26 January 2023
EMA/63140/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Orladeyo

berotralstat

Procedure no: EMEA/H/C/005138/P46/004

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	28 Nov 2022	28 Nov 2022	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2023	03 Jan 2023	☐
☐	CHMP members comments	16 Jan 2023	16 Jan 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	24 Jan 2023	24 Jan 2023	☐
☒	CHMP adoption of conclusions:	26 Jan 2023	26 Jan 2023	☐

Table of contents

1. Introduction

On 4th October 2022 the MAH submitted the final clinical study report for Parts 2 and 3 of study BCX7353-302 (Study 302), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study 302 was a Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of berotralstat (BCX7353) as an oral treatment for the prevention of attacks in subjects with hereditary angioedema, which comprised 3 parts. An interim CSR (dated 31 October 2019) concerning Part 1 only of the study was already submitted and assessed during the assessment of the marketing authorisation for Orladeyo. Study 302 recruited adults (i.e. > 18 years) and a smaller number of paediatric patients (adolescents aged 12-17 years) in a substudy.

This submission provides the final study report for Study 302, whereby Parts 2 and 3 of Study 302 are presented together in a CSR dated 29 September 2022.

These data are also submitted as part of a post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Berotralstat is an inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high-molecular-weight-kininogen (HMWK), releasing bradykinin, a potent vasodilator that increases vascular permeability. In patients with HAE due to 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).

The MAH stated that study BCX7353-302 (Study 302) is part of a clinical development program. A line listing of all the concerned studies is annexed, see Annex 1.

Note: A separate Article 46 submission is running in parallel, wherein the applicant presents the paediatric data for another study, Study BCX7353-204 (Study 204).

Orladeyo was authorised on 30 April 2021 for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

2.2. Information on the pharmaceutical formulation used in the study

In Study 302 all Subjects were given berotralstat capsules orally once daily, as outlined below according to treatment group.

- Treatment Group 1 (110 mg QD):
    - o Parts 1 and 2: two 55 mg capsules of berotralstat QD × 48 weeks
    - o Part 3: one 110 mg capsule of berotralstat QD until the subject can be transitioned to the 150 mg dose
- Treatment Group 2 (150 mg QD):
    - o Parts 1 and 2: two 75 mg capsules of berotralstat QD × 48 weeks
    - o Part 3: one 150 mg capsule of berotralstat QD × up to 96 weeks
- Treatment Group 3a:
    - o Parts 1 and 2 (placebo in Part 1, 110 mg in Part 2): two capsules of placebo QD

× 24 weeks (Days 1 to 168) followed by two 55 mg capsules of berotralstat QD
× 24 weeks (Days 169 to 337)
o Part 3: one 110 mg capsule of berotralstat QD until the subject can be transitioned to the 150 mg dose.

- Treatment Group 3b:
  - o Parts 1 and 2 (placebo in Part 1, 150 mg in Part 2): two capsules of placebo QD × 24 weeks (Days 1 to 168) followed by two 75 mg capsules of berotralstat QD × 24 weeks (Days 169 to 337)
  - o Part 3: one 150 mg capsule of berotralstat QD × up to 96 weeks

Treatment group 2 (150mg) remained on 150mg daily throughout the 3 parts of the study; whereas Treatment groups 1 (110mg) and 3 (placebo) all eventually transitioned to 150mg in either Part 2 or Part 3.

The final approved dose for both adults and adolescent patients weighing ≥40kg is 150mg daily, which is taken as one 150mg berotralstat capsule once daily. The same dose and capsule formulation applies to both adult and paediatric patients, and at present there is no other approved formulation.

As outlined in the PIP for Orladeyo (berotralstat), an age-appropriate paediatric formulation for patients 2 to < 12 years of age (i.e., granules for oral administration) is currently in development.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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

Note: As this final CSR concerns Part 2 and 3 of Study 302 (a final report for Part 1 was submitted in support of the initial MAA), the emphasis will be on Parts 2 and 3 and the adolescent participants therein. However, as the same adolescent patients crossed from Part 1 to Part 2 to Part 3 reference to Part 1 and its results is necessary in some instances for context.

2.3.2. Clinical study

Description

Study 302 was a randomised, placebo-controlled, double-blind, parallel-group, 3-part study in adult and paediatric (aged 12 to 17 years) subjects. The same patients transitioned form Part 1 to Part 2 to Part 3, in sequence.

