0%) [1]	3 (21.4%) [5]	24 (44.4%) [51]	28 (35.9%) [57]	3 (13.6%) [5]
Diarrhoea	1 (10.0%) [1]	1 (7.1%) [1]	13 (24.1%) [16]	15 (19.2%) [18]	1 (4.5%) [2]
Nausea	0	1 (7.1%) [1]	8 (14.8%) [11]	9 (11.5%) [12]	1 (4.5%) [2]
Abdominal pain upper	0	1 (7.1%) [1]	6 (11.1%) [9]	7 (9.0%) [10]	0
Dyspepsia	0	1 (7.1%) [1]	3 (5.6%) [3]	4 (5.1%) [4]	0
Abdominal distension	0	0	3 (5.6%) [3]	3 (3.8%) [3]	0
Abdominal pain	0	0	2 (3.7%) [3]	2 (2.6%) [3]	0
Epigastric discomfort	0	0	2 (3.7%) [2]	2 (2.6%) [2]	0
Flatulence	0	0	2 (3.7%) [2]	2 (2.6%) [2]	0
Nervous system disorders	0	3 (21.4%) [3]	10 (18.5%) [11]	13 (16.7%) [14]	2 (9.1%) [2]
Headache	0	3 (21.4%) [3]	6 (11.1%) [6]	9 (11.5%) [9]	2 (9.1%) [2]
Dizziness	0	0	3 (5.6%) [3]	3 (3.8%) [3]	0
General disorders and administration site conditions	0	1 (7.1%) [1]	2 (3.7%) [2]	3 (3.8%) [3]	0
Skin and subcutaneous tissue disorders	0	0	3 (5.6%) [3]	3 (3.8%) [3]	1 (4.5%) [1]
Metabolism and nutrition disorders	0	1 (7.1%) [1]	1 (1.9%) [1]	2 (2.6%) [2]	1 (4.5%) [1]
Psychiatric disorders	0	0	2 (3.7%) [2]	2 (2.6%) [2]	1 (4.5%) [1]
Respiratory, thoracic and mediastinal disorders	0	2 (14.3%) [4]	0	2 (2.6%) [4]	0
Nasal congestion	0	2 (14.3%) [3]	0	2 (2.6%) [3]	0

1 subject in the Phase 1 multiple-dose healthy subject pool experienced a Grade 3 or Grade 4 TEAE. A subject who had received a berotralstat dose of > 150 mg (ie, 500 mg) experienced a Grade 3 TEAE of Type IV hypersensitivity reaction considered probably related to study drug.

3 subjects in the berotralstat dose group > 150 mg discontinued due the TEAEs of upper abdominal pain (Subject randomized to berotralstat 350 mg [SN] × 14 days) and upper abdominal pain and diarrhoea (Subject randomized to berotralstat 500 mg [SN] × 7 days) both in Study 101, and noncardiac chest pain (Subject A) in Study 106. All events were Grade 2 in severity and considered possibly or probably related to study drug.

Table 52: Non-Integrated Phase 3 Prophylactic Long-term Study in HAE Subjects (Study 301) Overall Summary of Treatment-emergent Adverse Events (Study 301, Part 1 Safety Population)

TEAE Summary	Berotralstat			Placebo N = 6 n (%)
	110 mg N = 6 n (%)	150 mg N = 7 n (%)	All Active N = 13 n (%)	
Number of subjects with:				
Any TEAE	6 (100.0%)	7 (100.0%)	13 (100.0%)	6 (100.0%)
Any drug-related TEAE [a]	2 (33.3%)	2 (28.6%)	4 (30.8%)	2 (33.3%)
Any SAE	1 (16.7%)	0	1 (7.7%)	0
Any drug-related SAE [a]	0	0	0	0
Any G3 or G4 TEAE	0	0	0	1 (16.7%)
Any drug-related G3 or G4 TEAE [a]	0	0	0	0
Any TEAE leading to interruption of study drug [b]	1 (16.7%)	2 (28.6%)	3 (23.1%)	0
Any TEAE leading to discontinuation of study drug	0	0	0	1 (16.7%)
Any investigator-identified rash (event of special interest) [c]	0	2 (28.6%)	2 (15.4%)	1 (16.7%)
Any GI abdominal TEAE [d]	3 (50.0%)	3 (42.9%)	6 (46.2%)	1 (16.7%)
Any GI abdominal TEAE leading to discontinuation of study drug	0	0	0	0

Among the 13 subjects treated with berotralstat, 7 subjects were treated with a daily dose of berotralstat 150 mg, 6 subjects were treated with berotralstat 110 mg. 6 subjects were treated with placebo. Overall, the mean (SD) duration of study drug dosing was 168.0 (0.0) days in subjects who received berotralstat.

The subject population was comprised of 3 male and 16 female subjects 21 to 69 years of age from 10 sites in Japan. Baseline demographic characteristics were generally similar across treatment groups and representative of the HAE patient population in general. Overall, 16 of 19 subjects (84%) were female, the mean age was 42.1 years, and 18 of 19 subjects (95%) were Asian. One elderly subject 65 to 74 years of age took part in the study (berotralstat 110 mg treatment group).

Table 53: Treatment-emergent Adverse Events Reported by ≥ 2 % of Berotralstat-treated Subjects by System Organ Class or Preferred Term (Study 301, Part 1 Safety Population)

System Organ Class Preferred Term	Berotralstat			Placebo (N = 6) n (%) [events]
	110 mg (N = 6) n (%) [events]	150 mg (N = 7) n (%) [events]	All Active (N = 13) n (%) [events]	
Any event	6 (100%) [56]	7 (100%) [16]	13 (100%) [72]	6 (100%) [13]
Infections and infestations	4 (66.7%) [5]	3 (42.9%) [3]	7 (53.8%) [8]	4 (66.7%) [5]
Nasopharyngitis	2 (33.3%) [2]	2 (28.6%) [2]	4 (30.8%) [4]	4 (66.7%) [5]
Otitis media	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Pneumonia	1 (16.7%) [2]	0	1 (7.7%) [2]	0
Tinea pedis	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Gastrointestinal disorders	4 (66.47%) [16]	4 (57.1%) [5]	8 (61.5%) [21]	2 (33.3%) [2]
Abdominal pain	1 (16.7%) [4]	1 (14.3%) [1]	2 (15.4%) [5]	0
Diarrhoea	1 (16.7%) [8]	1 (14.3%) [1]	2 (15.4%) [9]	0
Abdominal discomfort	1 (16.7%) [1]	0	1 (7.7%) [1]	1 (16.7%) [1]
Abdominal pain upper	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Dental caries	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Flatulence	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Gastritis	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Nausea	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Oesophageal discomfort	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Skin and subcutaneous tissue disorders	2 (33.3%) [2]	2 (28.6%) [4]	4 (30.8%) [6]	1 (16.7%) [1]
Urticaria	0	1 (14.3%) [1]	1 (7.7%) [1]	1 (16.7%) [1]
Dermatitis contact	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Eczema	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Miliaria	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Pruritus	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Rash	0	1 (14.3%) [1]	1 (7.7%) [1]	0
General disorders and administration site conditions	2 (33.3%) [29]	1 (14.3%) [1]	3 (23.1%) [10]	0
Pyrexia	1 (16.7%) [1]	1 (14.3%) [1]	2 (15.4%) [2]	0
Injection site reaction	1 (16.7%) [28]	0	1 (7.7%) [28]	0
Injury, poisoning and procedural complications	0	1 (14.3%) [1]	1 (7.7%) [1]	2 (33.3%) [2]
Ankle fracture	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Nervous system disorders	1 (16.7%) [1]	1 (14.3%) [1]	2 (15.4%) [2]	1 (16.7%) [1]
Headache	1 (16.7%) [1]	0	1 (7.7%) [1]	1 (16.7%) [1]
Somnolence	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Respiratory, thoracic and mediastinal disorders	2 (33.3%) [2]	0	2 (15.4%) [2]	0
Cough	2 (33.3%) [2]	0	2 (15.4%) [2]	0
Musculoskeletal and connective tissue disorders	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Back pain	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Reproductive system and breast disorders	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Dysmenorrhoea	1 (16.7%) [1]	0	1 (7.7%) [1]	0

Table 54: Treatment-Emergent Adverse Events Assessed by the Investigator as Related to Study Drug by System Organ Class and Preferred Term (Study 301, Part 1 Safety Population)

System Organ Class Preferred Term	Berotralstat 110 mg (N = 6) n (%) [events]	Berotralstat 150 mg (N = 7) n (%) [events]	Berotralstat All Active (N=13) n (%) [events]	Placebo (N = 6) n (%) [events]
Any drug-related adverse event	2 (33.3%) [11]	2 (28.6%) [4]	4 (30.8%) [15]	2 (33.3%) [2]
Gastrointestinal disorders	2 (33.3%) [10]	2 (28.6%) [2]	4 (30.8%) [12]	1 (16.7%) [1]
Abdominal discomfort	1 (16.7%) [1]	0	1 (7.7%) [1]	1 (16.7%) [1]
Abdominal pain upper	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Diarrhoea	1 (16.7%) [8]	0	1 (7.7%) [8]	0
Gastritis	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Nausea	1 (16.7%) [1]	0	1 (7.7%) [1]	0
General disorders and administration site conditions	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Pyrexia	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Nervous system disorders	1 (16.7%) [1]	1 (14.3%) [1]	2 (15.4%) [2]	0
Headache	1 (16.7%) [1]	0	1 (7.7%) [1]	0
Somnolence	0	1 (14.3%) [1]	1 (7.7%) [1]	0
Skin and subcutaneous tissue disorders	0	0	0	1 (16.7%) [1]
Urticaria	0	0	0	1 (16.7%) [1]

There were no Grade 4 TEAEs on study and no Grade 3 TEAEs in any berotralstat treated subjects. No berotralstat-treated subjects discontinued study drug due to TEAEs in Part 1 of Study 301.

Non-integrated Prophylactic HAE Studies

a) Phase 2 dose ranging study (study 203)

The most common drug-related TEAEs reported among subjects treated with berotralstat were nausea (11.3%), abdominal pain (7.5%), and diarrhoea and fatigue (5.7% each).

Most TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Overall, 5.7% of subjects (3 of 53) treated with berotralstat and no placebo-treated subject experienced a Grade 3 TEAE. All Grade 3 TEAEs occurred in subjects treated with berotralstat 350 mg and no Grade 3 TEAEs occurred in more than 1 subject. Two of the Grade 3 TEAEs (abdominal pain and ALT increased) led to study drug. 2 subjects (1 subject treated with berotralstat 350 mg [SN] and 1 subject treated with berotralstat 250 mg [SN]) interrupted study drug due to the TEAEs of fatigue and gastroenteritis (the subject took 1 additional dose and then discontinued due to liver disorder), and GI infection discontinuation. The Grade 3 TEAE of GI infection began 7 days after study drug was completed and resolved 2 days later.

b) Study 202 dose ranging study acute attack treatment in subjects with HAE

Diarrhoea, nausea and abdominal pain were the most frequently reported GI events in this study for all attacks combined. GI events occurred in a higher proportion of attacks treated with berotralstat 500 and 250 mg (20.0% and 19.0%, respectively) compared to the highest dose, 750 mg (9.4%). One subject was withdrawn due to moderate (Grade 2) nausea and vomiting considered related to berotralstat 500 mg.

Three subjects discontinued study drug after experiencing an AE (Part 1, berotralstat 750 mg: Grade 1 macular rash in 1 subject; Part 1, placebo: Grade 2 abdominal pain in 1 subject; Part 2, berotralstat 500 mg: Grade 2 vomiting and nausea in 1 subject). All events were considered related to study drug and resolved within 2 days of onset.

Serious adverse events and deaths

No subjects in the Phase 1 single-dose subject pool or in the Phase 1 multiple-dose subject pool experienced a treatment-emergent SAE.

One subject in the non-integrated phase 3 study (study 301) experienced a treatment-emergent SAE of pneumonia that resulted in hospitalization but was considered by the investigator to be unlikely related to study drug.

In study 202, three SAEs occurred in 2 subjects during the study (Part 1, placebo: ligament sprain and kidney contusion in 1 subject; Part 2, berotralstat 500 mg SN: ankle fracture). These SAEs were considered not related to study drug.

