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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Orladeyo (berotralstat hydrochloride, (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride)
Treatment of hereditary angioedema
EU/3/18/2028

Sponsor: Biocryst Ireland Limited

Note

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

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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	(R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride
Other name(s)	-
International Non-Proprietary Name	Berotralstat hydrochloride
Tradename	Orladeyo
Orphan condition	Treatment of hereditary angioedema
Sponsor's details:	Biocryst Ireland Limited Block 4 Harcourt Centre Harcourt Road Dublin 2 D02 HW77 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	BioCryst UK Ltd
COMP opinion	24 May 2018
EC decision	27 June 2018
EC registration number	EU/3/18/2028
Post-designation procedural history	
Transfer of sponsorship	Transfer from BioCryst UK Ltd to Biocryst Ireland Limited – EC decision of 26 March 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	P. Kiely / M. Bego
Applicant	Biocryst Ireland Limited
Application submission	9 March 2020
Procedure start	26 March 2020
Procedure number	EMEA/H/C/005138/0000
Invented name	Orladeyo
Proposed therapeutic indication	Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Further information on Orladeyo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Orladeyo
CHMP opinion	25 February 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	M. Mozina / D. Vitezic
Sponsor's report submission	16 October 2020

COMP discussion and adoption of list of questions	19-21 January 2021
Oral explanation	16 March 2021
Sponsor's removal request	18 March 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

The sponsor BioCryst UK Ltd submitted on 18 January 2018 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing

(R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride for treatment of hereditary angioedema (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride was considered justified based on preliminary clinical data showing a significant reduction in attacks in patients with the condition;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- the condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a significant reduction in the number of attacks, the use of intravenous C1 inhibitor replacement therapy and an alternative to using an oral formulation where currently none exists. The Committee considered that this constitutes a clinically relevant advantage and major contribution to patient care.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-

carboxamide dihydrochloride as an orphan medicinal product for the orphan indication: treatment of hereditary angioedema.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hereditary angioedema is a rare, potentially life-threatening disorder characterized by attacks of cutaneous and submucosal swelling. The fundamental defect of hereditary angioedema is a deficiency of functional C1 inhibitor protein, a protease inhibitor in the serpin superfamily, that is linked to bradykinin the biologic mediator of swelling.

Angioedema is the physical manifestation of transient increases in vascular permeability. Bradykinin, generated by activation of the plasma contact system, has been conclusively identified as the mediator of swelling in hereditary angioedema with C1 inhibitor deficiency. The plasma contact system comprises coagulation factor XII, plasma prekallikrein, and high-molecular-weight kininogen; plasma prekallikrein and high-molecular-weight kininogen circulate as a 1:1 bimolecular complex. Despite the interactions between the activated plasma contact and fibrinolytic systems, patients with hereditary angioedema do not appear to be at an increased risk for bleeding or thrombosis.

The fundamental abnormality in hereditary angioedema types I and II is a deficiency of functional C1 inhibitor (due to a mutation in SERPING1), which regulates multiple proteases involved in the complement, contact-system, coagulation, and fibrinolytic pathways. Within the contact cascade, C1 inhibitor inactivates plasma kallikrein, factor XIIa, and factor XIIf, operating as a "molecular mousetrap." When the Arg444–Thr445 bond in the reactive loop of the molecule is cleaved, a conformational rearrangement is triggered — called suicide inactivation — that irreversibly buries the protease in the C1 inhibitor molecule. Suicide inactivation results in a thermodynamically stable C1 inhibitor–protease complex.

The mutations that lead to hereditary angioedema type I are diverse, with missense, nonsense, frameshift deletion or insertion, or splicing defects scattered throughout the gene, resulting in truncated or misfolded C1 inhibitor that is not efficiently secreted. In hereditary angioedema type II, the defect is typically a missense mutation in exon 8, affecting the mobile loop and interfering with the ability to inhibit target proteases, with rare exceptions. The critical functional threshold for C1 inhibitor control of the plasma contact system is approximately 40%. Functional C1 inhibitor levels in hereditary angioedema with C1 inhibitor deficiency are generally 5 to 30% of the normal level, despite the presence of one normal gene. The cause of this discrepancy has been proposed to involve enhanced clearance of C1 inhibitor–protease complexes, cleavage of C1 inhibitor into an inactive, 94-kD form, and inhibition of the normal gene product by the abnormal one, designated as "transinhibition." A dominant negative effect on C1 inhibitor protein secretion has also been reported.