Adults were recruited as well as a smaller number of paediatric patients (adolescents aged 12-17 years) within a substudy.

Part 1 was designed to test the hypothesis that the HAE attack rate during 24 weeks of prophylactic berotralstat treatment at 2 dosage levels (berotralstat 110 and 150 mg QD) was less than that observed during 24 weeks of placebo. The primary efficacy endpoint was assessed after the last subject completed Part 1 (through Week 24).

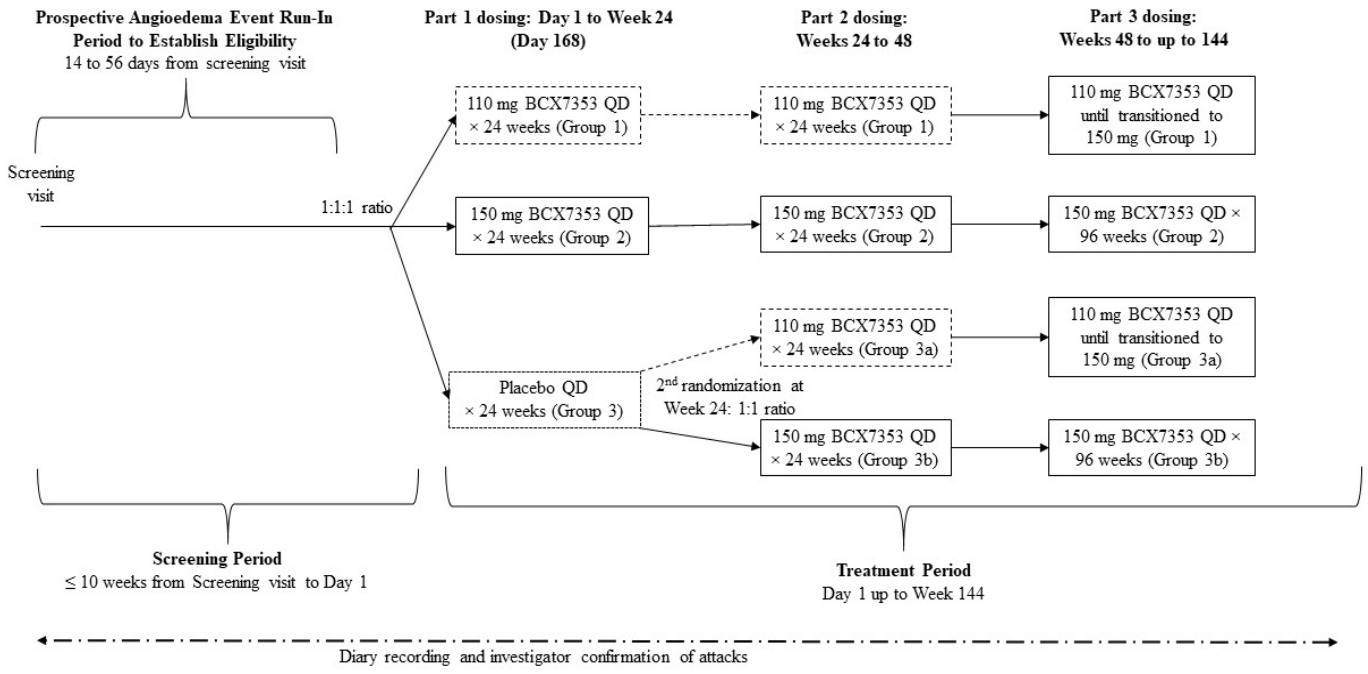
Part 2 was designed to primarily evaluate the long-term safety of berotralstat at 2 dose levels (110 and 150 mg QD).

Part 3 was open-label and designed to primarily evaluate the long-term safety of berotralstat.

All subjects received berotralstat in Parts 2 and 3, including those randomised to receive placebo in Part 1. Based on the results of the Part 1 analysis demonstrating greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects were transitioned to the 150 mg dose of berotralstat on or after their Week 48 visit (in Part 3), regardless of their initial or Week 24 treatment allocation.

The overall study schema is provided below: the study recruited from 40 sites in 11 countries. As was outlined in the CSR for Part 1, 71.9% of patients were recruited at North American sites, versus 28.1% at European sites.