In study 203 a single SAE was reported in a male patient who experienced possible gastrointestinal infection (grade 2) which required overnight hospitalisation. The event was not considered related to study treatment.

Study 302

One berotralstat 110 mg subject experienced the treatment-emergent SAE of plasma cell myeloma diagnosed at Week 8 after follow-up investigations of elevated serum protein present since baseline, and 3 placebo subjects experienced a total of 4 SAEs: 1 subject each experienced uterine leiomyoma and pneumonia; and 1 subject experienced both a hemorrhagic intestinal diverticulum and a transient ischemic attack, occurring on separate occasions.

No treatment-emergent SAEs were considered related to study treatment.

Study 204

Subjects experiencing a treatment-emergent SAE was reported at 13.2%.

Treatment-emergent SAEs that occurred in > 1 subject were HAE attacks (12 subjects [5.3%]) and medical observation (3 subjects [1.3%]). Three subjects (1.3%) experienced 4 treatment-emergent SAEs assessed by the investigator as related to study drug; Grade 3 gastroenteritis and Grade 2 hepatic enzyme increased (n = 1), Grade 3 abnormal LFT (n = 1), and Grade 3 abdominal pain (n = 1). The 2 subjects with treatment-emergent SAEs of gastroenteritis, hepatic enzyme increased, and abnormal LFT resulted in study drug discontinuation.

Integrated Phase 2/3 prophylactic long-term study population

9.9% of subjects treated with berotralstat and 5.1% of placebo subjects experienced a treatment-emergent SAE.

No increase in treatment-emergent SAEs was observed with 150 mg compared to 110 mg berotralstat. The most common treatment-emergent SAEs reported in subjects treated with berotralstat were HAE

attacks (3.5%) and medical observation (1.2%). A total of 3 subjects (< 1%) experienced 4 treatment-emergent SAEs assessed by the investigator as related to study drug, all on Study 204.

No deaths have occurred in the berotralstat clinical development program to date.

Laboratory findings

Integrated Phase 1 Single-dose Studies in Healthy Subjects

Overall, 0.8% and 5.6% of berotralstat- and placebo-treated subjects, respectively, experienced a Grade 3 laboratory abnormality. No subject experienced a Grade 4 abnormality and no Grade 3 laboratory abnormality occurred in > 1 subject.

Two subjects experienced a Grade 3 chemistry laboratory abnormality. Grade 3 direct bilirubin of 0.4 mg/dL 19 days after a single dose of berotralstat 150 mg. The second subject had an ALT increase from a baseline value of 63 IU/L (Grade 1) to 124 IU/L (Grade 3).

16 of 241 (6.6%) of berotralstat-treated subjects entered study with mild elevations in ALT, 2 of whom (0.8%) had ALT elevations > 1.5 × ULN but < 3 × ULN.

Additionally, 14 of 241 (5.8%) of berotralstat-treated subjects entered study with mild elevations in total bilirubin (i.e. > 1 × ULN), 1 of whom (0.4%) had total bilirubin elevations > 1.5 × ULN.

Integrated Phase 1 Multiple-dose Studies in Healthy Subjects

Three subjects experienced a Grade 3 abnormality no subjects experienced any grade 4 abnormality.

Two subjects enrolled in Study 101 had a single Grade 3 elevation in lipase that returned to within normal range or Grade 1 at the next visit. No signs of pancreatitis were reported. One subject enrolled in Study 106 had a 1-grade shift in direct bilirubin to 0.4 mg/dL (Grade 3) on Day 7. At the next visit, direct bilirubin was within normal range.

Non-Integrated Phase 3 Long-term Prophylactic Study in HAE Subjects (Study 301)

A single subject treated with placebo experienced the post-baseline Grade 3 laboratory abnormality of Grade 3 platelet (laboratory abnormalities were graded by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (DRAFT, Publish Date: November 2007). The investigator considered the event not related to study drug.

Non-integrated Prophylactic HAE Studies phase 2 dose ranging study (study 203)

Four subjects experienced a Grade 3 or Grade 4 treatment-emergent chemistry laboratory abnormality; 3 subjects treated with berotralstat 350 mg (SN) and 1 subject treated with berotralstat 250 mg (SN). Three subjects had a treatment-emergent Grade 3 liver enzyme abnormality (ALT or GGT) and 1 subject had a treatment-emergent Grade 4 liver enzyme abnormality (GGT); 3 of the 4 subjects had elevated liver enzymes at baseline. All 4 patients had previously been treated with androgens, though only 2 were treated in the last year. A further patient experienced Grade 3 leukocytosis as an isolated finding.

Study 302

There were few Grade 3 or Grade 4 laboratory toxicities reported, as graded by DMID, with a similar number of such events reported across the treatment groups. Five subjects (6.2%) treated with berotralstat experienced DMID Grade 3 laboratory toxicities compared with 4 subjects (10.3%) in the placebo treatment group. One subject on 150 mg berotralstat who had previously been exposed to androgens had Grade 4 ALT and Grade 3 AST without symptoms or elevation of bilirubin, which

resolved after discontinuing study drug. No subjects with elevations in ALT and/or AST met the criteria of Hy's law.

Study 204

The most common clinically significant chemistry abnormalities were liver-related abnormalities, and the most common abnormality was ALT increased. The majority of treatment-emergent liver abnormalities were Grade 1 or Grade 2; however, 13 subjects (5.7%) experienced a treatment-emergent Grade 3 or Grade 4 ALT, and all of these subjects had previously used androgens. No subjects with elevations in ALT and/or AST met the criteria of Hy's law.

There were no notable changes over time in the cardiac injury markers (ie, CK-MB, troponin I and troponin T). Changes in renal parameters were also unremarkable with no notable mean or individual changes in creatinine or CLCR. Additionally, changes over time for the markers of glomerular (UACR) and tubular injury (NGAL) did not reveal any effects of berotralstat on the kidneys. No notable changes in vital signs were reported during the study. No subject discontinued due to QT prolongation and no subject had treatment emergent QTcF intervals that met stopping criteria.

Events of special interest (EOSI)

EOSI included Rash/hypersensitivity events, GI abdominal events and hepatic disorders.

Although drug-related rash events are reported below for the integrated Phase 1 single- and multiple-dose studies, a more realistic incidence of drug-related rash events is based on the integrated Phase 2/3 prophylactic long-term Studies 204 and 302 and the non-integrated Phase 3 long-term prophylactic Study 301 in HAE subjects.

Rash/hypersensitivity events,

Non-Integrated Phase 3 Long-term Prophylactic Study in HAE Subjects

(Study 301)

Two subjects treated with berotralstat 150 mg and 1 subject treated with placebo experienced investigator-identified rash on study (PTs rash, urticaria, and urticaria, respectively).

Integrated Phase 2/3 Prophylactic Long-term Studies in HAE Subjects

Overall, 10 subjects (2.9%) treated with berotralstat experienced a drug-related rash/hypersensitivity TEAE. No dose response was observed and no rash occurred in the placebo group. The most commonly reported rash/hypersensitivity TEAE was rash (5 subjects, 1.5%); all other rash events occurred in 1 subject each. These included Angioedema, dermatitis psoriasiform, drug eruption, rash generalised, rash pruritic and Urticaria.

The single event of angioedema (verbatim term histamine mediated angioedema) was reported on Day 253 for one subject enrolled in Study 204 who was treated with berotralstat 110 mg. The event was Grade 1 in severity and assessed as possibly related to berotralstat. The subject had intermittent episodes of histaminergic angioedema, initially thought to be related to berotralstat; however, it was later assessed as unlikely related to any sort of allergic reaction to berotralstat. Eight of the rash events began within the first month of initiating treatment with berotralstat. 2 subjects interrupted treatment and rash did not recur when berotralstat was restarted; and 2 subjects discontinued berotralstat due to the rash event. There were no notable differences between berotralstat doses and the reports of drug-related rash.

Of note there were no drug-related EOSIs on study 302; the single rash identified was recorded as an unrelated petechiae due to mechanical irritation. In Study 204 Investigators reported drug-related rash events as EOSIs in 8 subjects receiving berotralstat.

GI abdominal events

Non-Integrated Phase 3 Long-term Prophylactic Study in HAE Subjects (Study 301).

Overall,6 subjects reported GI abdominal TEAE's. 3 (50.0% and 42.9%, respectively) berotralstat 110 and 150 mg subjects each had GI abdominal TEAEs vs. 1 placebo subject (16.7%). None of the GI abdominal TEAEs were SAEs, Grade 3 or Grade 4, or led to discontinuation of study drug.

Two GI abdominal TEAEs were reported by 2 subjects each: abdominal discomfort (1 berotralstat 110 mg treated subject and 1 placebo subject) and abdominal pain and diarrhoea (1 berotralstat 110 and 150 mg treated subject each). Eleven of the 19 GI abdominal TEAEs experienced by subjects treated with berotralstat were considered related to study drug.

Integrated Phase 2/3 Prophylactic Long-term Studies in HAE Subjects

A higher incidence of GI abdominal TEAEs were reported among berotralstat-treated subjects compared to placebo-treated subjects (46.2% vs 35.9%). No dose response was observed for the berotralstat dose groups. In the total berotralstat treatment group, the most frequently reported GI abdominal TEAEs were diarrhoea (12.6%), abdominal pain (12.3%), and nausea (11.1%). The GI TEAEs more frequently reported (> 2% difference) in the berotralstat group vs. the placebo group were diarrhoea (12.6% vs. 0), abdominal pain (12.3% vs 5.1%), vomiting (7.9% vs 2.6%), abdominal pain upper (5.8% vs. 2.6%), flatulence (5.3% vs. 2.6%) and gastroesophageal reflux disease (5.3% vs. 0).

Conversely, events occurring more frequently on placebo (> 2% difference) were nausea (17.9% vs. 11.1%) and abdominal discomfort (7.7% vs 5.0%). Most GI abdominal TEAEs were Grade 1 or Grade 2 in severity and overall, 3.2% of subject discontinued due to a GI abdominal event.

Initially during the first month 107 of 342 subjects (31.3%) reported a GI abdominal TEAE. During Month 2, reports of new onset of GI events reporting declined to 9.4%, and by Month 3, 5.2% of subjects reported GI abdominal TEAEs. The monthly incidence was similar for Months 4 and 5 (4.9% and 4.4%, respectively), and increased slightly to 5.9% in Month 6.

Hepatic events

A strong correlation between elevated transaminases and androgen exposure, particularly close temporal association between discontinuation of androgens and initiation of berotralstat, has been noted. Section 4.8 of the SmPC includes information regarding prior/recent androgen use as a risk factor for LFT elevations during berotralstat use.

No hepatic disorder TEAEs were reported for HAE subjects enrolled in Part 1 of Study 301.

Integrated Phase 2/3 Prophylactic Long-term Studies in HAE Subjects.

Overall, no differences were observed between the berotralstat dose groups and a < 5% difference was observed between berotralstat- and placebo-treated subjects. The most commonly reported hepatic disorders reported in the berotralstat-treated subjects were ALT increased (4.4%) and AST increased (3.2%). No subjects had clinical signs of jaundice, synthetic liver dysfunction, or liver injury.

Table 55: Hepatic Disorders (Potentially Drug Related) Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Integrated Phase 2/3 Prophylactic Long-term Studies Safety Population)

System Organ Class Preferred Term	Berotralstat			Placebo (N = 39) n (%) [events]
	110 mg (N = 158) n (%) [events]	150 mg (N = 184) n (%) [events]	Total (N = 342) n (%) [events]	
Any hepatic disorders (potentially drug related) event	11 (7.0%) [18]	14 (7.6%) [34]	25 (7.3%) [52]	1 (2.6%) [1]
Investigations	10 (6.3%) [17]	13 (7.1%) [33]	23 (6.7%) [50]	1 (2.6%) [1]
Alanine aminotransferase increased	6 (3.8%) [7]	9 (4.9%) [18]	15 (4.4%) [25]	0
Aspartate aminotransferase increased	5 (3.2%) [6]	6 (3.3%) [7]	11 (3.2%) [13]	0
Gamma-glutamyltransferase increased	1 (0.6%) [1]	4 (2.2%) [4]	5 (1.5%) [5]	1 (2.6%) [1]
Liver function test abnormal	1 (0.6%) [1]	2 (1.1%) [2]	3 (0.9%) [3]	0
Hepatic enzyme increased	1 (0.6%) [1]	1 (0.5%) [1]	2 (0.6%) [2]	0
Blood bilirubin increased	1 (0.6%) [1]	0	1 (0.3%) [1]	0
Transaminases increased	0	1 (0.5%) [1]	1 (0.3%) [1]	0
Hepatobiliary disorders	1 (0.6%) [1]	1 (0.5%) [1]	2 (0.6%) [2]	0
Hepatic steatosis	1 (0.6%) [1]	1 (0.5%) [1]	2 (0.6%) [2]	0

Source: Integrated SCS, Table S.15.3.

