26 April 2023
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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/P46/005

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	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	19 Jan 2023	19 Jan 2023	☐
☐	CHMP adoption of conclusions:	26 Jan 2023	26 Jan 2023	☐
☐	Submission	03 Apr 2023	09 Feb 2023	☐
☐	Re-start	04 Apr 2023	28 Mar 2023	☐
☐	CHMP Rapporteur Assessment Report	12 April 2023	5 Apr 2023	☐
☐	CHMP members comments	17 April 2023	N/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 April 2023	N/a	☐
☒	CHMP adoption of conclusions:	26 April 2023	26 April 2023	☐

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1. Introduction

On 20th October 2022 the MAH submitted a completed study report study BCX73553-204 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study BCX7353-204 (Study 204) was an *open-label study to evaluate the long-term safety of daily oral BCX7353 (berotralstat) in subjects with Type I and II hereditary angioedema.*

An interim CSR (dated 30 October 2019) was already submitted and assessed during the assessment of the marketing authorisation for Orladeyo.

Study 204 recruited both adults (i.e., > 18 years) and a smaller subset of paediatric patients (adolescents aged 12-17 years) in a substudy in participating countries. The focus of this assessment is the data for the paediatric subjects only.

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 BCX7353-204 (Study 204) is part of a clinical development program. A line listing of all the concerned studies is annexed, see Annex 1.

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.

An interim clinical study report (CSR) for Study 204 dated 24 November 2019 was submitted with and assessed during the MAA for Orladeyo.

Note: A separate Article 46 submission is running in parallel, wherein the MAH presents the paediatric data for another study, BCX7353-302 (Study 302).

2.2. Information on the pharmaceutical formulation used in the study

The test drug in this study was berotralstat powder in capsules.

Subjects were administered berotralstat dihydrochloride containing 110 mg or 150 mg total free base weight of berotralstat:

- Subjects initially allocated to the 110 mg QD treatment group received a daily dose of capsules supplied as 110 mg (1 capsule per day). (These patients were later transitioned to 150mg)
- Subjects allocated to the 150 mg QD treatment group received a daily dose of

capsules supplied as either 50 mg (3 capsules per day) or 150 mg (1 capsule per day).

The capsules administered in this study were considered appropriate for adult and adolescent

subjects, and no acceptability or palatability issues were reported.

The final approved dose for both adults and adolescent patients weighing ≥40kg is 150 mg daily, which is taken as one 150 mg berotralstat capsule once daily. The same dose and capsule formulation apply 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 BCX7353-204 an open-label study to evaluate the long-term safety of daily oral BCX7353 in subjects with type 1 and 2 hereditary angioedema.

2.3.2. Clinical study

Description

Study BCX7353-204 or Study 204 was a multinational open-label study to evaluate long-term safety of daily berotralstat in patients with Type 1 and 2 hereditary angioedema. Recruited subjects had to have participated in a previous study of berotralstat, or were expected to derive benefit from an oral treatment to prevent HAE attacks.

The study was conducted at multiple study sites in Asia-Pacific, Europe, Israel, South Africa, and North America.

Methods

The study evaluated berotralstat at doses of 110 mg and 150 mg QD; however, based on the final results from Part 1 of the randomized, double-blind, placebo-controlled Phase 3 efficacy study (Study BCX7353-302 [Study 302]) which showed better efficacy at the 150 mg dose compared to the 110 mg dose with no increase in safety risk, the protocol was amended to a single-arm study with a 150 mg QD dose of berotralstat.

On-treatment study visits occurred at Weeks 4, 12, 24, 48, 72, and 96 in the US. For all other countries, per Protocol Version 7.0, subjects could have been treated for up to 240 weeks with visits occurring every 12 weeks after Week 48.

All subjects were instructed to complete diaries to document all angioedema attacks that occurred.

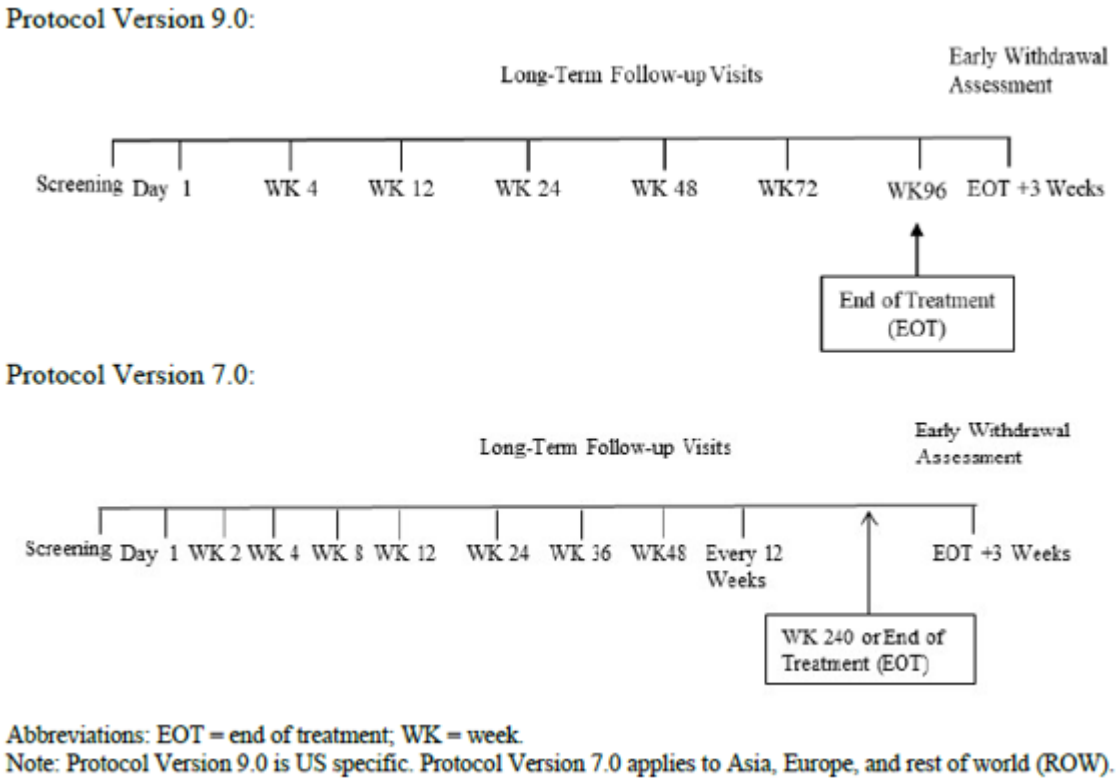
Acute attacks of angioedema were treated in accordance with the subject's normal standard of care. Treatment for acute attacks of HAE was not provided by the sponsor.