Adolescent subjects were only eligible to enroll at sites in the US and Canada.



Of note, the maximum duration of treatment was 240 weeks in most countries, and 144 weeks in the U.S. (the extension of treatment up to 240 weeks was introduced in amendment 2, protocol 3.0).

The CSR for Parts 2 and 3 only provides data up to week 144; this is acceptable for this Article 46 procedure as all adolescents were recruited at US sites.

Methods

Study participants

Main criteria for inclusion:

1. Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (substudy).

2. Subject weight of ≥ 40 kg.
3. A clinical diagnosis of HAE Type I or Type II, defined as having a complement 1 esterase inhibitor (C1-INH) functional level below 50% and a complement 4 (C4) level below the lower limit of the normal (LLN) reference range, as assessed during the screening period.

   • In the absence of a low C4 value drawn during the intercritical period (ie, subject was not having an HAE attack), 1 of the following was acceptable to confirm the diagnosis of HAE:

   1) a SERPING-1 gene mutation known or likely to be associated with HAE Type I or II assessed during the screening period;
   2) a confirmed family history of C1-INH deficiency;
   3) a C4 redrawn and retested during an attack in the screening period with the results below the LLN reference range.
   4) For subjects with C1-INH function ≥ 50% but less than the assay LLN, a SERPING-1 gene mutation known or likely to be associated with HAE Type I or II, as assessed during the Screening period OR a repeat C1-INH functional level < 50% was considered acceptable for enrollment.

4. Access to and ability to use one or more acute medications for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH). Cinryze used for acute treatment of HAE attacks is an acceptable medication for this purpose.
5. Subjects were medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.
6. The subject must have had at least 2 HAE attacks which met all of the requirements below during the run-in period of a maximum of 56 days from the screening visit:
   • The attacks were unique, which was defined as an attack that did not begin within 48 hours of the end of a previous attack.
   • The attacks must have either been treated, required medical attention or documented to cause functional impairment based on subject entry in the diary.
7. Willingness to comply with specified effective contraception methods- as outlined for both male and female participants.

Subjects were excluded if they had: any other cause for recurrent angioedema, prolonged QT interval, any clinically significant cardiovascular disease including family history of sudden cardiac death, creatinine clearance ≤30ml/min, transaminases ≥3ULN, or were using androgens/tranexamic acid/C1-INH for HAE attack prophylaxis, or were taking certain medications metabolised by CYP2D6, 2C9, 2C91, 3A4. For full exclusion criteria, see the CSR for Parts 2 and 3.

Treatments

Part 1: 0-24 weeks
Treatment group allocations: (randomization in a 1:1:1 (active: active: placebo) ratio))
• Group 1: Berotralstat 110 mg administered orally QD for 24 weeks
• Group 2: Berotralstat 150 mg administered orally QD for 24 weeks
• Group 3: Placebo administered orally QD for 24 weeks

Part 2: 24-48 weeks
Subjects in Groups 1 and 2 continued to receive the same berotralstat dose to which they were randomized in Part 1 of the study in a blinded manner. Subjects randomized to Group 3 (placebo) underwent a second randomization in a 1:1 ratio to receive either a 110 or 150 mg dose in a blinded manner. The active dose a subject received in Part 2 was blinded for all subjects; subjects were informed that they received an active dose of berotralstat in Part 2.

Part 3: 48 to 144 (or 240 weeks for non US sites only- *of note all adolescents were at US sites*)- Open label

Based on the results of the Part 1 analysis of greater efficacy and no increase in safety or tolerability risk at the 150 mg dose vs. the 110 mg dose, all subjects were transitioned to the 150 mg dose of berotralstat on or after their Week 48 visit, regardless of their initial or Week 24 treatment allocation.

The overall schema and Section 2.2 describe the treatments administered to the subjects according to initial allocation treatment group in Part 1, and then as the patients transitioned into Parts 2 and 3.

Treatment group 2 (150mg) remained on 150mg daily throughout the 3 parts of the study, whereas Treatment groups 1 (110mg) and 3 (placebo) all eventually transitioned to 150mg in either Part 2 or Part 3.