Safety in special populations

Subgroup analyses were conducted by gender, race, and ethnicity for all integrated analysis population. For the age subgroup, only the integrated Phase 2/3 prophylactic long-term studies in HAE subjects were analysed.

Gender

Gender was tested as a covariate in the population PK model but was not found to have a significant effect on PK of berotralstat.

Among the berotralstat-treated subjects in the integrated Phase 1 single-dose studies, Subgroup analysis by gender was not associated with a different safety risk than observed in the overall population. Overall TEAEs were numerically higher for female subjects compared to male subjects, 42.2% vs. 31.1%, primarily due to Grade 1 TEAEs. Laboratory abnormalities were higher among female subjects compared to male subjects (43.8% vs. 29.4%), there was no difference in Grade 3 or Grade 4 laboratory abnormalities.

A similar picture was seen in Phase 1 multiple-dose studies but gender was not associated with a different safety risk than observed in the overall population. However, some differences were observed. The incidence of overall TEAEs was higher for female subjects compared to male subjects, 16 of 19 subjects (84.2%) vs. 36 of 59 subjects (61.0%). More female subjects experienced a GI abdominal TEAE, 12 of 19 subjects (63.2%) vs. 18 of 59 subjects (30.5%) of male subjects. More

female subjects had a graded laboratory abnormality, 15 of 19 subjects (78.9%) vs. 34 of 59 subjects (57.6%), although most abnormalities were Grade 1 in severity.

More male subjects experienced a potentially clinically significant QTcF value, 22 of 59 subjects (37.3%) vs. 4 of 19 female subjects (21.1%); 21 of the 26 subjects with threshold QTcF values had received ≥ 150 mg berotralstat.

Age

The effect of age on clearance of berotralstat was modest in the population PK model. No dose adjustments are proposed for adolescents or elderly patients.

Overall, among berotralstat-treated subjects in the integrated Phase 2/3 prophylactic long-term studies, 16 of 342 subjects (4.7%) were adolescents, 312 of 342 subjects were adults (91.2%), and 14 of 342 subjects (4.1%) were elderly subjects.

The adolescent group had the lowest proportion of subjects with reported TEAEs, 13 of 16 subjects (81.3%), vs. 283 of 312 adult subjects (90.7%), and 13 of 14 elderly subjects (92.9%)`. The elderly group had the highest incidence of Grade 3 or Grade 4 TEAEs; 3 of 14 elderly subjects (21.4%), vs. 40 of 312 adult subjects (12.8%), and 2 of 16 adolescent subjects (12.5%).

The elderly age group had the highest proportion of subjects who discontinued study drug due to a TEAE; 2 of 14 subjects (14.3%) vs. 25 of 312 adult subjects (8.0%), and 1 of 16 adolescent subjects (6.3%).

A higher incidence of potentially drug-related hepatic disorders was observed in the elderly adult age group, 3 of 14 subjects (21.4%) compared to 22 of 312 adult subjects (7.1%), and 0 adolescent subjects.

A higher incidence of GI abdominal TEAEs was reported in elderly subjects, 8 of 14 elderly subjects (57.1%) vs. 145 of 312 adult subjects (46.5%) and 5 of 16 adolescent subjects (31.3%).

A higher incidence of graded laboratory abnormalities occurred in the elderly age group, 13 of 14 elderly subjects (92.9%) compared to 270 of 312 adult subjects (86.5%) and 13 of 16 adolescent subjects (81.3%). Additionally, the incidence of Grade 3 and Grade 4 laboratory abnormalities was also higher in the elderly group, 3 of 14 elderly subjects (21.4%) vs. 28 of 312 adult subjects (9.0%) and 2 of 16 adolescent subjects (12.5%).

No adolescent subject had a post baseline ALT elevation > 3 × ULN compared to 1 of 14 elderly subjects (7.1%) and 15 of 312 adult subjects (4.8%). The lack of ALT elevation among adolescent subjects may be due to low relative androgen exposure.

Race

Four categories of race were evaluated: white, black or African American, Asian, and Other Race was tested as a covariate in the population PK model but was not found to have a significant effect on PK of berotralstat.

Generally, subgroup analysis by race was not associated with a different safety risk than observed in the overall population. Overall, there was a higher percentage of white patients compared to other races and some individual differences were observed, but different safety profile base on race is not expected.

Hepatic Impairment

No subgroup analyses by hepatic impairment were conducted for the pooled populations.

Phase 1, Phase 2, and Phase 3 studies, subjects were excluded if they had elevated ALT or AST values at screening (ie, ≥ 2 × ULN for healthy subjects or ≥ 3 × ULN for HAE subjects).

A Phase 1 study, Study 108, was designed to evaluate the PK and safety of berotralstat in subjects with varying degrees of hepatic impairment.

The increases in plasma concentrations of berotralstat in subjects with moderate and severe hepatic impairment were not clinically significant based on accumulated knowledge of berotralstat safety from clinical studies. No dose adjustment of berotralstat is necessary in subjects with mild, moderate, or severe hepatic impairment. However, in patients with moderate or severe hepatic impairment, the increased risk of prolonged QT associated with increased serum berotralstat concentrations is mentioned in the product information. In these patients berotralstat should be avoided.

Renal Impairment

No subgroup analyses by renal impairment were conducted for the pooled populations. A Phase 1 study, Study 107, was designed to evaluate the PK and safety of berotralstat in subjects with varying degrees of renal impairment.

Subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m2; not yet on dialysis) had a 5-fold lower CLR of berotralstat than matched healthy subjects. When compared to a concurrent cohort with normal renal function (CLCR greater than 90 mL/min); Cmax was increased by 47%, while AUC0-last was increased by 14%. This just under threshold for risk of QT concern.

At steady state, it would be anticipated that the GM Cmax of berotralstat in subjects with renal impairment would be increased to approximately 220 ng/mL from approximately 160 ng/mL in healthy subjects administered berotralstat for 14 days (Study 106), with no increase in GM AUC anticipated.

Use in Pregnancy and Lactation

There is no data on the background risk of birth defects in this population. There is no proven association of HAE with other genetic diseases.

In total, 3 pregnancies have been reported across the berotralstat clinical development program, 2 subject pregnancies and 1 partner pregnancy. One subject pregnancy is ongoing. The estimated foetal study drug exposure was 24 days. One subject pregnancy with an estimated foetal drug exposure of 8 to 29 days resulted in live birth of a healthy girl during week 38 of pregnancy. The partner pregnancy resulted in live birth of a healthy girl during week 39 of her pregnancy.

The SmPC section 4.6 states as a precautionary measure, it is preferable to avoid the use of berotralstat during pregnancy.

Special populations

A brief summary of TEAEs and Grade 3 or 4 clinical laboratory abnormalities reported in elderly subjects is shown in Table 61. Subjects randomized to placebo were observed for only 24 weeks prior to re-randomizing to active drug. The overall summary of safety for adults 18 to 64 years of age is included for comparison.

Table 56: Integrated Studies 204 and 302: Summary of TEAEs in Elderly Subjects ≥ 65 Years of Age (Safety Population)

	Adults 18 to 64 years	Elderly ≥ 65 years			
	Berotralstat				Placebo (N = 3)
	Total (N = 365)	110 mg [a] (N = 8)	150 mg (N = 8)	Total (N = 16)	
Subjects with, n (%)					
Any TEAE	313 (85.8%)	8 (100%)	6 (75.0%)	14 (87.5%)	2 (66.7%)
Grade 3 or 4 TEAE	40 (12.8%)	3 (37.5%)	0	3 (18.8%)	2 (66.7%)
SAE	39 (10.7%)	1 (12.5%)	0	1 (6.3%)	2 (66.7%)
Fatal SAE (death)	0	0	0	0	0
TEAE(s) leading to discontinuation of study drug	30 (8.2%)	1 (12.5%)	1 (12.5%)	2 (12.5%)	0
Grade 3 or 4 laboratory abnormalities	270 (86.5%)	1 (12.5%)	2 (25.0%)	3 (18.8%)	0

Abbreviations: GI = gastrointestinal; SAE = serious adverse event; TEAE = treatment-emergent adverse event
[a] Subjects who received 110 mg were transitioned to 150 mg at the Week 52 visit. Data were analyzed according to the original assignment to 110 mg.
Source: Tables MAA.2, S.8.3.1.2, S.8.3.1.3, S.28.3.1.2, S.28.3.1.3; Listings SU.45.3.A, SU.68.3

TEAEs reported by > 1 elderly subject are shown in Table 62.

Table 57: Studies 204 and 302: TEAEs Reported by >1 Elderly (≥ 65 Years of Age) Subject

PT	Berotralstat 110 mg (N = 8) n (%) [events]	Berotralstat 150 mg (N = 8) n (%) [events]	Total (N=16) n (%) [events]	Placebo (N=3) n (%) [events]
Flatulence	2 (25.0%) [2]	3 (37.5%) [3]	5 (31.3%) [5]	0
Diarrhoea	1 (12.5%) [1]	2 (25.0%) [3]	3 (18.8%) [4]	0
Nasopharyngitis	2 (25.0%) [2]	1 (12.5%) [1]	3 (18.8%) [3]	1 (33.3%) [1]
Abdominal discomfort	1 (12.5%) [1]	1 (12.5%) [1]	2 (12.5%) [2]	0
Abdominal distension	1 (12.5%) [1]	1 (12.5%) [1]	2 (12.5%) [2]	0
Alanine aminotransferase increased	2 (25.0%) [3]	0	2 (12.5%) [3]	0
Depression	1 (12.5%) [1]	1 (12.5%) [1]	2 (12.5%) [2]	0
Dyspnoea	2 (25.0%) [2]	0	2 (12.5%) [2]	0
Fatigue	1 (12.5%) [1]	1 (12.5%) [1]	2 (12.5%) [2]	0
Gastrooesophageal reflux disease	1 (12.5%) [1]	1 (12.5%) [1]	2 (12.5%) [2]	0
Headache	1 (12.5%) [1]	1 (12.5%) [2]	2 (12.5%) [3]	0
Iron deficiency	2 (25.0%) [2]	0	2 (12.5%) [2]	0
Nausea	1 (12.5%) [1]	1 (12.5%) [2]	2 (12.5%) [3]	1 (33.3%) [2]
Sinusitis	1 (12.5%) [1]	1 (12.5%) [1]	2 (12.5%) [2]	0
Anxiety	1 (12.5%) [1]	0	1 (6.3%) [1]	1 (33.3%) [1]
Vomiting	1 (12.5%) [2]	0	1 (6.3%) [2]	1 (33.3%) [2]

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities;
TEAE = treatment-emergent adverse event

Notes:

- Subjects in Study 302 who received placebo in Part 1 and later received berotralstat in Part 2 were summarized according to each exposure. Dose levels were reported in free base equivalents.
- AEs were coded using MedDRA v19.1. Only TEAEs, defined as those events that occur after initiation of study drug through the last dose of study drug + 30 days, are summarized. For subjects who experienced the same coded event more than once within a given treatment group, only 1 event is presented, but all events are reported for the events column.

Overall, 3 elderly subjects, 1 allocated to berotralstat 110 mg in Study 204 and 2 randomized to placebo in Study 302, experienced a total of 4 serious adverse events (SAEs). A by-subject display of SAEs occurring on study is provided in Table 63.