Subjects completed the Angioedema Quality of Life Questionnaire (AE-QoL) to assess health-related QoL and the Treatment Satisfaction Questionnaire for Medication (TSQM) to assess their satisfaction with the study medication.

Safety and tolerability were evaluated through assessments of adverse events (AEs), laboratory analyses vital signs, ECGs and physical examinations at the study visits.

Subjects were dosed orally with berotralstat QD for up to 96 weeks (US) or up to 240 weeks (i.e. Rest of World [ROW]; Europe, Asia-Pacific, South Africa, and Israel), respectively. A schema from Protocol 9.0 (U.S.) and 7.0 (Rest of World) is shown below, by which time the study was a single arm study (150 mg dose only).

Figure 1: Study 204: Study Schema



Abbreviations: EOT = end of treatment; WK = week.
Note: Protocol Version 9.0 is US specific. Protocol Version 7.0 applies to Asia, Europe, and rest of world (ROW).

Study participants

Main inclusion criteria

Males and nonpregnant, nonlactating females ≥18 years of age (main study) or ≥12 years to < 18 years of age (substudy) with a clinical diagnosis of Type 1 or Type 2 HAE, weighing ≥40kg and who, in the opinion of the investigator, were expected to benefit from an oral treatment for the prevention of angioedema attacks. Subjects may have participated in a previous study of berotralstat. A clinical diagnosis of HAE Type 1 or 2 was defined as:

- A C1 esterase inhibitor (C1-INH) functional level below the assay lower limit of normal as assessed during the screening period by chromogenic assay OR
- Laboratory documentation of historical C1-INH functional level below the assay lower limit of normal OR
- Subjects who currently use plasma derived or recombinant C1-INH based therapies for acute attacks or prophylaxis may use one of the following to confirm their diagnosis:
    - SERPING-1 gene mutation known or likely to be associated with HAE Type 1 or 2 as assessed during the screening period OR
    - A confirmed family history of C1-INH deficiency

Subjects were excluded if they had an abnormal ECG, had used androgens within 28 days of recruitment, or if they required daily medications metabolised by CYP2D6 or 3A4 and that have a narrow therapeutic range.

Treatments

The test drug in this study was berotralstat powder in capsules.

- Subjects initially allocated to the 110 mg QD treatment group received a daily dose of capsules supplied as 110 mg (1 capsule per day).
- Subjects allocated to the 150 mg QD treatment group received a daily dose of capsules supplied as either 50 mg (3 capsules per day) or 150 mg (1 capsule per day).

All subjects who were initially allocated to the 110 mg QD treatment group were transitioned to a berotralstat dose of 150 mg QD following the results from Part 1 of Study 302 and once the subject had reached Week 48.

Objectives

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing of oral berotralstat in subjects with HAE

Secondary Objectives

- To assess the effectiveness (i.e., HAE attack frequency, severity, and disease activity over time) of berotralstat during long-term administration
- To evaluate QoL during long-term administration of berotralstat
- To evaluate subject's satisfaction with medication during long-term administration of berotralstat

Outcomes/endpoints

Safety Endpoints

- The proportion of subjects who discontinue berotralstat due to a treatment-emergent adverse event (TEAE)
- The proportion of subjects with treatment-emergent serious adverse events (SAEs)
- The proportion of subjects with TEAEs
- The proportion of subjects with treatment-emergent Grade 3 or 4 AEs
- The proportion of subjects with treatment-emergent, treatment-related AE consistent with a drug rash
- The proportion of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities

Effectiveness Endpoints

- Number and rate of HAE attacks
- Durability of response (attack rate trend over time)
- Number of attacks requiring attack medication
- Severity of attacks
- Number and proportion of days with angioedema symptoms
- Patient-reported outcomes (HAE disease-specific AE-QoL questionnaire scores and TSQM Global Satisfaction scores)
- Discontinuations due to lack of efficacy (through Week 48 only)

Sample size

No sample size calculations were conducted for this open-label, long-term safety and effectiveness study. The purpose of the study was to characterize the safety and effectiveness profile of 110 and 150 mg daily doses of berotralstat.