Objectives

Part 2:

Primary objective:

- To evaluate the long-term safety and tolerability of berotralstat 110 and 150 mg administered QD over a 24- to 48-week administration period in subjects with HAE

Secondary Objectives:

- To assess the effectiveness (ie, HAE attack frequency over time) of berotralstat over a 24- to 48-week administration period
- To evaluate QoL and HAE disease activity of berotralstat over a 24- to 48-week administration period
- To evaluate subject's satisfaction with berotralstat over a 24- to 48-week administration period

Part 3:

Primary objective:

- To evaluate the long-term safety and tolerability of berotralstat administered QD over a 48- to up to 144-week administration period in subjects with HAE

Secondary Objectives:

- To assess the effectiveness (i.e., HAE attack frequency over time) of berotralstat over a 48- to up to 144-week administration period
- To evaluate QoL and HAE disease activity of berotralstat over a 48- to up to 144-week administration period
- To evaluate subject satisfaction with berotralstat over a 48- to up to 144-week administration period

Outcomes/endpoints

Part 2 Primary Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality
- The proportion of subjects with a treatment-emergent, treatment-related AE

consistent with a drug rash

Part 2 Secondary Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of HAE attack medications
- Discontinuations due to lack of efficacy
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

Part 3 Primary Endpoints

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent Grade 3 or 4 laboratory abnormality
- The proportion of subjects with a treatment-emergent, treatment related AE consistent with a drug rash

Part 3 Secondary Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number and proportion of days with angioedema symptoms
- Use of HAE attack medications
- Durability in AE-QoL questionnaire scores
- Durability in EQ-5D-5L scores
- Durability in TSQM scores
- Durability in WPAI scores

Sample size

Approximately 96 subjects were planned for enrollment in this study (n = 32 per group), which included any adolescent subjects enrolled in the substudy.

The sample size assumed a normalized placebo attack rate of 1 unit and a common standard deviation (SD) of± 0.55 attacks/week for berotralstat and placebo attack rates. A sample size of 32 subjects had a 94% power to detect a 50% attack rate reduction (a treatment difference of 0.5 attacks/week) between berotralstat and placebo, based on a 2-sided test at significance level of 0.05.

A blinded interim analysis was planned to estimate the standard deviation from the pooled treatment groups after 50% of the subjects completed Part 1 of the study (through 24 weeks). The sample size may have been re-estimated based on the variability from the pooled data. The final sample size was planned to be 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.

Actual
In Part 1, a total of 160 subjects were screened, 121 subjects were randomized (intent-to-treat [ITT] population), and 120 subjects (99%) were randomized and treated (safety population). The sample size for Parts 2 and 3 was determined by the sample size and enrolment numbers for Part 1.

Randomisation and blinding (masking)

Part 1: Approximately 40 subjects per arm were randomized by interactive (web or voice) response system in a 1:1:1 (active:active:placebo) ratio to 1 to the 3 groups described above: first randomisation. Enrollment into treatment groups was stratified by the baseline angioedema attack rate over the period from screening to randomization (≥ 2 attacks per month vs. < 2 attacks per month. All patients were blinded to allocation in Part 1.

Part 2: Subjects in Groups 1 and 2 continued to receive the same berotralstat dose to which they were randomized in Part 1 of the study in a blinded manner. Subjects randomized to Group 3 (placebo) underwent a second randomization in a 1:1 ratio to receive either a 110 or 150 mg dose in a blinded manner. The active dose a subject received in Part 2 was blinded for all subjects; subjects were informed that they received an active dose of berotralstat in Part 2.

Part 3: There was no further randomization, and no blinding, all were treated open label in Part 3. Initially all of the Part 2 group continued into Part 3 on the same dose as Part 2. After analysis of Part 1 results, all subjects in Part 3 moved to 150mg.

Main study and substudy (adolescent) subjects were randomized via a separate randomization scheme; however, study-mandated procedures were identical, and analyses included all subjects who participated in the study.

Statistical Methods

The statistical methods used for Part 1 have already been described and assessed in the course of the Orladeyo MAA assessment.

The analyses of effectiveness for Parts 2 and 3 are primarily descriptive, as the primary objective for both parts was to examine safety. It had initially been planned that the Part 1 placebo subjects who switched to an active berotralstat dose in Part 2, would be summarized for effectiveness. Instead, descriptive analyses of effectiveness data are provided for Parts 2 and 3.