Table 58: SAEs Occurring in Elderly Subjects **≥65** Years of Age

Subject / Dose	Race/ Sex/ Age (y)	SAE PT	Start Date (Day)	Duration (Days)	Causality	Toxicity Grade	Med Taken	Outcome of AE
204-113-403/ 110 mg	Asian/F/72	Hereditary angioedema	26 Sep 2018 (14)	2	Not related	Moderate/ Grade 2	Yes	Recovered/ resolved
			24 Oct 2018 (42)	1	Not related	Moderate/ Grade 2	No	Recovered/ resolved
			30 Nov 2018 (79)	2	Not related	Life-threatening/ Grade 4	Yes	Recovered/ resolved
302-074-002/ placebo	White/M/72	Transient ischaemic attack	28 Jul 2018 (30)	4	Not related	Severe/ Grade 3	Yes	Recovered/ resolved
		Diverticulum intestinal hemorrhage	11 Sep 2018 (75)	6	Not related	Life-threatening/ Grade 4	Yes	Recovered/ resolved
302-093-002/ placebo	White/M/68	Pneumonia	04 Nov 2018 (55)	23	Unlikely related	Severe/ Grade 3	Yes	Recovered/ resolved

Abbreviations: AE = adverse event; F = female; med = medication; M = male; PT = preferred term; SAE = serious adverse event

TEAEs leading to discontinuation

Two elderly berotralstat-treated subjects discontinued due to TEAEs:

- Subject, a 74-year-old female receiving berotralstat 110 mg, experienced Grade 3 multiple purpura on Day 129. The event was considered probably related to study drug. There were no laboratory abnormalities observed; specifically, the subject had no clinically significant changes from baseline in chemistry, hematology, and coagulation laboratory findings throughout the study. The subject discontinued study drug on Day 138 but continued to experience purpura. The subject reported a resolution of the event 78 days after discontinuing berotralstat. A narrative for this subject is provided in Section 14.3.3 of the Study 302 Part 1 interim CSR.
- Subject, a 69-year-old female receiving berotralstat 150 mg, experienced Grade 1 palpitations on Day 172 and Grade 1 tachycardia on Day 183. Study drug was withdrawn as a result of these events. The events were considered possibly related to study drug. Electrocardiograms (ECG) done during the symptomatic period were assessed as normal (heart rate between 64 and 80 bpm and corrected QT interval using Fridericia's method [QTcF] ranging from 409.34 to 425.05 msec with a change from BL < 30 msec at all timepoints). A narrative for this subject is provided in Appendix A.

Grade 3 or 4 TEAEs

Grade 3 or 4 TEAEs reported by elderly berotralstat-treated subjects are shown in Table 64.

Table 59: Studies 204 and 302: Grade 3 and 4 TEAEs by SOC and PT in Elderly Subjects Aged **≥65** Years (Safety Population)

SOC PT	Berotralstat 110 mg (N = 8) n (%) [events]	Berotralstat 150 mg (N = 8) n (%) [events]	Total (N=16) n (%) [events]	Placebo (N=3) n (%) [events]
Any Grade 3 or 4 Event	3 (37.5%) [7]	0	3 (18.8%) [7]	2 (66.7%) [3]
Congenital, familial and genetic disorders	1 (12.5%) [1]	0	1 (6.3%) [1]	0
Hereditary angioedema	1 (12.5%) [1]	0	1 (6.3%) [1]	0
Gastrointestinal disorders	1 (12.5%) [1]	0	1 (6.3%) [1]	1 (33.3%) [1]
Large intestine polyp	1 (12.5%) [1]	0	1 (6.3%) [1]	0
Diverticulum intestinal haemorrhagic	0	0	0	1 (33.3%) [1]
Investigations	1 (12.5%) [1]	0	1 (6.3%) [1]	0
Alanine aminotransferase increased	1 (12.5%) [1]	0	1 (6.3%) [1]	0
Skin and subcutaneous tissue disorders	1 (12.5%) [4]	0	1 (6.3%) [4]	0
Purpura	1 (12.5%) [4]	0	1 (6.3%) [4]	0
Infections and infestations	0	0	0	1 (33.3%) [1]
Pneumonia	0	0	0	1 (33.3%) [1]
Nervous system disorders	0	0	0	1 (33.3%) [1]
Transient ischaemic attack	0	0	0	1 (33.3%) [1]

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = prothrombin time; SOC = system organ classification; TEAE = treatment-emergent adverse event

Grade 3 and 4 laboratory toxicities are described in Table 65.

Table 60: Studies 204 and 302: Details of Grade 3 and 4 Clinical Laboratory Elevations Occurring in Elderly Subjects ≥ 65 Years

Subject # / Dose	Age (y), Race, Sex	Event	Grade / Causality (if TEAE)	Onset Day, Outcome: Resolution Day (Duration [Days])	Treatment	Prior Androgen Use, Duration, Latency (Transaminase Elevations Only)
204-113-403 / 110 mg	72, Asian F	ALT increased AST increased	G3 / probably related G2 / probably related	Onset: D106 Recovered: D121 (15)	No	Yes Duration: approx. 16.5y Latency: 8d
	Clinical course: The subject had discontinued long-term danazol 8 days prior to first dose of berotralstat. BL transaminases were WNL. At Week 4 (D28), ALT was 51 U/L (G1), AST WNL. At Week 8 (D56), ALT was 72 U/L (G1) and AST 49 U/L (G1). Patient discontinued berotralstat on D84 for perceived lack of efficacy. She returned for EOS visit on D106, 22d after the last dose of study drug. ALT was 130 U/L (G3), AST 75 U/L (G2). She continued follow-up for her transaminase elevations: on D112: ALT was 67 U/L (G1), AST 32 U/L (WNL). ALT was WNL (28 U/L) by D132. No concurrent elevation in BILI or ALP. Patient was asymptomatic; study drug discontinued on D84 for perceived lack of efficacy. The subject restarted danazol after discontinuing berotralstat. Transaminase elevations occurred 22d after last dose of berotralstat.					
204-034-401 / 150 mg	72, White, M	Prothrombin INR	G3/ N/A	Onset: D29 Recovered: D57 (28)	No	N/A
	Clinical course: BL and screening prothrombin INR had been elevated at 1.7 (G2). On Day 29, prothrombin INR was 2.0 (G3); ALT, AST, ALP, BILI, and aPTT were WNL. On Days 57 and 81, prothrombin INR had declined to 1.3 and 1.4 (G1), respectively. TEAEs ongoing at the time of the laboratory abnormality included G2 abdominal distension (Days 18 to 33), G2 abdominal pain (Days 18 to 33), and G2 dyspepsia (Days 18 to 33). The subject was chronically on rivaroxaban 15 mg QD for atrial fibrillation, which is known to cause elevated prothrombin INR in some patients. On Day 169, the subject's prothrombin INR was similarly elevated to 1.9 (G3).					
204-083-405 / 150 mg	65, White, F	Neutrophils	G3/ N/A	Onset: D29 Recovered: D57 (28)	No	N/A
	Clinical course: The subject experienced a transient single G3 (low) neutrophil count of $0.73 \times 10^3/\mu L$ (LLN = $1.0 \times 10^3/\mu L$) on Day 29. At all other time points including BL, neutrophil counts were WNL. No associated AEs were reported at the time of the abnormality.					

Hepatic disorders

One elderly berotralstat-treated subject had a post-BL ALT > 3 × the upper limit of normal (ULN) and no subjects had any other post-BL liver function test > 3 × ULN (Table 7). No elderly subjects experienced transaminase elevations during placebo treatment. Most transaminase elevations occurred in conjunction with recent androgen discontinuation, which was prohibited in Study 302, where all placebo subjects enrolled.

Three elderly subjects experienced potentially drug-related hepatic disorders, as shown in Table 66.

Table 61: Studies 204 and 302: By-Subject Display of Potentially Drug-related Hepatic Disorders Occurring on Berotralstat (Safety Population)

Table 8: Studies 204 and 302: By-Subject Display of Potentially Drug-related Hepatic Disorders Occurring on Berotralstat (Safety Population)

Subject # / Treatment	Sex / Age (y) / Race	Prior Androgen Use / Time Since Stopping Androgens	First Dose / Last Dose	Event	Start Date/ Time (Study Day)	Stop Date/ Time (Study Day)	Outcome	Severity	Related	Action Taken
204-113-403 / 110 mg	F/72/ Asian	> 10 y / < 2 wks	13 Sep 2018/ 5 Dec 2018	ALT increased	10 Oct 2018 (28)	26 Dec 2018 (105)	Recovered/ resolved	Mild/ Grade 1	Probably related	Dose not changed
				AST increased	7 Nov 2018 (56)	26 Dec 2018 (105)	Recovered/ resolved	Mild/ Grade 1	Probably related	Dose not changed
				ALT increased	27 Dec 2018 (106)	22 Jan 2019 (132)	Recovered/ resolved	Severe/ Grade 3	Probably related	N/A
				AST increased	27 Dec 2018 (106)	22 Jan 2019 (132)	Recovered/ resolved	Moderate/ Grade 2	Probably related	N/A
302-010-001 / 110 mg	F/74/ White	N/A	26 Sep 2018 / 11 Feb 2019	GGT increased	21 Nov 2018 (57)	19 Dec 2018 (85)	Recovered/ resolved	Mild/ Grade 1	Definitely related	Dose not changed
302-067-002 / 110 mg followed by 150 mg	M/72/ White	5 to < 10 y / ≥ 2 mo	3 Oct 2018 / 1 Dec 2019	ALT increased	21 Dec 2018 (80)	6 Feb 2019 (127)	Recovered/ resolved	Mild/ Grade 1	Probably related	Dose not changed

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = female; GGT = gamma-glutamyl transferase; M = male; N/A = not applicable
Source: Summary of Clinical Safety Listing SU.31.3.A

GI abdominal TEAEs

GI abdominal TEAEs were reported in 57.1% of elderly subjects on berotralstat (62.5% on 110 mg and 50.0% on 150 mg). In the adult non-elderly (18 to 64 years) berotralstat-treated population, GI abdominal events were reported in 46.5% of the population (48.6% on 110 mg and 44.7% on 150 mg).

The most common GI abdominal TEAEs in elderly subjects receiving berotralstat were flatulence (28.6%); diarrhoea; abdominal discomfort, abdominal distention, and nausea (14.3% each). In adults, the most common GI abdominal TEAEs were diarrhoea (13.1%), abdominal pain (12.8%), nausea (11.2%) and vomiting (8.3%). Nausea occurred more frequently in the placebo treated subjects. There were no GI abdominal TEAEs that were SAEs or led to discontinuation of berotralstat. An unrelated Grade 3 GI event of large intestine polyp occurred in a subject who switched from placebo to 110 mg. All other GI TEAEs were Grade 1 or 2.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

The effects of berotralstat on CYP drug-metabolizing enzymes are dose-dependent, with greater degrees of inhibition observed at 350 mg [SN] QD compared to 150 mg QD.

An in vivo drug interaction study (Study 102) conducted with sensitive substrates for CYP3A (midazolam), CYP2C9 (tolbutamide), CYP2C19 (omeprazole), and CYP2D6 (dextromethorphan) suggested that berotralstat at 350◦mg [SN] QD is a strong inhibitor of CYP2D6 (approximate 8-fold increase in AUC), a moderate inhibitor of CYP2C9, CYP2C19, and intestinal CYP3A4 (exposure increased between 2- and 4-fold), and a weak inhibitor of hepatic CYP3A4 (< 2-fold increase in exposure).

A second “cocktail study” was conducted to evaluate the interaction on the sensitive CYP substrates already tested in Study 102 to definitively inform the drug interaction liability of berotralstat on CYP2D6, CYP2C9, CYP2C19 and CYP3A4 at the clinically relevant dose of 150◦mg QD (Figure 19). At 150◦mg QD, berotralstat is a moderate inhibitor of CYP3A4 (approximate 2-fold increase in AUC) and

CYP2D6 enzyme activities (approximate 3-fold increase in AUC); and weak inhibitor of hepatic CYP2C9 enzyme activity (< 2-fold increase in AUC).