Approximately 475 total subjects were planned to be enrolled. Of that, 225 subjects outside the US (approximately 110 subjects at each dose level) were planned to be enrolled in this study, with an additional 250 planned to be enrolled in the US, to allow continued access to berotralstat following a subject's participation in a prior berotralstat study, or to provide access to berotralstat for additional subjects who, in the opinion of the investigator, were expected to benefit from treatment.

The planned 475 subjects also included adolescents which were to be recruited in a substudy in participating countries. There was no specific target enrollment for adolescents.

Randomisation and blinding (masking)

- There was in the main no randomisation, except for those subjects recruited in South Korea, see below.
- There was no blinding as this was an open label study.

Method for allocation to 110mg or 150mg:

- Regions/ countries initiated the study under different versions of the protocol, and consequently treatment allocation was based on the version of the protocol applicable. Initially, the study was a single-arm study and all subjects received treatment with berotralstat 150 mg (Protocol Version 1). Under Protocol Versions 2.0 through 5.0, subjects were manually allocated to 1 of 2 treatment groups: Group 1: berotralstat 110 mg administered orally QD, Group 2: berotralstat 150 mg administered orally QD. At this time a higher percentage were recruited on 110mg to balance the initial 150mg recruitment.
- While allocation of dose was manually determined for most subjects; subjects in South Korea were randomized 1:1 to 110 mg QD or 150 mg QD, upon request of the South Korean regulator
- With protocol versions 4.0 and 5.0 (following Part 1 of Study 302's results) subjects were transitioned to berotralstat 150 mg.
- All subjects enrolled under Protocol Version 6.0 or later, received treatment with berotralstat 150 mg. Therefore, all subjects enrolled into the study after the data cut-off of 20 August 2019 for the interim CSR received 150 mg.

Statistical Methods

No hypothesis testing was intended for this open label, non-randomised study.

Safety: The following were summarised using descriptive statistics:

- Vital signs, weight, ECG parameters, and clinical laboratory results
- the proportion of subjects: 1) with TEAEs; 2) who discontinued berotralstat due to TEAEs; 3) with treatment-emergent serious adverse events (SAEs); 4) with treatment-emergent Grade 3 (G3) or Grade 4 (G4) AEs; 5) with treatment-emergent, treatment-related AEs consistent with a drug rash (eg, rash,maculo-papular rash, papular rash), and 6) with treatment-emergent G3 or G4 laboratory abnormalities.

- Time to discontinuation due to a TEAE, and time to development of drug-related rash were estimated using the Kaplan-Meier (KM) method.
- For those with a drug-related rash, clinical and laboratory findings, and the proportion of subjects who successfully continued therapy following onset of rash were summarized.
- The number and percentage of subjects having elevations in liver enzymes in relation to fold above the upper limit of normal.

Effectiveness: The following were summarised using descriptive statistics:

- The number of subject-reported and programmatically adjusted HAE attacks * were analyzed by treatment group using appropriate descriptive statistics.
- The number and proportion of days with angioedema symptoms, number and proportion of subjects who were attack free, and discontinuations due to lack of efficacy
- The characteristics of adjusted attacks (e.g., duration, location, triggers)
- The time to the first adjusted attack was estimated using KM.
- Use of HAE medications and the number of subject-reported HAE attacks requiring treatment

** Subject-reported attacks had to meet the following criteria to be considered an adjusted attack: 1) the attack must have included at least 1 symptom of swelling; 2) there must not have been an alternative explanation for the subject's symptoms other than an HAE attack 3) the attack must have been unique (attack began > 24 hours from the end of the prior attack); 4) any attack that began within 24 hours from the end of a prior attack was combined with the prior attack; and 5) if the entire adjusted attack was untreated, it must have had a duration > 24 hours.*