Results

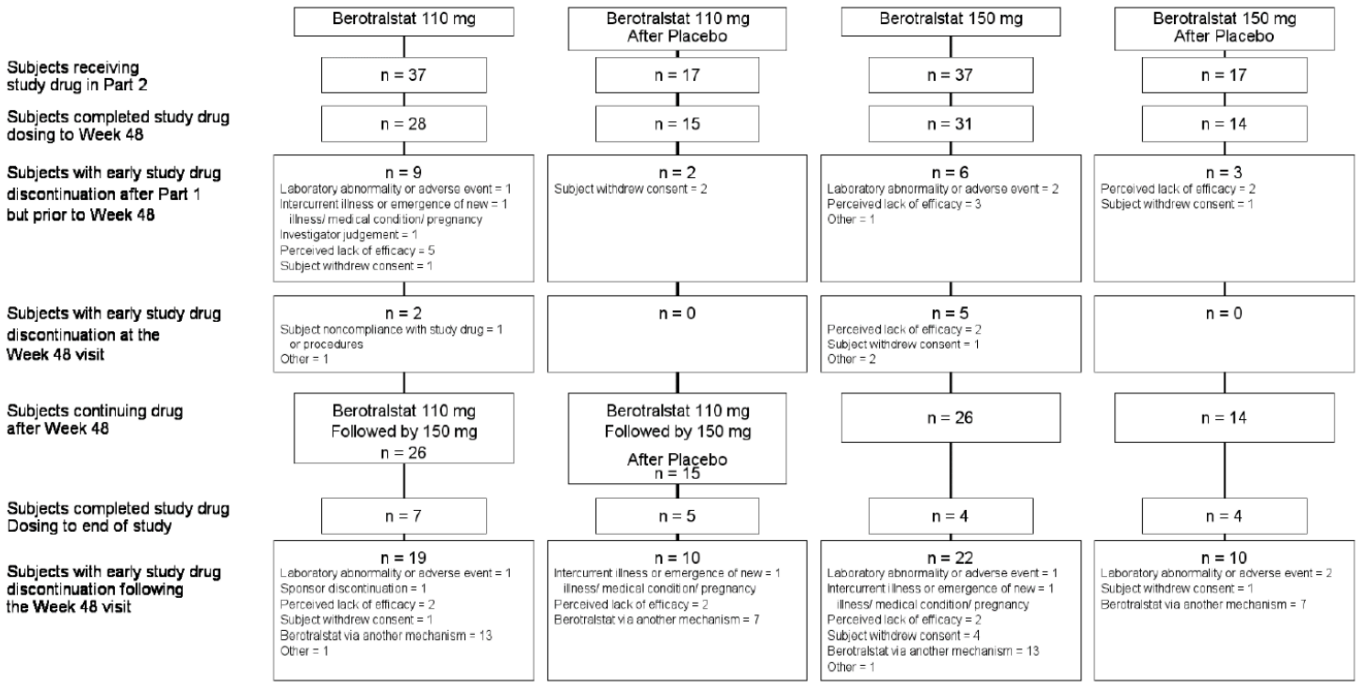
Participant flow

Entire population:

- 108/115 subjects (93.7%) who originally received study drug in Part 1 participated in Part 2.
- Of the 34 placebo subjects in Part 1 who participated in Part 2, 17 were randomized to 110 mg of berotralstat and 17 were randomized to 150 mg of berotralstat for Part 2.

- 20 subjects completed study drug dosing to the end of the study (Week 144), while 61 subjects discontinued following the Week 48 visit, including 40 subjects who discontinued to obtain berotralstat via another mechanism (e.g., such as an early access program or commercially available Orladeyo®). Subjects who remained on study until Week 144 or transitioned to the post-marketing study following receipt of marketing approval on 03 December 2020 were considered to have completed this study.
- Compliance was high in Parts 2 and 3 overall; mean study drug compliance was 96.1% in Part 2 and 95.7% in Part 3.

Study 302: Consort Diagram, Entire Study, ITT Population



Focussing on adolescents:

- 6 adolescents were recruited in Part 1: 2 subjects each were randomised to berotralstat 110 mg, berotralstat 150 mg, and placebo. All 6 paediatric subjects completed Part 1.
- The 2 subjects who received placebo were re-randomised in Part 2, 1 each to berotralstat 110 and 150 mg, respectively. All 6 paediatric subjects completed Part 2.
- All 6 paediatric subjects then entered Part 3: 3/6 paediatric subjects completed study drug dosing to the end of the study, and 3 subjects (50.0%) discontinued during Part 3, 1 due to pregnancy, and 2 eventually discontinued the study when berotralstat became available via another mechanism (e.g., such as an early access program or commercially available Orladeyo).
- Overall, the mean (SD) compliance was 93.8% (5.58) with 66.7% of subjects having compliance of 90% to 110%.