The AUC and Cmax of the CYP2C19 substrate omeprazole were increased less than 25% with concomitant administration of berotralstat and the metabolic ratio of omeprazole:5-hydroxy omeprazole was unchanged with concomitant administration of berotralstat; therefore, berotralstat is not considered an inhibitor of CYP2C19.

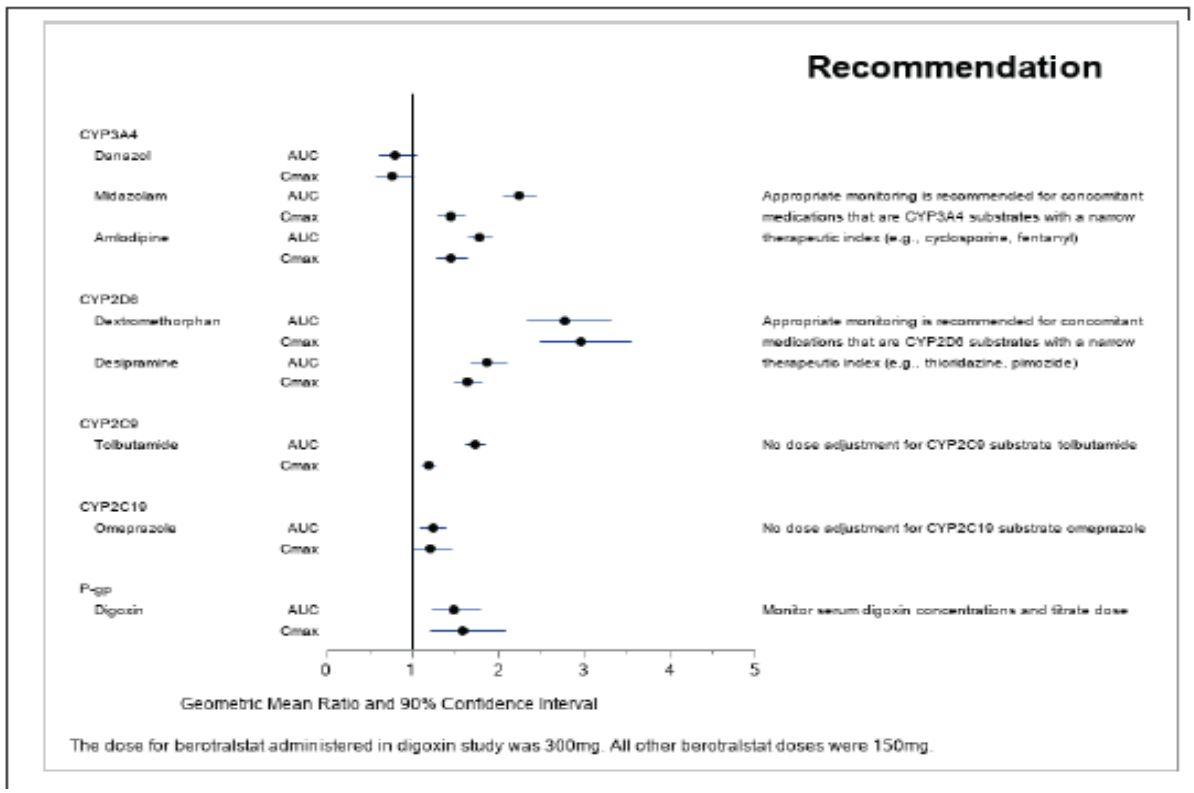
Berotralstat 150 mg QD reduced the exposure of danazol (CYP3A and CYP2D6 substrate) by approximately 25%, primarily due to lower Cmax. Berotralstat 150 mg is a weak inhibitor of amlodipine (CYP3A substrate) metabolism, increasing exposure < 2-fold. The exposure of desipramine, a sensitive CYP2D6 substrate, increased approximately 2-fold.

CYP2D6 is a polymorphic enzyme, and variations of the gene give rise to alleles resulting in no, decreased, normal or increased enzymatic activity. In Studies 102, 112, and 115, subjects with no enzymatic activity and increased enzymatic activity, known as poor and ultra-rapid metabolizers, respectively, were excluded.

An early in vivo drug interaction study (Study 105) was performed to investigate the potential for berotralstat 350 mg (SN) QD to interact with probe substrates digoxin (P-gp substrate) and rosuvastatin (BCRP substrate). Berotralstat 350 mg was a weak inhibitor of P-gp, increasing exposure to digoxin by approximately 50%. Berotralstat 350 mg (SN) was not an inhibitor of BCRP, as rosuvastatin exposure was decreased by approximately 20%.

In summary, at clinical dose of berotralstat 150 mg QD, the CYP and P-gp inhibitory effects of berotralstat are unlikely to be of clinical importance except for drugs with a narrow therapeutic index. It is recommended that such medications are appropriately monitored, either through therapeutic drug monitoring or assessment of exaggerated PD effects of the offended drug.

Figure 19: Forest Plot of Exposure Changes in Probe Substrates with Berotralstat 150 mg Coadministration



Discontinuation due to AES

Integrated Phase 2/3 Prophylactic Long-term Studies in HAE Subjects

Overall, 8.2% and 2.6% of subjects treated with berotralstat and placebo, respectively, experienced a TEAE leading to study drug discontinuation. No dose response was observed. The most common TEAEs leading to study drug discontinuation were in the GI disorders and investigations SOCs (3.2% and 2.6%, respectively). The most common TEAE leading to discontinuation of study was ALT increased (1.2%); the next most common TEAEs that led to discontinuation each occurred in 0.9% of subjects and included upper abdominal pain, nausea, vomiting, and liver function test abnormal.

Most berotralstat-treated subjects with TEAEs leading to study drug discontinuation occurred in subjects enrolled in Study 204 (19 of 28 subjects [67.9%]), had TEAEs that were considered related to berotralstat (24 of 28 subjects [85.7%]), and most subjects recovered. One subject (Subject 106-410) with ALT and AST increased withdrew consent and no additional follow-up data were available and the treatment-emergent SAEs for 2 subjects, plasma cell myeloma and acute myelomonocytic leukaemia, respectively, were ongoing at the time of discontinuation.

Integrated Phase 1 Single-dose and Multiple-dose Studies in Healthy Subjects

Two percent of subjects in the Integrated Phase 1 Single-dose Studies in Healthy Subjects discontinued due to TEAEs. Two AE of Grade 2 transaminases increase and Grade 1 eczema were assessed by the investigator as possibly related to study drug In the Integrated Phase 1 Multiple-dose Studies in Healthy Subjects 3.8% discontinued study treatment due to TEAEs. (3 subjects in the berotralstat dose group > 150 mg upper abdominal pain, diarrhoea and non-cardiac chest pain).

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety of berotralstat has been evaluated overall in 14 Phase 1 clinical studies and 5 Phase 2 or 3 clinical studies in HAE subjects.

3 separate subject pools provided integrated data from 241 single-dose berotralstat-treated healthy subjects (doses ranged from 8.7 to 871 mg), 78 multiple-dose berotralstat-treated healthy subjects (doses ranged from 110 to 450 mg for 7 to 14 days), and 342 subjects with HAE treated long-term at QD doses of 110 or 150 mg. The latter subject pool in HAE subjects was comprised of 1 pivotal placebo-controlled Phase 3 Study 302 and 1 Phase 2 long-term safety Study 204.

Safety data from a second Phase 3, randomized, double-blind, placebo-controlled Study 301 provides non-integrated, stand-alone, berotralstat-treated safety data at QD doses of 110 or 150 mg in subjects with HAE enrolled at 10 sites in Japan. However, this is limited as only 13 patients were enrolled.

In addition, 9 non-integrated Phase 1 studies provide berotralstat-treated data from 182 healthy subjects (doses ranged from 150 mg to 675 mg), 7 subjects with renal impairment (200-mg dose), and 18 subjects with hepatic impairment (150-mg dose).

Two non-integrated Phase 2 studies provided berotralstat-treated safety data in subjects with HAE; the 28-day prophylactic Study 203 and the acute (2 single active liquid doses) Study 202 provided berotralstat-treated safety data for 58 HAE subjects (doses ranged from 218 to 650 mg).

The main safety data in the HAE population and intended dose of 150mg arises from the pivotal phase 3 study 302 and the phase 2 study 204.

Study 302

In this study, overall berotralstat treatment appears safe and well tolerated at both treatment doses.

During Part 1, 34 of 41 berotralstat 110 mg subjects (82.9%), 34 of 40 berotralstat 150 mg subjects (85.0%), and 30 of 39 placebo subjects (77%) experienced a TEAE.

The drug related TEAEs most frequently reported were related to GI disturbances. Nausea, dyspepsia and diarrhoea were the most frequently reported drug related events. With the exception of nausea (which was more frequently reported in the placebo group [15% vs 9%]) the events were more frequently reported in the berotralstat treatment groups. Dyspepsia was more frequently reported in the berotralstat 110mg vs 150 mg group and diarrhoea was more frequently reported in the berotralstat 150 mg group.

During Part 1, 1 (2%) berotralstat 110 mg subjects, no berotralstat 150 mg subjects, and 3 (8%) placebo subjects experienced a treatment-emergent SAE.

Skin rash was an EOSI in this study. There were no drug-related EOSIs on study; the single rash identified was recorded as an unrelated petechiae due to mechanical irritation.

There were few DMID Grade 3 or Grade 4 laboratory toxicities reported, with a similar number of such events reported across the treatment groups. Five subjects (6.2%) treated with berotralstat experienced DMID Grade 3 laboratory toxicities compared with 4 subjects (10.3%) in the placebo treatment group. One subject on 150 mg berotralstat who had previously been exposed to androgens had Grade 4 ALT and Grade 3 AST without symptoms or elevation of bilirubin, which resolved after discontinuing study drug.

Study 204 is an ongoing Phase 2 open-label safety study designed to assess the long-term safety and effectiveness of berotralstat as a prophylactic treatment for HAE.

Overall, oral treatment with berotralstat 150 mg and 110 mg QD was safe and generally well tolerated. No new safety signals were identified, safety risks were consistent with the risks previously noted. No subjects experienced a TEAE that led to death.

The most frequently reported TEAEs were nasopharyngitis (30.8%), headache (17.6%), abdominal pain (13.2%), and diarrhoea (13.2%).

Overall, 13.2% of subjects experienced a treatment-emergent SAE. Three subjects (1.3%) experienced 4 treatment-emergent SAEs assessed by the investigator as related to study drug; Grade 3 gastroenteritis and Grade 2 hepatic enzyme increased (n = 1), Grade 3 abnormal LFT (n = 1), and Grade 3 abdominal pain (n = 1). The 2 subjects with treatment-emergent SAEs of gastroenteritis, hepatic enzyme increased, and abnormal LFT resulted in study drug discontinuation.

In addition, 27 subjects (11.9%) interrupted study drug due to TEAEs. The most common TEAE that led to study drug interruption was HAE attack in 5 subjects (2.2%). Overall, TEAEs in the GI SOC led to study drug interruption in the greatest number of subjects. Overall, 6 subjects (2.6%) discontinued study drug due to a GI TEAE; 2 subjects (2.0%) and 4 subjects (3.1%) in the berotralstat 110-mg and 150-mg dose groups, respectively.

For this study, non-serious treatment-emergent rashes were considered EOSIs for investigator-reporting purposes. Overall, 8 subjects (3.5%) had rash EOSIs assessed by the investigator as related to study drug. There were no serious rash events and all drug-related rash events were Grade 1 or Grade 2 in severity.

GI events were considered a potential safety signal; 105 subjects (46.3%) experienced a GI abdominal TEAE and 6 subjects (2.6%) discontinued due to a GI abdominal event. The most common GI

abdominal TEAEs were diarrhoea (13.2%), abdominal pain (13.2%), and nausea (7.9%). No dose response was observed. Most events were Grade 1 or Grade 2 in severity, most events occurred within the first month of initiating berotralstat.

The most common clinically significant chemistry abnormalities were liver-related abnormalities, and the most common abnormality was ALT increased. The majority of treatment-emergent liver abnormalities were Grade 1 or Grade 2; however, 13 subjects (5.7%) experienced a treatment-emergent Grade 3 or Grade 4 ALT, and all of these subjects had previously used androgens.