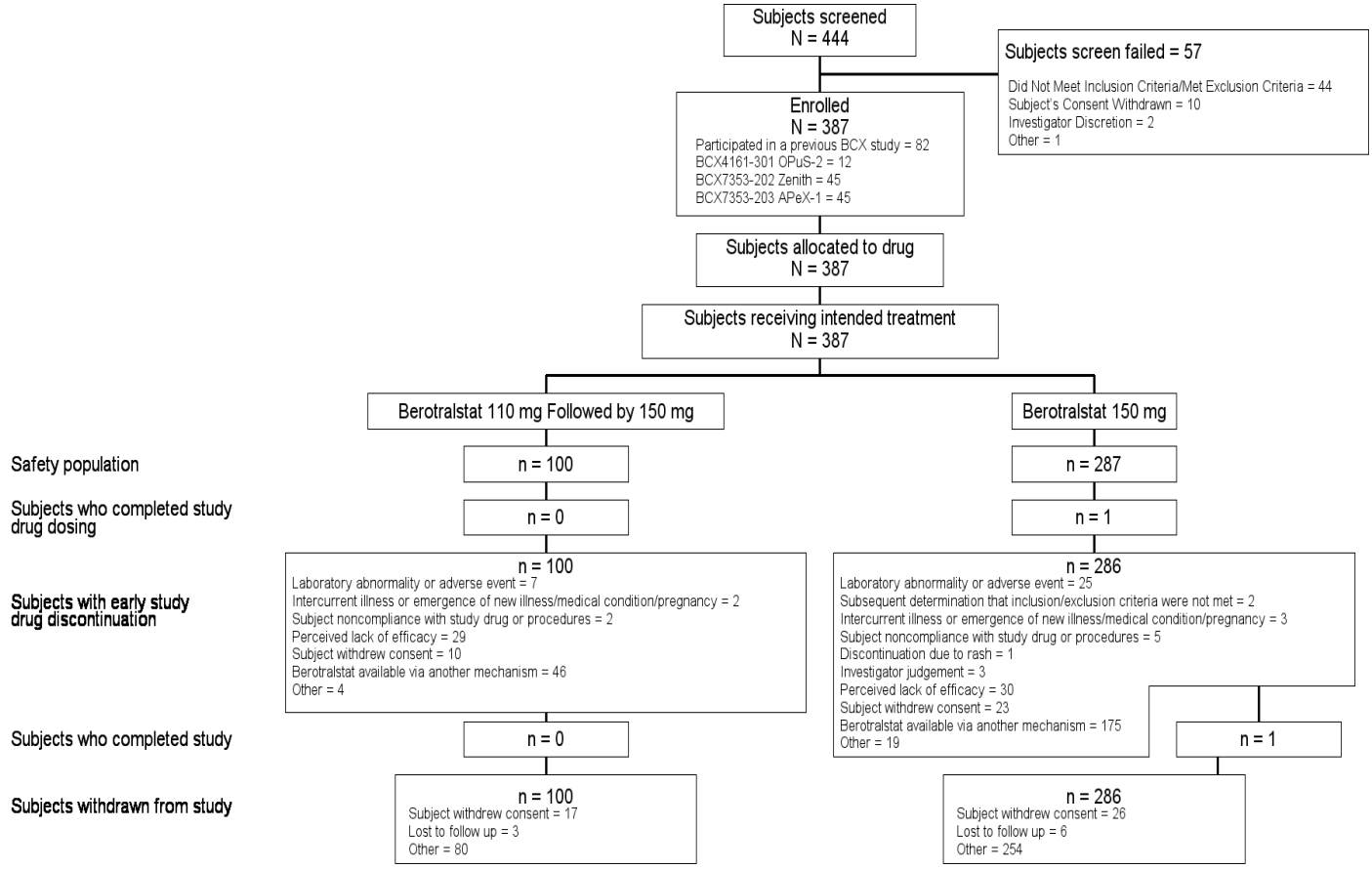
PK:

- Analyses of PK concentration data were based on the safety population and data were listed by subject, treatment, day, and time.
- A by-subject analysis of the berotralstat concentrations over time as well as the percentage of subjects with drug concentrations 4, 6, or 8 × the half-maximal effective concentration (EC50) for kallikrein inhibition were summarized.
- A by-sample analysis of berotralstat concentrations overall and the number and percentage of samples with berotralstat concentrations > 4 × EC50, > 6 × EC50, and > 8 × EC50 were summarized.

Results

Participant flow

The participant flow chart below is for the entire study population, for context.



Overall, 36.1% of the subjects were listed to have had a major deviation, however the majority of these related to minor dosing errors, or informed consent issues, and are not considered to affect the overall interpretation of the results.

Focussing on adolescents:

- 28 adolescents were enrolled, of which 5 were initially allocated to 110 mg and 23 were initially allocated to 150 mg.
- Of the 28 subjects enrolled, all 28 discontinued treatment early, so 0/28 completed the study to 96 weeks.
- 22/28 adolescents discontinued study drug early because berotralstat was available via another mechanism, and for the remaining 6 the reasons were as follows: 2 due to perceived lack of efficacy, 1 due to an AE or laboratory abnormality (see later discussion under Safety results), 1 due to intercurrent or new illness, 1 due to withdrawal of consent, and 1 due to other reason(s). See Table 1 below.
- Compliance was generally high in adolescent subjects, at 85.6%. 57.1% of the adolescents had a compliance of ≥90%. 8 subjects (28.6%) had compliance of less than 80%.

Table 1: Summary of Subject Disposition by Country and Site All Paediatric Subjects

Country Site Summary	Berotralstat 110 mg Followed by 150 mg (N = 5)	Berotralstat 150 mg (N = 23)	All Subjects Screened [1] (N = 28)
Country: Overall Site: Overall			
Subjects with early study drug discontinuation	5 (100.0%)	23 (100.0%)	28 (100.0%)
Laboratory abnormality or adverse event	1 (20.0%)	0	1 (3.6%)
Subsequent determination that inclusion/exclusion criteria were not met	0	0	0
Intercurrent illness or emergence of new illness/medical condition/pregnancy	0	1 (4.3%)	1 (3.6%)
Subject noncompliance with study drug or procedures	0	0	0
Discontinuation due to QT prolongation	0	0	0
Discontinuation due to rash	0	0	0
Investigator judgement	0	0	0
Sponsor discontinuation	0	0	0
Perceived lack of efficacy	2 (40.0%)	0	2 (7.1%)
Subject withdrew consent	0	1 (4.3%)	1 (3.6%)
Berotralstat available via another mechanism	2 (40.0%)	20 (87.0%)	22 (78.6%)
Other	0	1 (4.3%)	1 (3.6%)
Subjects completed study [2]	0	0	0

Recruitment

Overall:

- 444 subjects were screened and 387 subjects were allocated to drug, at 86 sites, in 22 countries.
- 117 subjects enrolled in Europe, 19 in Asia, 162 in N. America and 89 in rest of world (Australia, New Zealand, South Africa, Israel).
- 100 subjects were initially allocated to berotralstat 110 mg and 287 subjects were initially allocated to berotralstat 150 mg.