Recruitment

Focussing on adolescents: Demographics (n=6)

- The mean (standard deviation [SD]) age was 13.7 (2.07) years

- More female subjects were enrolled in the study compared with male subjects (66.7% vs. 33.3%)
- Most subjects were white (83.3%), and all subjects were non-Hispanic (100%).
- The mean subject weight was 68.95 kg (range 54.0 to 88.5 kg), and the mean subject body mass index (BMI) was 26.40 kg/m^2 (range 21.8 to 34.0 kg/m^2).
- All 6 adolescents were recruited at U.S. sites.

Safety results (Part 2 and 3)

Focussing on adolescents: (n=6)

In the 6 adolescents, the overall mean exposure to berotralstat was 886.8 days (638-1009 days), which is suggestive of good tolerability.

There were 29 AEs overall in adolescent subjects across the entire study. All 6 (100%) adolescents had at least one TEAE, and 4/6 had a drug related TEAE. This is a higher rate of TEAEs overall than in the safety population where 68.5% experienced a TEAE and 21.3% had a drug related TEAE. However, apart from the 2 SAEs later discussed, all TEAEs in adolescents were grade 1 or 2 in terms of severity.

No TEAE PT was reported by > 1 subject receiving berotralstat.

The body system with the most frequently reported TEAEs was GI disorders, where 4 adolescent subjects (66.7%) experienced 6 events, over the entire study. Gastrointestinal AEs were reported commonly in the clinical development, and listed as very common (abdominal pain, diarrhoea) or common (vomiting, gastroesophageal reflux, flatulence) in Section 4.8 of the SmPC.

There were no AEs in adolescents relating to LFT/transaminase rises, or other blood laboratory abnormalities.

There were no AEs in adolescents relating to vital sign or ECG abnormalities, or cardiovascular events.

There was no death in Study 302 in adolescents (nor in any other age group).

No adolescent subject discontinued study drug due to a TEAE. One female subject interrupted study drug due to a SAE of worsened bipolar disorder with depression.

There were 2 treatment emergent SAEs overall, experienced in one female subject, while being treated with berotralstat 110mg; neither of which were considered related (First SAE: worsened bipolar disorder with depression. Second SAE: pregnancy which ended in miscarriage):

SAE 1: worsened bipolar disorder with depression. The subject had a baseline medical history that included bipolar affective disorder (diagnosed 5 years previously), as well as a renal artery stent, and fibromuscular dysplasia. Her baseline medications included aripiprazole, lisdexamfetamine, alprazolam, and prazosin. The AE of worsened BPAD/depression event included self-harm (self-cutting) and required an ambulance and psychiatric hospitalisation for assessment and occurred on Day 593 of berotralstat therapy; IMP (berotralstat 110mg) was temporarily interrupted. The admission occurred during a time of emotional distress, and there were indications of both alcohol and cannabis use. She was discharged after 3 days and IMP was resumed. This event was considered not related by the investigator, and related to her underlying diagnosis, and external factors.

SAE 2: pregnancy which ended in miscarriage. Approximately 6 weeks after discharge for BPAD acute episode, a positive home pregnancy test was reported, and IMP (berotralstat 110mg) was stopped. Approximately 7 weeks later the subject had early pregnancy bleeding and an early pregnancy scan suggested an unviable pregnancy as only a fetal pole was seen with no fetal heartbeat. 2 days later she had heavier bleeding that required admission, and surgical intervention for an incomplete

miscarriage. Considered not related to IMP by the investigator, as miscarriage (first trimester) is not uncommon, and most frequently is caused by chromosomal abnormalities. It was also noted that her baseline medications carry warnings about use in pregnancy.

Of note, apart from the SAE of worsening of bipolar affective disorder, there were no other AEs falling under the SOC Psychiatric Disorders.

Diffuse maculo-papular rash assessed as drug related were to be treated as AEs of special interest, but no such AESIs were observed in the adolescent subjects.