For the integrated Phase 2/3 analysis, TEAEs were also evaluated by calculating the rate per 100 patient years of exposure (PYE) to normalize for length of time on study and account for differential observation time bias. The per 100 PYE rates of TEAEs occurring in at least 5% of the total number of berotralstat exposures. The results of the analyses of rates of TEAEs per 100 PYE were consistent with those for subject incidence of TEAEs. The events of diarrhoea, headache, and abdominal pain had the largest differences in rate per 100 PYE relative to placebo.

ADRs were identified in study 302 and the integrated phase 2/3 long-term study data. Nasopharyngitis, nausea and dyspepsia, occurred at a higher or similar rate on placebo as on 150 mg berotralstat and were not included as ADRs. ADRs were calculated based on an analysis of AEs in ≥ 10% of subjects with a ≥ 5% difference to placebo. The most common berotralstat ADRs, occurring in ≥ 10% of subjects with a ≥ 5% difference to placebo, were abdominal pain, vomiting, diarrhoea, and back pain. URTi, Headache was frequently reported AE in the phase 2 and phase 3 studies.

Abdominal pain, headache, vomiting and diarrhoea are included as ADRs in Section 4.8. Back pain is not proposed to be included due to occurrence in the study that is lower than would be expected according to global prevalence of back pain.

In their responses the applicant provides further discussion on URTI and headache ADRs with respect to their inclusion in the SmPC. In relation to URTIs the applicant argues that although individual PTs show a difference in incidence between berotralstat and placebo groups, when looking at the medical concept of 'common cold' (which encompasses several PTs relating to differ verbatim of, presumably, the same illness), and shown as a Rate per 100 person-years of Exposure, no imbalance is observed. The same results (lack of an imbalance) are observed when HLT of URTI (as Rate per 100 person-years of Exposure) is reviewed. These explanations are acceptable and URTI does not need to be placed in Section 4.8 of the SmPC based on evidence available.

The relative frequency of events of headache is larger in all berotralstat groups compared to placebo, including when expressed as events per 100 PYE despite placebo group having more patients with a history of headache. It should also be taken into account that the investigators defined events of headache as possibly/probably/definitely related to berotralstat (both doses) in 21.8% (12/55) of cases. Based on all of the above, a causal relationship between headache and berotralstat is a reasonable possibility. Due to the fact that there is a reasonable possibility of a causal relationship between berotralstat and headache the ADR of headache is included in Section 4.8 SmPC.

Overall, 9.9% of subjects (12.7%;110mg and (7.6%;150mg) treated with berotralstat and 5.1% of placebo subjects experienced a treatment-emergent SAE. The most common treatment-emergent SAEs reported in subjects treated with berotralstat were HAE attacks (3.5%) and medical observation (1.2%). A total of 3 subjects (< 1%) experienced 4 treatment-emergent SAEs assessed by the investigator as related to study drug (gastroenteritis, hepatic enzyme increased, abdominal pain, LFTs increased). The most common treatment-emergent SAE events per 100 PYE were also HAE attacks and medical observation. All other treatment-emergent SAE events per 100 PYE was < 1.

No deaths occurred during any of the clinical studies.

A 120-day safety update was provided during the assessment, which includes all subject data through 1 December 2019 for Studies 204 and 302. Broadly speaking it may be agreed that there were no new safety signals identified as part of this analysis. In this integrated analysis of phase 2/3 prophylactic studies 204 and 203 10.5% of subjects treated with berotralstat and 5.1% placebo subjects experienced a treatment-emergent SAE. SAEs in the berotralstat 110/150 mg treatment group included HAE attack n=4, pneumonia n=1, enteritis n=1 and cholelithiasis (n = 2), acute myocardial infarction (n = 1), and syncope (n = 1) in the berotralstat 150 mg treatment group. None of the newly reported SAEs were considered by reporting investigator to be related to berotralstat. The CHMP agreed with the applicant that these events (included the MI which occurred in a 41-year-old woman who had significant cardiovascular risk factors including hypertension, hypercholesterolemia, history of transient ischemic attack, intra-cerebral aneurysm, anaemia, tobacco abuse, and carotid artery dissection) were unrelated to treatment.

In terms of updated data on dropouts and discontinuations, there was a similar proportion of subjects in the 2 berotralstat treatment groups having discontinued study drug (30.4% of patients in the 110mg followed by 150mg group versus 28.3% of patients in the 150mg group). Similar reasons for withdrawal were cited between the groups, with the exception of perceived lack of efficacy 15.8% in in the 110mg followed by 150mg group versus 9.4% of patients in the 150mg group). Similar proportions of patients discontinued due to TEAEs (7% in the 110mg followed by 150mg group v 9.4% in the 150 mg group) though it is noted the number of patients who had dose interrupted due to study drug was twice as large in the 150mg group (6.3% of the 110mg followed by 150 mg group vs 12.6% in the 150mg group).There were 4 additional subjects (1 subject in the 110/150 mg dose group and 3 subjects in the 150 mg dose group) who discontinued study drug to cut off date of the SUR. New TEAEs leading to discontinuation included the following: blood creatine phosphokinase(CPK) increased and troponin T increased (n = 1, Subject 204-013-401) in the 110/150 mg dose group; diarrhoea and gastroesophageal reflux disease (GERD; n = 1, Subject 204-035-401), folliculitis (n = 1, Subject 204-080-402), and systemic lupus erythematosus (n = 1, Subject 204-106-407) in the 150 mg dose group. The rapporteur notes the additional event of blood CPK increased and troponin T increased which occurred in a 22 year old male patient who experienced intermittent elevations in CPK and Troponin T approximately 9 months after initiating treatment in the 110mg treatment group in the context of non-clinical data which identified the potential of cardiac injury. The applicant was requested to discuss this case in the context of the potential for cardiac injury and to present the cumulative data to date for events relating to myocardial muscle injury (comparing the frequency in treated patients to placebo patients). It can be agreed that to date there have not been any observations which suggest cardiac injury that is associated with the use of berotralstat.

No new drug-related rash or hepatic events were reported through the cut-off date for this safety update (ie, 20 August 2019 through 1 December 2019). There was one new Grade 3 or 4 laboratory abnormality (a single, transient Grade 3 result for Leukocytes on day 507 in a patient treated in the 110mg followed by 150mg group).

In terms of ECG findings, of the 2511 ECG assessments among berotralstat-treated subjects during the reporting period through 1 December 2019, 5.7% met a QTcF protocol-defined threshold (ie, QTcF threshold > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, or a change from baseline (CFB) of > 30 to ≤ 60 msec); no subjects met the QTcF threshold > 500 msec or a CFB > 60 msec. No events representing arrhythmias were reported.

TEAE in the single-dose group (6.2%) and diarrhoea was the most frequently-reported TEAE in the multiple-dose group (23.1%) Mild to moderate GI abdominal events were observed with a higher incidence at multiple berotralstat once-daily doses of > 150 mg. The most frequent GI abdominal TEAEs with single and/or multiple doses of berotralstat included diarrhoea, nausea, and abdominal pain.

Overall, 3 potential safety signals were identified from the integrated and non-integrated Phase 1 studies: QT prolongation, drug-related rash, and LFT elevations.

The safety profile observed for berotralstat in the non-integrated Phase 1 studies (182 healthy subjects, 7 subjects with severe renal impairment, and 18 subjects with hepatic impairment) was consistent with the integrated study pools, with no new safety signals identified.

Special populations included investigation in patients with renal and hepatic impairment.

While subjects with severe renal impairment excreted 4-fold lower amounts of the administered dose of berotralstat in urine as unchanged drug than and had a 5-fold lower renal clearance (CLR) than matched healthy subjects. Although <3% of administered drug was excreted in the urine in matched healthy subjects, No dose adjustment of berotralstat in renal impairment is proposed by the applicant.

In patients with hepatic impairment plasma berotralstat Cmax was approximately 27% higher in subjects with severe hepatic impairment than in matched healthy subjects with normal hepatic function, while AUCs were roughly equivalent between the 2 groups. Plasma exposure of berotralstat was increased the most in subjects with moderate hepatic impairment. Plasma berotralstat Cmax and AUC0-inf were approximately 77% and 78% higher in subjects with moderate hepatic impairment than in matched healthy subjects, respectively. The increase in plasma berotralstat Cmax and AUC0-inf were approximately 50% and 38%, respectively, for the combined group of moderate and severe hepatic impairment.

Potentially drug related hepatic disorders were observed in the clinical studies. In the dose finding studies, patients with a history of prior androgen use demonstrated an imbalance in terms of elevations >3 ULN for ALT, AST and bilirubin when patients treated with 350mg and 250mg berotralstat are compared to those treated with placebo. Similar findings from the phase 2/3 prophylactic long-term studies were observed, so findings may not be purely confounding from the prior androgen and a causal relationship to berotralstat seems likely. It is noteworthy that half of the patients in study 203 who experienced elevations>3ULN were unresolved at follow up.

Furthermore, it is noted that while no patient across the clinical development program met the criteria for Hy's Law there were a number of patients treated with berotralstat in thee phase 2/3 prophylactic long-term studies who fell into "Temple's Corollary" (elevated ALTs but not total bilirubin) versus none for placebo when maximum total bilirubin vs. maximum ALT was plotted for these patients as part of the Hy's Law Plot presented by the applicant (Figure S.41.3).At this stage in clinical development it is uncertain if hepatic injury could occur in a larger treatment population. Hepatotoxicity has been identified by the applicant as a potential risk in the summary of safety concerns and this is endorsed.

QTc effects in the clinical studies performed sporadic cases of QTc prolongation occurred in some of the studies where ECG tracing was conducted however a strong signal was not demonstrated. In dose finding phase 2 study 203 no dose effect was observed and no findings >450msec or a change from baseline was seen. There were no dose response or notable changes from baseline in the experimental measure of renal tubular injury NGAL or cardiac CK-MB, Troponin I, or Troponin T biomarkers. Vital sign data (ie, diastolic BP, systolic BP, HR) and ECG data remained relatively constant throughout treatment with no marked differences between the berotralstat treatment groups or between berotralstat group and placebo. However, in light of the concerns raised in the PD section on estimation of the risk, and in light of a number of potentially overlapping risks could potentially result in increased exposure as well as increased risk of QT prolongation updates to the SmPC regarding risk of QT prolongation have been agreed to and 'QT prolongation' is considered a potential risk.

A number of DDI studies were conducted and the results suggested that berotralstat was a moderate inhibitor of CYP2D6 (approximate 3-fold increase in AUC) and CYP3A4 (approximate 2-fold increase in AUC), and a weak inhibitor of hepatic CYP2C9 (< 2-fold increase in AUC). The AUC and Cmax of the

CYP2C19 substrate omeprazole were increased less than 25% with concomitant administration of berotralstat and the metabolic ratio of omeprazole:5-hydroxy omeprazole was unchanged with concomitant administration of berotralstat; therefore, berotralstat is not considered an inhibitor of CYP2C19.

This is adequately reflected in section 4.5 of the SmPC.

Overall, among berotralstat-treated subjects in the integrated Phase 2/3 prophylactic long-term studies, 16 of 342 subjects (4.7%) were adolescents, 312 of 342 subjects were adults (91.2%), and 14 of 342 subjects (4.1%) were elderly subjects.

The number of elderly population enrolled was low. The elderly experienced highest incidence of Grade 3 or Grade 4 TEAEs, were the highest proportion of subjects who discontinued study drug due to a TEAE.

Also, the elderly had a higher incidence of potentially drug-related hepatic disorders, GI abdominal TEAS, and had a higher incidence of Grade 3 and Grade 4 laboratory abnormalities compared to adolescents and adults. While it is agreed that the reported rates of TEAEs and SAEs, do not appear to identify specific concerns in relation to age, there is uncertainty relating to the applicant's position that differences in incidence of Grade 3 or 4 TEAEs and discontinuations due to TEAEs are an artefact of the smaller elderly population, and indeed uncertainty around the characterisation of the safety profile in elderly patients in general. There are also specific concerns relating to QT prolongation with berotralstat in the context of risk factors for increased exposure including moderate to severe hepatic impairment, severe renal impairment, low body weight and concomitant medications which is concerning in the context of use in elderly, given that these risk factors are common in elderly patients, who are themselves already at increased risk of QT prolongation.