Focussing on adolescents:

- Overall, 28 adolescent subjects were enrolled at 28 sites in 5 countries (Israel, New Zealand, Poland, South Africa, and the US) and received at least 1 dose of berotralstat.
- 5 adolescents were enrolled in the berotralstat 110 mg followed by 150 mg group, and 23 subjects were enrolled in the 150 mg treatment group.

Baseline data

Focussing on adolescents: n=28

- Mean age - 14.3 years
- 57.1% female, 42.9% male
- 78.1% white, 10.7% black or African American, 3.6% American Indian or Alaska native
- 82.1% Not Hispanic or Latino, 14.3% Hispanic or Latino
- Mean weight - 65.13kg
- Mean BMI - 23.96 kg/m^2

PK results

Focussing on adolescents:

PK samples were obtained in the first 12 weeks for 23 adolescent subjects in the berotralstat 150 mg group. In accordance with Study BCX7353-PPK1 of the agreed PIP, the sparse concentration data collected in this study will be used to conduct population PK analyses as agreed in PIP Study 5. No

updates to Section 5.2 of the summary of product characteristics (SmPC) are proposed based on this limited PK sampling.

Safety results

Focussing on adolescents:

Exposure: For the 28 adolescents concerned, the overall mean exposure to berotralstat was 439.5 days (range 19-1149 days). Overall, 17/28 had at least 337 days or 48 weeks of exposure. A summary of berotralstat exposure for the adolescent subgroup is provided below in Table 2:

Table 2: Study 204: Summary of Treatment Exposure (Safety Population: Paediatric Subjects)

	Berotralstat		
	110 mg Followed by 150 mg N=5	**150 mg N=23**	**Total n=28**
Duration of exposure (days)[a]			
N	5	23	28
Mean (SD)	593.4 (541.39)	406.0 (295.00)	439.5 (345.93)
Median	682.0	393.0	396.5
Min, max	19, 1135	57, 1149	19, 1149
Duration of exposure (days)			
≤ 84 days	2 (40.0%)	2 (8.7%)	4 (14.3%)
85 to 168 days	0	2 (8.7%)	2 (7.1%)
169 to 252 days	0	3 (13.0%)	3 (10.7%)
253 to 336 days	0	2 (8.7%)	2 (7.1%)
337 to 504 days	0	11 (47.8%)	11 (39.3%)
505 to 672 days	0	0	0
> 672 days	3 (60.0%)	3 (13.0%)	6 (21.4%)
PYE[b]	8.1	25.6	33.7

Adverse events:

For the 28 adolescents there were 91 TEAEs; 20/28 (71.4%) had at least one TEAE, and 11/28 (39.3%) had at least one drug-related AE.

In terms of severity, there were no Grade 4 AEs in adolescents, and only 4 Grade 3 AEs in 3 adolescents (dizziness, facial paralysis, headache, sinusitis).

No AE in adolescents resulted in treatment interruption, but one AE resulted in treatment discontinuation (upper abdominal pain). This AE which was assessed as probably related was reported in a subject who experienced upper abdominal pain on first day of treatment with berotralstat 110mg; after 19 days treatment was discontinued on account of this abdominal pain and consent was withdrawn soon after.

The most common SOC for AEs was Infections and infestations (42.9% of adolescents - most commonly influenza, respiratory, GI) followed by Gastrointestinal disorders (39.3% of adolescents - mainly abdominal pain, diarrhoea, vomiting), Nervous system disorders (17.9% of adolescents - mainly headache and syncope), and Psychiatric disorders (14.3% of adolescents).

The most frequent AEs (preferred term level) were abdominal discomfort, influenza, sinusitis, URTI, abdominal pain upper, diarrhoea and headache, all of which were very common.

There were 4 events of suicidality/self-harm in 2 adolescents, which were not reported as SAEs, were graded as mild. As no background detail is available on these 2 subjects, the MAH was asked to discuss the occurrence of psychiatric disorders, and specifically suicidality/self-harm in adolescents treated with berotralstat, providing the narratives and background to the adolescents concerned. The MAH was also asked to provide further context to this discussion by referencing suicidality/self-harm seen rates in adults treated with berotralstat.

The MAH has provided a detailed response on the 4 events of suicidality and self-harm reported in 2 adolescents in Study 204. It is noted that in both cases the events were considered as unrelated, the events resolved within a short timeframe without hospital admission, and in one case was against a background history of depression and previous self-harm/suicidality. For context the MAH also reviewed in detail relevant AEs of depression/suicidality/self-harm from the clinical trials overall (for both adults and adolescents), from the global safety database, and from the literature. An increased tendency towards depression and other psychiatric events in patients with HAE versus the general population has also been discussed by the MAH and can be agreed. It can be agreed that there does not appear to be a signal with regard to increased tendency to severe depression, suicidality or self-harm in the adolescent population treated with berotralstat.

There were 2 adolescents/4 events of with LFT rises - one ALT rise, and one GGT rise- both of which were considered related.

There were no deaths in adolescents in Study 204 (and also no deaths in any study participants overall).