Upon request the MAH provided paediatric only safety tables, including a listing of all treatment emergent adverse events for the entire study, which are consistent with the discussion in the supporting clinical overview, and which do not raise any new safety concerns in adolescents.

Effectiveness results

Part 1

As was discussed during the original MA assessment, the primary efficacy endpoint for Study 302 was the rate of investigator confirmed HAE attacks during dosing from week 0-24 (Part 1). The study met its primary endpoint for both dose levels in all subjects, with the 110 and 150 mg berotralstat doses reducing HAE attacks by 30% ($p = 0.024$) and 44% ($p < 0.001$), respectively, compared with placebo.

Paediatric subjects from Part 1 were analysed as a subgroup. However due to the very limited numbers, with only 4 subjects aged from 12 to 17 exposed to berotralstat this sub-group analysis by age-group was uninformative. While there did not appear to be any difference in efficacy between adolescent and adult patients however, the data remain limited.

Parts 2 and 3

Descriptive statistics only are provided for Parts 2 and 3 as these parts were designed to mainly examine safety.

Part 2: The monthly investigator-confirmed attack rates for the 150 mg group declined from 3.06(± 1.497) attacks/month at baseline to 1.39 (± 1.765) at Week 24, 1.31 (± 1.533) at Week 28, and 1.06 (± 1.427) at Week 48. For the 110 mg group, attack rates were 2.94 (± 1.212) at baseline, 1.56 (± 1.950) at Week 24,1.79 (± 1.995) at Week 28, and 1.35 (± 1.853) at Week 48. The overall investigator-confirmed attack rate through the end of Part 2 was 1.834 (± 1.6963) attacks/month for the 110 mg group, 1.184 (± 0.8966) for the 110 mg after placebo group, 1.534 (± 1.5579) for the 150 mg group, and 1.794 (± 2.4296) for the 150 mg after placebo group.

Part 3 (open label): The mean rate of adjusted subject-reported attacks in the all active group declined from 3.06 (± 1.743) attacks/month at baseline to 0.63 (± 1.217, N = 70) at week 96 and 0.90 (± 1.693, N = 26) at Week 144. The overall attack rate (mean ± SD) of adjusted subject-reported attacks during Part 3 was 0.917 (± 1.240) attacks/month for the all active group.

Subjects reported improvements in AE-QoL total scores through Part 2 and this continued through Part 3.

Focussing on adolescents: (n=6):

The design of Study 302, as well as the very small numbers of adolescents recruited limits any interpretation of the results with regards to efficacy. Looking at the 6 adolescent results individually for the blinded parts of the study (Parts 1 and 2), in all 6 adolescent subjects a reduction versus baseline monthly investigator-confirmed attack rates was seen in Part 1, and a reduction versus baseline was also seen in Part 2. In 3/6 adolescent subjects the Part 2 monthly investigator-confirmed attack rate

was less than the attack rate for Part 1, and in the other 3 subjects the Part 2 rate was slightly higher than Part 1, but still reduced versus baseline.

Upon request the MAH has provided paediatric only tables, including effectiveness data. All 6 paediatric subjects had an investigator confirmed attack in Part 2. In the All Active group (n=6) the mean investigator confirmed attack rate (per month) through end of Part 2 was well below one at 0.287 (n=6), and 0.140 in the All 150mg group (n=3). While the numbers of paediatric subjects are too small to draw any conclusions, the paediatric tables provided on effectiveness can be considered consistent with the overall study findings, and with the discussion provided in the supporting clinical overview.

2.3.3. Discussion on clinical aspects

The MAH has provided the final CSR for the 3-part Study BCX7353-302 (Study 302): A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353/ berotralstat as an oral treatment for the prevention of attacks in subjects with hereditary angioedema. Part 1 final results were already provided during the MAA assessment, and so the focus of this Article 46 procedure are the results of Parts 2 and 3 insofar as they relate to paediatric/adolescent patients.

As was noted during the MAA assessment, very limited numbers of adolescents (age 12-17 years) were recruited into Study 302 Part 1: only 6 adolescents altogether. All 6 adolescents were recruited at U.S. sites.