2.6.2. Conclusions on the clinical safety

The safety profile observed to date appears to indicate that berotralstat is a safe and generally well-tolerated treatment for HAE patients. The most common adverse events associated with treatment are mostly GI disturbances such as abdominal pain, vomiting nausea and diarrhoea as well as transaminase elevations, headache and rash. Hepatotoxicity has been identified as a potential risk in the summary of safety concerns and this is endorsed by CHMP.

Due to the potential risk of QTc prolongation, in patients with severe renal impairment, it is preferable to avoid the use of berotralstat. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered as mentioned in the SmPC in section 4.4.

Cardiac effects were identified as a safety concern from nonclinical studies. While abnormalities in ECG were of borderline clinical significance, it is noted that in the exposure-response analysis, there was a statistically significant positive relationship between ΔΔQTcF and berotralstat concentration. Therefore, the SmPC has been amended to reflect the potential risk of QT prolongation and recommend that it is preferable to avoid the use of berotralstat in these patients. If treatment would be required, appropriate monitoring (e.g. ECGs) should be considered.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	Hepatoxicity Hypersensitivity

	QT prolongation Drug-drug interaction with narrow therapeutic index drugs metabolized by CYP2D6 and CYP3A4 Phospholipidosis Carcinogenicity
Missing information	Safety profile in pregnancy and lactation Long-term safety in paediatric patients

Pharmacovigilance plan

Study and Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
BCX7353-401: Non-interventional Post-Authorization Study to Evaluate Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema in a Real-World Setting Planned	Primary Objective: To monitor safety and tolerability of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients Secondary Objectives: To evaluate the effectiveness of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients in a real-world setting; To assess quality of life during long-term administration of berotralstat in a real-world setting; To assess long-term growth and development in adolescent patients 12 to 17 years of age.	Long-term safety in patients receiving Orladeyo as marketed product Long-term impact of berotralstat administration on growth and development of pediatric patients. Hepatotoxicity and phospholipidosis in adult and pediatric subjects.	Annual reports	To be submitted with annual re-assessments Final report anticipant approximately 5.5 years after last patient enrolls

Study and Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
BCX7353-204: An open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with Type I and II hereditary angioedema Ongoing	Primary Objective: To evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 in subjects with hereditary angioedema (HAE) Secondary Objective: To assess the effectiveness (ie, HAE attack frequency, severity and disease activity over time) of BCX7353 during long-term administration; To evaluate quality of life (QoL) during long-term administration of BCX7353; To evaluate subject's satisfaction with medication during long-term administration of BCX7353	Long-term safety in adults and adolescents receiving berotralstat	Completion of study when berotralstat is commercially available or subjects transition to other means of access	CSR submitted 6 months after study end
BCX7353-302: A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema Ongoing	Part 3 Primary Objective: To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 48- to up to 240-week administration period in subjects with HAE Part 3 Secondary Objectives: To assess the effectiveness (ie, HAE attack frequency over time) of BCX7353 over a 48- to up to 240-week administration period; To evaluate QoL and HAE disease activity of BCX7353 over a 48- to up to 240-week administration period; To evaluate subject satisfaction with BCX7353 over a 48- to up to 240-week administration period	Long-term safety in adults and adolescents receiving berotralstat	Completion of study when berotralstat is commercially available or subjects transition to BCX7353-312	CSR submitted 6 months after study end

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatoxicity	Routine risk minimisation measures: SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hypersensitivity	Routine risk minimisation measures: SmPC Sections 4.3, 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
QT prolongation	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted questionnaire for all reported adverse events with PTs contained in the broad terms of the TdP SMQ Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Use of berotralstat in patients weighing < 40 kg should be avoided It is preferable to avoid use of berotralstat in patients with severe renal impairment Appropriate monitoring for patients with independent risk factors for QT prolongation will be considered Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	
Drug-drug interaction with narrow therapeutic index drugs metabolized by CYP2D6 and CYP3A4	Routine risk minimisation measures: SmPC Sections 4.5, 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: For concomitant medicines that are predominantly metabolised by CYP2D6 (e.g. thioridazine, pimozide) or CYP3A4 (e.g. cyclosporine, fentanyl), particularly those with a narrow therapeutic index, dose adjustments of these medicines may be required. (SmPC, Section 4.5) Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Phospholipidosis	Routine risk minimisation measures: SmPC Section 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Additional pharmacovigilance activities: None
Carcinogenicity	Routine risk minimisation measures: SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety profile in pregnancy and lactation	Routine risk minimisation measures: SmPC Sections 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Use during pregnancy is not recommended and use during lactation should take into consideration the individual benefit-risk Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: For all reported pregnancies, use of a specialized pregnancy form to ensure all pertinent details obtained. Attempts will be made to follow any reported pregnancy to outcome Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term safety in paediatric patients	Routine risk communication: SmPC Sections 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the SmPC: Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: PASS

In conclusion the CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 3 December 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of berotralstat with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Orladeyo (berotralstat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is seeking an indication for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

Hereditary angioedema is a rare autosomal dominantly inherited condition, which can be disabling painful and occasionally life threatening. The most common form of the condition affecting about 85% those with HAE, known as Type 1 HAE is caused by a deficiency of the C 1 inhibitor. Roughly 15% have Type 2 HAE where C1 inhibitor levels may be normal but the C1 inhibitor has a reduced function. C 1 inhibitor is a serine protease inhibitor that regulates a number of inflammatory pathways including controlling the production of bradykinin. Patients with HAE have intermittent cutaneous or mucosal swellings, that typically evolve over a number of hours and can persist for a few days. The orofacial region, abdominal viscera, the peripheries and occasionally the larynx may be affected. Laryngeal attacks can be life threatening.

3.1.2. Available therapies and unmet medical need

Two medicinal products are currently licensed for the prophylaxis of HAE attacks. There are also a number of products licensed for the treatment of acute attacks.

Cinryze (C1 inhibitor derived from human plasma) is licensed for routine prophylaxis of attacks in adults, adolescents and children (6 years and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. Initially the medicinal product is administered intra-venously every 3 to 4 days.

Takhzyro (lanadelumab) a fully human monoclonal antibody that inhibits active plasma kallikrein activity, thereby limiting production of bradykinin is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. It is administered subcutaneously every two weeks.

3.1.3. Main clinical studies

In support of the application the applicant submitted a phase 2 randomised double blind placebo-controlled dose finding and proof of concept study (BCX7353-203), a phase 3 randomised double blind placebo controlled trial conducted in North American and European populations (BCX7353-302), a smaller phase 3 study with the same design conducted in a Japanese population (BCX7353-301) and an open label uncontrolled phase 2 study (BCX7353-204).

Study BCX7353-302 is the main clinical study and compared two doses of berotralstat 110mg (n = 41) and 150mg (n = 40) versus placebo (n = 40) in patients with Type 1 or Type 2 HAE. Efficacy was assessed following 24 weeks of treatment (Part 1). The study is ongoing (Part 2 and 3).

The patient population were required to have a diagnosis of either Type 1 or Type 2 HAE. Adolescents were eligible to participate in both Study BCX7353-302 and 301 studies. However, only 6 adolescent

patients (2 per study arm) were recruited to Study BCX7353-302. Study BCX7353-203 subjects were required to have had a documented attack rate of at least 2 HAE attacks per month for 3 consecutive months within 6 months prior to screening. Whereas for Studies BCX7353-302 and 301 subjects were required to have had ≥ 2 HAE attacks during a 56-day run-in period.

Among berotralstat-treated subjects in the integrated Phase 2/3 prophylactic long-term studies, 16 of 342 subjects (4.7%) were adolescents, 312 of 342 subjects were adults (91.2%), and 14 of 342 subjects (4.1%) were elderly subjects. There were no adolescent patients enrolled into the phase 1 studies.

For both phase 3 studies the primary endpoint was the rate of confirmed HAE attacks during the entire 24-week dosing period of Part 1 evaluated in the ITT population, defined as the total number of investigator-confirmed HAE attacks experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2. Statistical analysis was based on a negative binomial regression model. Data on symptoms was recorded by the patient in an electronic diary to which the investigators had real time access.

3.2. Favourable effects

The pivotal study BCX7353-302 met its primary endpoint reduction in HAE attack rate for both berotralstat doses with a greater rate reduction (%) from placebo for berotralstat 150mg (-44.2% with 95% CI from -59.5 to -23%, p-value < 0.001) compared to berotralstat 110mg (-30% with 95% CI from -48.7, -4.6%, p-value 0.024). Investigator attack rates over the dosing period were 1.65/28 days for berotralstat 110mg, from a baseline of 2.97/28 days; 1.31/28 days for berotralstat 150mg from a baseline of 3.06/28 days; and 2.35/28 days for placebo, from a baseline of 2.91/28 days.

In this study, the number of days with angioedema symptoms over the 24 weeks was similar for both active treatment arms (19 and 20 days) and lower than placebo (29 days).

Similar results were reported in a supportive Study BCX7353-301 which demonstrated a decrease in the rate of angioedema events by 25% (p = 0.181) and 49% (p = 0.003), for 110 and 150 mg berotralstat doses compared with placebo respectively. The negative binomial analysis estimated event rates per 28 days were 1.64 for berotralstat 110 mg subjects, 1.11 for berotralstat 150 mg subjects, and 2.18 for placebo subjects over the 24-week Part 1 dosing period.

3.3. Uncertainties and limitations about favourable effects

A missing data sensitivity analysis conducted on the primary endpoint in which observed data post study drug discontinuation was used in combination with imputed data for subjects who discontinued study treatment prior to the end of Part 1 and did not continue to record HAE attacks showed a marked attenuation in the effect size for berotralstat 150mg but not for berotralstat 110mg with a rate reduction % from placebo of -35% (95% CI -9.2, -52.9%) as compared to -44.2% in the original analysis. Additional sensitivity analyses provided at the request of the CHMP demonstrated a lesser attenuation of effect for the 150 mg dose from 44.2% to 39% (using all observed data and imputing remaining missing data under a Jump to Reference assumption) and from 44.2% to 40% (imputing all data post-discontinuation of study drug under a Jump to Reference assumption). These data provided further reassurance to reduce the uncertainty around the effect size for the berotralstat 150mg dose.

The clinical relevance of the effect size seen in the primary endpoint is considered modest. An improvement in the Angioedema Quality of Life Scale (used as key secondary endpoint) was observed but without statistically significant difference between the groups.

A pre-planned subgroup analysis in Study 302 showed a greater rate reduction (%) from placebo in males in both berotralstat treatment arms compared to females. Additional analyses suggested also that the magnitude of the treatment effect on HAE attack rate could be smaller in females than males. Additionally, there was an imbalance in the proportion of females across treatment arms (73.2% in the berotralstat 110mg arm, 57.5% in the berotralstat 150mg arm and 66% in the placebo arm). Given the greater response seen for males, it is possible that the higher rate reduction from placebo seen in berotralstat 150mg may have been driven by the larger proportion of males in that treatment group (42.5%) compared to that of berotralstat 110mg (26.8%). Additional analyses provided could not fully exclude this possibility thus, no definite conclusion could be drawn on the basis of available data.

There has been limited exposure in the development programme to berotralstat of adolescents, with only 4 subjects aged from 12 to 17 and weighting ≥40kg exposed to berotralstat. Sub-group analysis by age-group was uninformative. There does not appear to be any difference in efficacy between adolescent and adult patients however, the data remain limited.

Maintenance of effect is observed up to 48 weeks, however given the small sample size and possible individual subjects' data influence, the interpretation of durability of response is not straightforward.

Evaluation of efficacy by attack site was an exploratory endpoint only and though numerically there was a reduction in attack rate for abdominal, peripheral and laryngeal attacks in the berotralstat treatment arms compared to placebo, these were not nominally or statistically significant. Available data seem to show that berotralstat 150mg produced a reduction in moderate to severe attacks, a reduction in acute attack medication usage and in the rate of laryngeal attacks.