In total, there were 3 adolescents with SAEs /5 SAE events. The SAEs were: facial nerve paralysis, HAE attacks, medical observation, pneumonia, and sinusitis. Of these, only one SAE was considered related (grade 3 sinusitis). Only 2 of these SAEs occurred following the interim CSR for Study 204 and are discussed below. The other 3 SAEs in adolescents were described in the interim CSR for Study 204 that was presented and assessed during the Orladeyo MAA procedure - facial nerve paralysis (1 subject), HAE, oral swelling, and medical observation after tooth extraction (both in same subject).

Of note all SAEs fully resolved.

<u>SAEs in adolescents following the Interim CSR for Study 204:</u>

In 1 subject: 2 SAEs while receiving berotralstat 110mg.

SAE1: worsening of right lobar pneumonia (considered unrelated by investigator)

SAE2: sinusitis (considered possibly related by investigator)

Initial onset of respiratory symptoms was on D401 of therapy (bronchitis, mild pneumonia) which became worsened right lobar pneumonia, SAE1, by D412 requiring hospitalisation (resolution by D415). On D447 sinus investigation/imaging following outpatient therapy of sinusitis revealed pansinusitis (grade 3, severe) which required endoscopic sinus surgery and septoplasty (hence an SAE due to hospitalisation), event resolved by D457. Berotralstat was not interrupted for either SAE. SAE2

(sinusitis) was considered by the investigator to be related, but considered unrelated by the sponsor due to the previous respiratory tract infection, and the anatomical factor requiring septoplasty.

Maculopapular rashes deemed related to berotralstat were considered AEs of special interest, however no such AEs were reported in paediatric patients in Study 204.

Laboratory/ECG findings:

No adolescent had a chemistry or haematology change > grade 2. No adolescent met the QTcF threshold of > 480msec, or >60msec change from baseline, or had a clinically significant ECG abnormality.

Efficacy results

Focussing on adolescents:

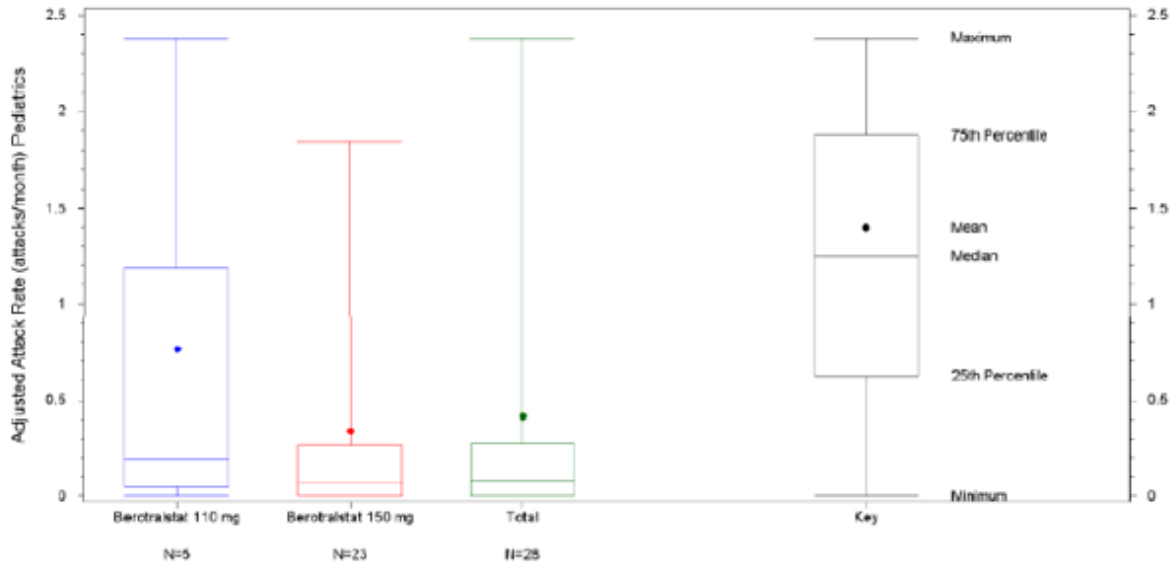
The percentage of subjects with at least 1 adjusted attack was 65.2% with 86.7% of these having at least 1 treated adjusted attack.

Overall, for the berotralstat 150 mg dose group, the mean (SD) attack rate was 0.34 (0.591) attacks per month and the median attack rate was 0 (range 0 to 1.85) attacks per month.

10 of 23 (43.5%) and 5 of 23 paediatric subjects (21.7%) were attack free from Weeks 0 to 24 and Weeks 0 to 48, respectively. No subject was attack free from Weeks 0 to 96 or over the entire study period.

Figure 2 below shows box plots of overall adjusted attack rate for the paediatric population, per berotralstat dose.

Figure 2: Study 204: Box Plot of Overall Adjusted Attack Rate (Safety Population: Paediatric Subjects)



Abbreviations: HAE = hereditary angioedema
Note: Includes all attacks occurring after the first dose of study drug to 24 hour post last dose of the study drug. The adjusted attack rate was defined as (total number of adjusted HAE attacks experienced in the period*28/(date of end of period – date of start of period + 1).

Improvements in mean CFB AE-QoL total that exceeded the MCID were observed at Week 4 and maintained through week 48 for those remaining in the study. Greater than 12-point improvements in

mean CFB for each of the domains (functioning, fatigue/mood, fear/shame, and nutrition) were also observed at Week 48. The mean TSQM global satisfaction score also improved through Week 48.