Hereditary angioedema with C1 inhibitor deficiency is an autosomal dominant disorder. Type I hereditary angioedema with C1 inhibitor deficiency accounts for 85% of cases, and type II accounts for

15%. A third group of patients with hereditary angioedema, those with normal levels of C1 inhibitor, was first reported in 2000. Hereditary angioedema with normal C1 inhibitor levels has an autosomal dominant inheritance pattern with incomplete penetrance.

For the diagnosis of the condition two types of C1 inhibitor functional analyses are available. The chromogenic assay (recommended when available) is more sensitive than the enzyme-linked immunosorbent assay. For children, measurement of the C4 level and the C1 inhibitor level appears to be accurate during the first year of life but should be repeated for verification. Genetic sequencing (if the mutation is known) can be used to establish an early diagnosis.

Figure 1.

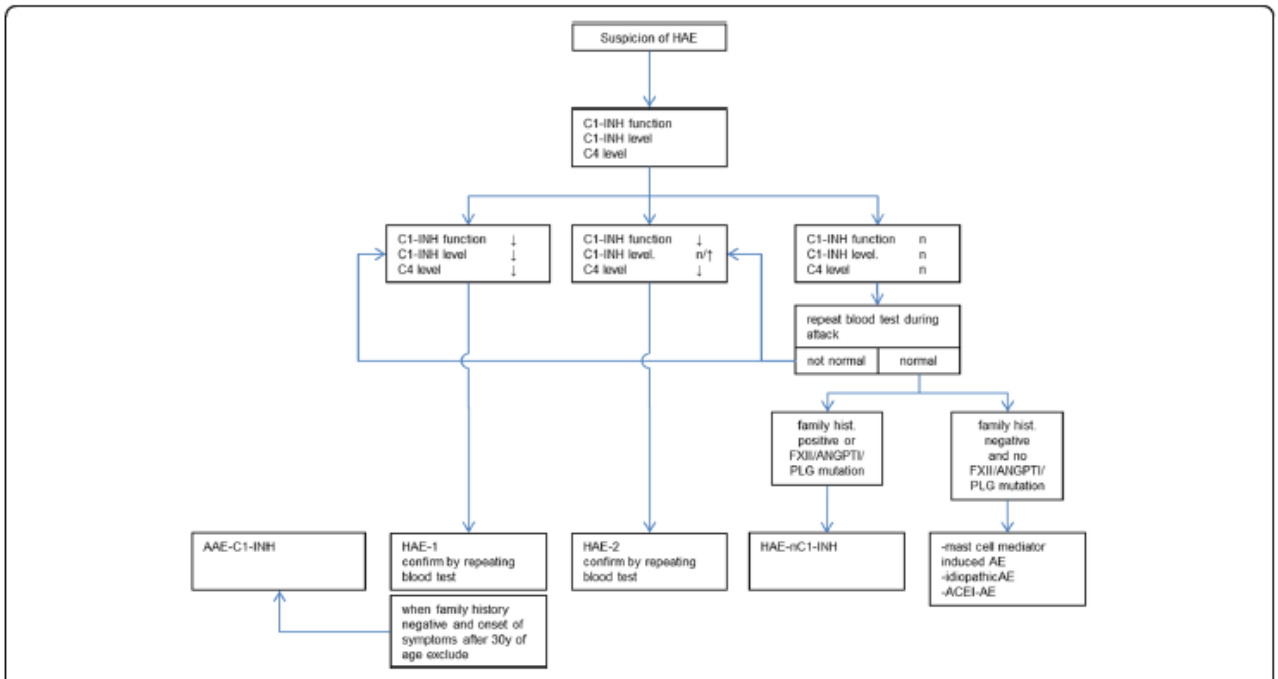

Fig. 2 Diagnostic work up in patients suspected to have HAE. Abbreviations: HAE-1: Hereditary angioedema due to C1-Inhibitor deficiency; HAE-2: Hereditary angioedema due to C1-Inhibitor dysfunction; AAE-C1-INH: acquired angioedema due to C1-Inhibitor deficiency; HAE nC1-INH: Hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in factor XII (FXII) angiopoetin (ANGPTI) or plasminogen (PLG); ACEI-AE: angiotensin converting enzyme inhibitor-induced angioedema

The COMP continues to designate this condition.

The approved therapeutic indication "ORLADEYO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older" falls within the scope of the designated orphan condition "treatment of hereditary angioedema".