3.4. Unfavourable effects

Berotralstat appears to have an acceptable safety profile. Most AEs were mild to moderate in severity, and recovery was documented. The overall rates for AEs and SAEs were low and similar across all treatment arms.

The main unfavourable effects associated with berotralstat are abdominal pain, diarrhoea and headache with a frequency very common. Gastroesophageal reflux, Flatulence vomiting are also reported as common GI effects. These reactions were generally mild rarely led to treatment interruptions.

Drug rash can occur with treatment with a frequency estimated as common.

The most common clinically significant chemistry abnormalities were liver-related abnormalities, (ALT and AST increased). The majority of treatment-emergent liver abnormalities were Grade 1 or Grade 2; however, some patients experienced more marked elevations with treatment-emergent Grade 4 ALT with Grade 3 AST. It acknowledged that these patients remained asymptomatic and that there have not been instances of transaminase elevations with concomitant evidence of jaundice or synthetic dysfunction to date. In studies 204 and 302, the incidence of ALT > 3 × ULN was significantly correlated with prior androgen duration of ≥ 5 years ($p < 0.001$) and recent discontinuation of androgens ($p < 0.001$). The odds of having an elevation were 10.7 × higher for those with ≥ 5 years of exposure (14 of 151 subjects [9.3%]) compared to those with < 5 years duration of exposure (2 of 230 subjects [0.9%]). The odds of having an elevation were 66.0 × higher for those with recent androgen use, defined as discontinuation of androgens within 30 days of commencing berotralstat, (14 of 49 subjects [28.6%]) compared to those without recent androgen use (2 of 332 subjects [0.6%]).

The adolescent group had the lowest proportion of subjects with reported TEAEs, 13 of 16 subjects (81.3%), vs. 283 of 312 adult subjects (90.7%), and 13 of 14 elderly subjects (92.9%). The elderly

group had the highest incidence of Grade 3 or Grade 4 TEAEs; 3 of 14 elderly subjects (21.4%), vs. 40 of 312 adult subjects (12.8%), and 2 of 16 adolescent subjects (12.5%).

The elderly were the highest proportion of subjects who discontinued study drug due to a TEAE and also had a higher incidence of potentially drug-related hepatic disorders, GI abdominal TEAS, and had a higher incidence of GRADE 3 and Grade 4 laboratory abnormalities compared to adolescents and adults.

While the lowest number of adverse events was observed in adolescent population, there remain uncertainty in the safety profile as the number of adolescent patients was very low. There is insufficient data to conclude on the safety in adolescent patients < 40kg.

3.5. Uncertainties and limitations about unfavourable effects.

There are a number of uncertainties in relation to the unfavourable effects observed with berotralstat treatment. The limited safety data set for berotralstat means rare events may not have been identified in the trials and are therefore remains unknown at this time.

Long term prior androgen use of ≥ 5 years and discontinuation of androgens within 2 weeks of berotralstat initiation were correlated with a higher subject incidence of liver-related TEAEs, but not other types of TEAEs.

Increases of liver enzymes were noted and while there were no incidences of Hy's law cases, some marked elevations in ALT were observed with concomitant elevations in AST. The potential for more serious hepatotoxicity cannot be ruled out in larger populations.

In the exposure-response analysis, a statistically significant positive relationship between ΔΔQTcF and berotralstat concentration has been observed. In addition, there is an up to 2-fold increase in the unbound fraction in moderate and severe hepatic impairment, which coupled with reduced clearance, may lead to increased, unbound (pharmacologically active) berotralstat concentrations. Further, the highest exposure estimate does not account for coadministration with metabolic or transporter inhibitors, nor does it account for the increased exposure in adolescents and low body weight subjects. These issues are of particular importance and Appropriate wording to the SmPC has been added to address recommendations regarding the need for appropriate monitoring in patient with renal impairment and the recommendation to avoid the use in case of moderate to severe haptic impairment.

The low number of elderly patients exposed is considered as another limitation of the safety data, considering elderly patients experienced the highest level of adverse events and there is uncertainty in relation to the safety profile in elderly patients.

To further characterise use in adolescent patients, a Post authorisation non interventional Safety Study (NI PAS; Study 401) has been agreed to further investigate the safety of berotralstat. The applicant will collect further information to evaluate long term safety, tolerability, and effectiveness of berotralstat in the real-world setting, including growth and development in adolescents.

Finally, the safety risk associated with phospholipidosis observed in preclinical studies, is incompletely investigated and insufficiently understood. Although it is acknowledged that no vital sign changes/ADRs/safety labs related to target organs were identified in clinical studies, changes were not expected in early phases of phospholipidosis. End-organ damage due to phospholipidosis may correlate with the total cumulative dose, as is the case with amiodarone pulmonary toxicity. Since berotralstat is intended as life-long treatment, the true potential of phospholipidosis in humans remains unknown. Section 5.3 of the SmPC has been amended to highlight this finding from the preclinical studies.

3.6. Effects Table

Table 62: Effects Table for berotralstat for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References
Favourable Effects							
			B 110mg	B 150mg	Placebo		
Primary endpoint	Mean investigator-confirmed attacks per 28 days over 24 weeks (SD)	Rate/ 28 days	1.9 (1.71)	1.63 (1.66)	2.47 (1.6)		Study BCX7353 302
Primary endpoint	Attack rate reduction from placebo over first 24 weeks (95% CI)	%	-30% (-4.6%, -48.7%) P < 0.024	-44.2% (-23%, -59.5%) P < 0.001			Study BCX7353 302
Key secondary endpoint	Change from baseline in AE-QoL at Week 24 (total score) diff from placebo (95% CI)		-2.77 (-10.08, 4.53) P = 0.453	-4.9 (-2.23, 2.43) P = 0.188			Study BCX7353 302
2nd secondary endpoint	Proportion of days with angioedema symptoms during first 24 weeks difference from placebo (95% CI) Mean (SD) number of days subjects had investigator confirmed angioedema symptoms	 Days	-0.062 (-0.117, -0.008) P = 0.025 20.8 (± 19.22)	-0.078 (-0.133, -0.023) P = 0.006 19.4 (± 21.50)	 29.2 (± 24.29)	Nominal p value only due to hierarchical approach to statistical testing.	Study BCX7353 302
3rd secondary endpoint	Attack Rate reduction from placebo – After Steady State (day 8 to day 168) 95% CI	%	-30.4% (-4.3, -49.3) P = 0.026	-46.5% (-25.6, -61.5) P < 0.001		Nominal p value only due to hierarchical approach to statistical testing.	Study BCX7353 302
Primary endpoint	Mean investigator-confirmed attacks per 28 days over 24 weeks (SD)	Rate/ 28 days	1.64	1.11	2.18		Study BCX7353 301
Primary endpoint	Attack rate reduction from placebo over first 24 weeks (95% CI)	%	-24.6% (-1.5, 14) P = 0.181	-49.1% (-67.5, -20.4)			Study BCX7353 301

Unfavourable Effects						
Drug-related TEAEs	Adverse events related to Orladeyo		150mgs 83 (45.1%)	Placebo 13 (33.3%)		Integrated studies 302, 204
GRADE 3 or Grade 4 TEAEs	Grade 3 and Grade 4 adverse drug related events		150mgs 25 (13.6%)	Placebo 3 (7.7%)		Integrated studies 302, 204
SAEs	Serious adverse events		150mgs 14 (7.6%)	Placebo 2 (5.1%)		Integrated studies 302, 204
TEAEs leading to discontinuation of study drug	Treatment emergent adverse events leading to discontinuation of treatment		150mgs 18 (9.8%)	Placebo 1 (2.6%)		Integrated studies 302, 204
Drug-related rash/hypersensitivity TEAEc	A Rash/Hypersensitivity TEAE was any AE that included a PT included in Hypersensitivity SMQ narrow terms		150mgs 4 (2.2%)	Placebo 0		Integrated studies 302, 204
Hepatic disorders (potentially drug related) TEAE	Adverse events related to liver disorders.		150mgs 14 (7.6%)	Placebo 1 (2.6%)		Integrated studies 302, 204
	Alanine aminotransferase increased		150mgs 9 (4.9%) [18]	Placebo 0		Integrated studies 302, 204
	Aspartate aminotransferase increased		150mgs 6 (3.3%) [7]	Placebo 0		Integrated studies 302, 204
GI abdominal TEAE			150mgs 83 (45.1%)	Placebo 14 (35.9%)		Integrated studies 302, 204

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Both the main study BCX7353 302 and the supportive study (study 301) with same design in a smaller population conducted in Japan met the primary endpoint for the berotralstat 150mg dose. However,

the clinical relevance of the effect size is modest given the lack of impact on quality of life measures. There is also a suspicion that the greater effect size seen for berotralstat 150mg compared to the 110mg dose may be driven by an imbalance of males/females across the treatment arms.

The studied population consisted of type 1 and type 2 patients only. Considering available scientific knowledge, it was considered acceptable to extrapolate efficacy to other types and grant a broader indication as initially proposed by the applicant.

There is very limited data in adolescents and there does not appear to be any difference in efficacy between adolescent and adult patients. There were no data in adolescents less than 40 kg, therefore there is no recommendation for use in this population.

From a safety perspective, berotralstat appears to have an acceptable safety profile. Most AEs were mild to moderate in severity, and recovery was documented. The overall rates for AEs and SAEs were low and similar across all treatment arms. The commonest adverse reactions were headache, GI adverse events such as abdominal pain, diarrhoea, GI reflux and vomiting and liver dysfunction. The concerns regarding risk of QTc prolongation, have been addressed in the SmPC with appropriate warning to clarify this to prescribers.

Hepatotoxicity has been identified as a potential risk in the summary of safety concerns in the RMP.

Cardiac effects were identified as a safety concern from nonclinical studies. While abnormalities in ECG morphology reported were of borderline clinical significance it is noted that in the exposure-response analysis, there was a statistically significant positive relationship between ΔΔQTcF and berotralstat concentration.

The elderly population appeared to have a worse safety profile perhaps due to underlying concomitant disease. No firm conclusion can be drawn. The safety profile in adolescents, although limited in terms of patient numbers to be conclusive, does not appear to highlight any different safety profile provided use is restricted to adolescent patients weighing 40 kg or more.

3.7.2. Balance of benefits and risks

Both the main study BCX7353 302 and a study with same design in a smaller population conducted in Japan met the primary endpoint for the berotralstat 150mg dose. However, the clinical relevance of the effect size is modest given the uncertainties of impact on quality of life measures. Further positive data has been provided which demonstrates efficacy in the reduction of moderate to severe attacks and laryngeal attacks which can be life threatening. Overall, it can be concluded that efficacy has been demonstrated in adults and adolescent patients weighing 40 kg or more for the berotralstat 150mg dose strength.

The safety profile appears to indicate that berotralstat is a safe and well-tolerated treatment for HAE patients. The most common adverse events associated with treatment are mostly GI disturbances such as abdominal pain, vomiting nausea and diarrhoea as well as transaminase elevations, headache and rash. Hepatotoxicity has been identified as a potential risk in the summary of safety concerns in the RMP.

Warnings related to cardiac effects and risk of prolonged QT associated with increased serum berotralstat concentrations have been introduced in the SmPC for patients with moderate or severe hepatic impairment and in patients with severe renal impairment. In these patients the use of berotralstat in these patients should be avoided. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered.

There are no data available for the use of berotralstat in patients with independent risk factors for QT prolongation such as electrolyte disturbances, known pre-existing QT prolongation (either acquired or familial), advancing age (see section 4.2), or concomitant use of other medicinal products known to prolong the QT. It is preferable to avoid the use of berotralstat in these patients. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered.

While an oral medication is welcomed, there is an increased rate of GI events, headache, liver dysfunction and concerns in tolerability for elderly patients.

There is limited data in the adolescent and the elderly population, with lack of information for older age groups (75 years and older). The applicant agreed to commit to a non-interventional post-authorization study (NI PAS; Study 401). With this NI PAS, the applicant plans to collect further information to evaluate long term safety, tolerability, and effectiveness of berotralstat in the real-world setting, including growth and development in adolescents.

3.8. Conclusions

The overall B/R of Orladeyo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that berotralstat is not similar to Takhzyro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Orladeyo is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that berotralstat is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.