2.3.3. Discussion on clinical aspects

The MAH has provided the final CSR for Study 204, an open label study evaluating the long-term safety of daily oral berotralstat in subjects with type 1 and 2 hereditary angioedema (mainly adults, with adolescents recruited in a substudy). An interim study report was already provided during the MAA assessment, and so the focus of this Article 46 procedure are the finalised results insofar as they relate to paediatric/adolescents.

As was noted during the MAA assessment, very limited numbers of adolescents (age 12-17 years) were recruited into Study 204; only 28 adolescents altogether.

Safety:

While the primary objective of Study 204 was to evaluate long term safety, it has to be borne in mind that the numbers of adolescents concerned are very small (n=28), and also that Study 204 was open label, which means that firm conclusions on the safety of berotralstat in adolescents are not possible. In general, however, the results from Study 204 indicate that berotralstat is safe and is well tolerated in adolescents, and also that tolerability with longer term therapy seems favourable. While no adolescents completed 96 weeks of therapy, this was because berotralstat became available through an alternative means in 22/28 of the cases. More than half of the 28 adolescents (17/28) had at least 337 days or 48 weeks of exposure, with satisfactory reported compliance rates. While AE rates are not low - 20/28 had at least one TEAE, the AE profile was in general mild and in keeping with the known safety profile for berotralstat. SAEs were also infrequent: for the entire study only 5 SAEs were reported in 3 adolescents, of which only one was reported as possibly related (sinusitis), and for which there is a plausible alternative explanation.

The MAH has provided a detailed response on the 4 events of suicidality and self-harm reported in 2 adolescents in Study 204. For context the MAH also reviewed in detail relevant AEs of depression/suicidality/self-harm from the clinical trials overall (for both adults and adolescents), from the global safety database, and from the literature. An increased tendency towards depression and other psychiatric events in patients with HAE versus the general population has also been discussed by the MAH and can be agreed. It can be agreed that there does not appear to be a signal with regard to increased tendency to severe depression, suicidality or self-harm in the adolescent population treated with berotralstat.

Overall, berotralstat was safe and generally well tolerated in the 28 paediatric subjects in Study 204 with a similar safety/AE profile as compared to the overall dataset.

Effectiveness:

Secondary objectives of Study 204 evaluated the effectiveness of long-term prophylactic administration of berotralstat. However, the sample size and design of the study (open label, non-randomised, no comparator) do not allow adequate statistical interpretation of efficacy/effectiveness results. Despite the limitations outlined, the effectiveness data suggest that adolescent patients treated with berotralstat 150mg experienced a reduction in self-reported monthly attack rate that is broadly consistent with that seen in the pivotal trials, and that the effect seemed to last.

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. CHMP 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 in Study 204, no conclusions on safety and efficacy could be made as the number of paediatric patients enrolled is too small.

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

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information 1

1. There were 4 AEs relating to suicidality/self-harm in 2 adolescents treated with berotralstat. While these were graded as non-serious and not severe, the MAH is asked to discuss the occurrence of psychiatric disorders, and specifically suicidality/self-harm, in adolescents treated with berotralstat. Narratives and background to the adolescents concerned should be provided. The MAH should also provide further context to this discussion by referencing suicidality/self-harm seen rates in adults treated with berotralstat.

5. Assessment of responses to RSI 1

There were 4 AEs relating to suicidality/self-harm in 2 adolescents treated with berotralstat. While these were graded as non-serious and not severe, the MAH is asked to discuss the occurrence of psychiatric disorders, and specifically suicidality/self-harm, in adolescents treated with berotralstat. Narratives and background to the adolescents concerned should be provided. The MAH should also provide further context to this discussion by referencing suicidality/self-harm seen rates in adults treated with berotralstat.

Assessment of response:

The MAH discusses an increased rate of depression and related disorders in HAE patients versus the general population and identifies possible reasons for this: stress due to the psychosocial burden of HAE attacks and their seriousness and unpredictability, painful/distressing symptoms, uncomfortable side effects from treatments, and inaccurate or late diagnosis. The MAH also cites one paper suggesting the disease itself may also cause depression due to the binding of bradykinin (raised in HAE) to B1 receptor, which has been shown in experimental models to mediate depression like behaviour.

The MAH has performed a review of the signal psychiatric symptoms, specifically suicidality and self-harm, in association with berotralstat use in HAE patients using 4 sources:

1. Search of the Global Safety Database (all SAEs during clinical development + post marketing serious and non-serious)
2. Clinical Trial data
3. Literature review
4. Search of FDA's Adverse Events Reporting System

Search of the Global Safety Database (all SAEs during clinical development + post marketing serious and non-serious)

From the Global Safety Database search 30 cases for suicidality/self-harm/or other relevant psychiatric AEs were found, 7 of which were graded as serious, 23 as non-serious. 3/7 serious cases were from the clinical development, and 4/7 were post marketing reports. Of the serious cases, only one was in an adolescent.

1 subject, solicited, SAE

Patient experienced mental disorder needing admission while receiving therapy with Orladeyo. The patient had no other medical history other than HAE. On 14-Apr-2022, the patient started Orladeyo 150 mg once daily orally for prophylactic treatment of HAE. At the time of reporting of the admission, the patient was not taking Orladeyo as the patient had run out of medication. The outcome of the event mental disorder was not recovered/not resolved. MAH considered the event of mental disorder as not assessable as very limited information was provided.