Intention to diagnose, prevent or treat

The medical plausibility has not yet been confirmed by a final positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The condition continues to be chronically debilitating and life-threatening. Recurrent attacks of cutaneous angioedema (asymmetric, nonpruritic, disfiguring, and nonpitting) without urticaria or spontaneously remitting, severe abdominal symptoms (pain and swelling) or both should alert the clinician to consider hereditary angioedema.

Although cutaneous and abdominal attacks are the most common feature, patients infrequently have genital swelling and, in rare cases, bladder, muscle, or joint swelling. Laryngeal episodes account for approximately 0.9% of all attacks; however, all patients are at risk for a laryngeal attack, and more than 50% have a laryngeal attack during their lifetime. A lethal laryngeal attack can be the initial presentation.

In summary, attacks of the upper airways can result in asphyxiation. Abdominal attacks are painful and debilitating. Peripheral attacks such as those of hands or feet result in impaired function (Maurer et al 2017).

Number of people affected or at risk

The sponsor refers to the prevalence estimate provided in 2018 at the time of their initial orphan designation as sufficient and unchanged. The sponsor indicates that only one new publication has appeared since and cites an epidemiology study in Austria. They have identified a prevalence in Austrian patients with HAE with C1-inhibitor deficiency (HAE Type 1) or dysfunction (HAE Type 2) of 1:64,396, or 0.16 in 10,000, which is consistent with previously reported prevalence estimates (Schoffl, Wiednig et al. 2019).

Based on the above assumptions it is concluded that the prevalence has not changed at 0.5 in 10,000 in the European Union. The COMP noted that at the time of a review for the Maintenance of the Orphan Designation it requests a more thorough prevalence estimate than the one provided at an initial orphan designation so it was considered necessary to raise a request for a revised more thorough prevalence estimate.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Authorized products in the EU for the treatment of acute attacks include intravenous (IV) human plasma-derived C1-INH (pdC1-INH) replacement products (Cinryze, Berinert), IV recombinant human C1-INH (Ruconest) and subcutaneous (SC) icatibant (Firazyr) a bradykinin B2 receptor antagonist.

Authorized products for the prevention of recurrent attacks, include two formulations of plasma-derived C1-INH (IV Cinryze and SC Berinert 2000/3000), and SC lanadelumab (Takhzyro) a recombinant monoclonal antibody inhibitor of plasma kallikrein.

The current European Guidelines are part of "The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update, Maurer et al. World Allergy Organization Journal (2018) 11:5" and states for

On-demand treatment:

- Early treatment with C1-INH concentrate, ecallantide (US only), or icatibant provides a better treatment response than late treatment. Early treatment is associated with a shorter time to resolution of symptoms and shorter total attack duration regardless of attack severity. As early treatment is facilitated by self-administration, all patients with HAE-1/2 should be considered for

home therapy and self-administration training. All C1-INH concentrates and icatibant are licensed for self-administration, although approved product indications vary around the world.

- Preprocedural prophylaxis with C1-INH concentrate is therefore recommended for all medical, surgical and dental procedures associated with any mechanical impact to the upper aerodigestive tract.
- Long-term prophylaxis of HAE refers to the use of regular medication to reduce the burden of the disease by preventing/attenuating attacks in patients with confirmed HAE-1/2. Long-term prophylaxis should be individualized and considered in all severely symptomatic HAE-1/2 patients taking into consideration the activity of the disease, frequency of attacks, patient's quality of life, availability of health-care resources, and failure to achieve adequate control by appropriate on demand therapy. As all of these factors can vary over time, all patients should be evaluated for long-term prophylaxis at every visit, at least once a year. Successful long-term prophylaxis requires a high degree of compliance; therefore, the patient's preferences should be taken into consideration. Patients with ongoing long-term prophylaxis should be assessed regularly for efficacy and safety of the therapy, and dosage and/or treatment interval should be adapted according to the clinical response. Upper airway edema and other attacks may occur despite the use of long-term prophylaxis. Therefore, all patients using long-term prophylaxis should also have on-demand medication (C1-INH concentrate, ecallantide, or icatibant).

Significant benefit

The sponsor believes that their product, berotralstat, offers significant benefit based on a major contribution to patient care. Berotralstat is the first oral formulation for the treatment of this condition to be authorised. All currently authorised products for the treatment are either subcutaneous injection or IV formulations. No claim regarding a clinically relevant advantage is made. To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with authorised medicinal products in the condition.

Berostralstat is a kallikrein inhibitor which binds to plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. In patients with HAE caused by C1-inhibitor deficiency or dysfunction, normal regulation of plasma kallikrein activity is not present, which leads to uncontrolled increases in plasma kallikrein activity resulting in angioedema attacks. Berotralstat was authorised by the FDA in December 2020.