All 6 of those Part 1 adolescents entered and completed Part 2 and all 6 also entered Part 3 of the study. 3 of the 6 adolescents that entered Part 3 then completed the study with 144 weeks of treatment; 1 having left the study due to a pregnancy and 2 leaving as berotralstat became available off trial. For the 6 adolescents, the overall mean exposure to berotralstat was 886.8 days (638-1009 days). Overall, while the numbers of adolescents are very small, this exposure duration and retention rate suggest reasonable tolerability.

Albeit within the confines of a limited dataset, and the fact that Part 3 of the study was open label, the adverse event analysis data do suggest that berotralstat was generally well tolerated when used for longer periods of time in the adolescent population. No adolescent subject discontinued study drug due to a TEAE; the only discontinuation occurred due to a pregnancy. While there were 2 SAEs in one female subject, one of worsened bipolar disorder with depression, followed by a second SAE of pregnancy/miscarriage, both the opinion of the investigator and the discussion and detail of these AEs do not suggest causality.

The body system with the most frequently reported TEAEs was GI disorders, where 4 subjects (66.7%) experienced 6 events. Gastrointestinal AEs were reported commonly in the clinical development, and listed as very common (abdominal pain, diarrhoea) or common (vomiting, gastroesophageal reflux, flatulence) in Section 4.8 of the SmPC.

Overall, berotralstat was safe and generally well tolerated in the 6 paediatric subjects with a similar safety/AE profile as compared to the overall dataset.

The design of Study 302, as well as the very small numbers of adolescents recruited limits any interpretation of the results with regards to efficacy. Descriptive data suggest that berotralstat 150 mg reduced the frequency of attacks in adolescent subjects compared with berotralstat 110 mg and that the response was maintained. The paediatric subjects treated with 150 mg of berotralstat (all 150 mg

group) maintained an HAE attack rate < 1 attack per month for all 12 months of the blinded portion of the study (i.e., Parts 1 and 2).

Orladeyo is already approved for the treatment of paediatric patients (adolescents) from age 12. Section 5.1 of the product information already outlines the extent of the data for use of Orladeyo in this age group, and no further update is proposed by the MAH, which is agreed.

3. Overall conclusion and recommendation

In the context of this PAM for a completed paediatric study for Orladeyo (berotralstat) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH has met their obligations.

In relation to paediatric patients, no conclusions on safety and efficacy could be made as the number of paediatric patients enrolled in the presented study are too small.

The request for further information, due to the omission of Paediatric Tables in the Submission, see Section 4 below, has been addressed, and has been resolved.

No further update is proposed by the MAH, which is appropriate.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

1. The Short Critical Expert Overview submitted lists and references Paediatric Tables in Appendix A, and it is understood that these are paediatric subjects only tables (i.e. without adult data). However, these paediatric tables could not be located in the dossier. For completeness the applicant is asked to submit for review the Study 302 Paediatric Tables that are listed in Appendix A of the Short Critical Expert Overview.

5. Assessment of responses

The MAH explained that no paediatric tables were submitted, and has not yet provided paediatric tables.

6. Request for supplementary information

1. The Short Critical Expert Overview submitted lists and references Paediatric Tables in Appendix A, however, these paediatric tables could not be located in the dossier. The MAH has since confirmed that paediatric specific tables were not submitted for this procedure. For completeness the applicant is asked to prepare and submit for review the Study 302 Paediatric Tables that are listed in Appendix A of the Short Critical Expert Overview.

7. Assessment of responses

The applicant has provided key paediatric specific tables for safety and efficacy, including summary tables of investigator confirmed attacks (for Part 2) and a line listing of all treatment emergent adverse events in the paediatric population for the entire study. The tables provided are consistent with the discussion provided in the Clinical Overview supporting this Art 46 procedure.

Issue is resolved.

Annex 1 Line listing of all the studies included in the paediatric development program

Clinical studies

Table 1: Clinical Studies

Study Number	Study Title	Date of Completion	Date of Submission of Final Study Report
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	06 April 2022	04 October 2022
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	27 April 2022	Expected 26 October 2022
BCX7353-304	A Phase 3 study to evaluate the safety and pharmacokinetics of berotralstat prophylaxis in children with hereditary angioedema who are 2 to < 12 years of age	Expected March 2026	Expected September 2026
BCX7353-401	Non-interventional post-authorisation study to evaluate the safety, tolerability and effectiveness of berotralstat for patients with hereditary angioedema in a real-world setting	Expected August 2027	Expected February 2028