The remaining 6 SAEs all occurred in adults, 3 in clinical trials and 3 from post marketing:

3 serious AE cases, all in adults, that occurred in clinical trials, as follows

1. *Suicide attempt (unspecified tablets) and hospital admission in a patient in Study 204, 288 days after starting berotralstat 150mg in a patient with HAE and mastocytosis but no prior psychiatric history, assessed as a severe attempt, and considered not related.*

2. *Admission for observation with anxiety/alcohol withdrawals and head injury in the context of exacerbated alcohol consumption, in a patient with HAE, anxiety diagnosis and arthritis, after 53 weeks of berotralstat 150mg, considered as not related.*
3. *Admission for worsening of pre-existing bipolar disorder and depression and self-harm, in a patient with a prior history of BPAD on D251 of berotralstat 150mg, considered not related.*

3 serious cases, all in adults, reported from post marketing, as follows:

1. *Worsening of suicidal ideation in a female of unspecified age, limited information, spontaneous report*
2. *Successful suicide (gun) in a patient, with medical history of HAE, depression, prostate cancer (on triptorelin), occurred after one month of therapy, assessed as unrelated.*
3. *Admission for worsening of pre-existing bipolar disorder in a patient after 9 months of berotralstat 150mg.*

Clinical Trial data

From a search of clinical trial data, 79 TEAEs were reported in studies 204, 301, 302 by 56(10.7%) subjects under Psychiatric disorders. Excluding events considered less relevant for the assessment of suicidality/self-harm, there were 43 events, of which 3 were serious, all in adults, all considered unrelated. The 3 SAEs from CTs were all in adults and are described above.

From the CT data search, and as discussed in the AR for this Art 46 procedure there were 4 non serious, non-related events reported by 2 adolescent subjects (suicidal ideation x2, intentional self-injury, self-injurious ideation) in Study 204. As requested, narratives of those 4 *non serious* events in 2 adolescent subjects are as follows:

1. *One subject who was being treated with 150 mg berotralstat, reported the non-serious events of intentional self-injury (mild) and suicidal ideation (moderate) on Day 357. The subject was in Study 204. Both events resolved the same day and were assessed as not related by the investigator. No medical history significant for psychiatric disorders were reported.*
2. *One subject who was being treated with 150 mg berotralstat reported the non-serious events of intentional self-injurious ideation (moderate) and suicidal ideation (moderate) on Day 16. The subject was in study 204; Both events resolved by Day 23 and were assessed as not related by the investigator. Significant medical history for psychiatric diseases and self-harm was reported (depression, threatening to self/self-harming behaviour, suicidal ideation). Significant concomitant medications were reported as sertraline and Prozac.*

Conclusion:

Overall, the MAH has provided a detailed response to the request for further information on the 4 events of suicidality and self-harm reported in 2 adolescents in Study 204 for which narratives were not presented in the CSR on account of them being graded as non-serious. It is noted that in both cases the events were considered as unrelated, the events resolved within a short timeframe without hospital admission, and in one case was against a background history of depression and previous self-harm/suicidality. For context the MAH has also reviewed in detail relevant AEs of depression/suicidality/self-harm from the clinical trials overall (for both adults and adolescents), from the global safety database, and from the literature. An increased tendency towards depression and other psychiatric events in patients with HAE versus the general population has also been discussed by the MAH and can be agreed.

It can be agreed that there does not appear to be a signal with regard to increased tendency to severe depression, suicidality or self-harm in the adolescent population treated with berotralstat.

There is however one point for clarification. The review provided of the global safety database and the clinical trial data review does not seem to include the SAE of worsened bipolar disorder with depression in subject that was discussed in the parallel Art 46 procedure for Study 302. The MAH is asked to verify that this omission was an error, and that the signal review otherwise captures all relevant cases.

Issue partially resolved, further clarification on the completeness of the signal review is sought.

6. Request for supplementary information 2

1. The review provided of the global safety database and of clinical trial data with regard to psychiatric events/suicidality/self-harm does not seem to include the SAE of worsened bipolar disorder with depression in subject that was discussed in the parallel Art 46 procedure for Study 302 (P46/004). The MAH is asked to verify that this omission was an error, and that the signal review otherwise captures all relevant cases.

7. Assessment of responses to the 2nd RSI

Assessment of response:

The MAH explained that the case in the SER relates to the serious event of worsened bipolar disorder with depression in Subject in study 302.

The case as discussed in the SER had not been clearly identifiable as the bipolar disorder worsening SAE reported in Subject in Study 302 for a few reasons:

- In the CSR of Study 302 the subject was described at recruitment age versus age at which SAE occurred in the Signal Evaluation Report.
- The SAE was described in relation to berotralstat 110mg in the CSR for Study 302 (initial dose), versus berotralstat 150mg in the Signal evaluation report (dose at which SAE occurred)
- Concomitant medication for Subject listed in the CSR for Study 302 did not seem to fully match an incomplete list provided in the main body of the Signal Evaluation Report.

Conclusion:
Sufficient clarification has been provided that psychiatric SAE case is in fact the bipolar disorder worsening SAE that occurred in subject in Study 302. The Rapp is satisfied that that the SAE of bipolar disorder worsening in subject had been included in the psychiatric Signal evaluation report.

Issue resolved.

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

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