Currently the only kallikrein inhibitor authorised in Europe is lanadelumab (Takhzyro) a recombinant monoclonal antibody inhibitor of plasma kallikrein which is delivered twice a month as a subcutaneous injection. The kallikrein inhibitor ecallantide (Kalbitor; Shire) is licensed only in the US.

The sponsor received Scientific Advice from the CHMP on October 12, 2017 on the Phase 3 program to support registration. Protocol assistance for the justification of significant benefit was not sought by the sponsor as part of this procedure, as the sponsor obtained Orphan Designation only in 2018.

To support their claim for major contribution to patient care the sponsor has provided a comparative table highlighting the differences between the drug administration approaches for Orladeyo, Cinryze, Bernisert and Takhzyro. No clinical data generated by the sponsor in the treatment of these patients has been submitted to support significant benefit for either efficacy equivalence nor major contribution

to patient care. The sponsor only highlights difficulties in preparation of the different formulations before administration and reported adverse events.

The COMP noted that Takhzyro, the only product with the same mode of action, also claimed a major contribution to patient care at the time of review for the maintenance of the orphan designation (OMAR Takhzyro 2017). It is a twice a month subcutaneous injection and was shown to have a major contribution to patient care to the IV formulations currently authorised at that time. No direct or indirect comparisons with Takhzyro have been made regarding similar efficacy or safety. During the plenary it was noted that Orladeyo may actually be less efficacious than Takhzyro.

The COMP noted that 5 clinical efficacy trials where submitted to the CHMP and are summarised below. In the orphan maintenance submission the sponsor only discusses the pivotal Phase III trial BCX7353 302. The main study is BCX7353 302 was conducted in a North American and European population. BCX 7353 301 was a smaller study with the same design as 302 conducted in Japan.

Table 1.

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagn Incl. criter
BCX7 353-202 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 Type HAE
BCX7 353-203	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 placebo orally QD (22	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 Type HAE
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 Type HAE
BCX7 353-301 Phase 3		Randomized double blind, Placebo controlled, Parallel group study	Berotraslat capsule 55mg x 2 daily Berotraslat capsule 75mg x 2 daily	To determine the efficacy of prophylactic berotralstat (BCX7353) 110 and 150 mg administered once daily	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 Type HAE

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 administered QD for 24 weeks compared to placebo	121 subjects were randomized (stratified by baseline attack rate, < 2 vs. ≥ 2 per 28 days), and 120 randomized subjects (99%) were treated. Berotralsta 110mg n= 41, Berotralstat 150mg n = 40, placebo n = 40	24 weeks	M/F 33.9% v 66.1£. Median age = 40 years	Type 1 or Type 2 HAE	The rate of investigato confirmed HAE attack during dosing in the entire 24-week treatment period (Day 1 to time o the first dose of study drug in Part 2)

Summary of key points of BCX7 353-302

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.

The COMP noted that in this trial only two parameters appear to be of interest namely the use of concomitant medicines (as an indirect measure of the use of healthcare resources) and the QoL measures for the purpose of the establishing the major contribution to patient care. These outcomes are presented below.

Table 2. BCX7353-302 Part 1: Concomitant Medications Taken for HAE Attacks [a] (ITT Population)

Concomitant Medications for HAE Attacks	Berotralstat 110 mg (N = 41) n (%)	Berotralstat 150 mg (N = 40) n (%)	Placebo (N = 40) n (%)	Total (N = 121) 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) a Medications were as recorded in the e-diary for each attack. The percentages provided were based on the number
b) of investigator-confirmed attacks.
c) b Medications displayed were those HAE medications recorded on the e-diary that were taken concomitantly with
d) 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.

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 3. 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	

The sponsor has not elaborated on how this data could show a significant benefit over Takhzyro let alone the other products currently authorised for use.

Claims of better safety as a basis for major contribution to patient care was for example highlighted by the sponsor as reportedin the literature that Takhzyro causes important patient discomfort. *Takhzyro is associated with a high incidence of injection site reaction (>50% of patients) including injection site pain, erythema, bruising, discomfort, haematoma, haemorrhage, pruritus, swelling, induration, paraesthesia, reaction, warmth, oedema and rash. Injection site reactions were associated with pain in 43% of subjects (Banerji, Riedl et al. 2018).*

The claim for better safety was not supported by data generated by the sponsor in their clinical trials programme.

For the COMP to establish significant benefit based on major contribution to patient care the sponsor should further elaborate on the comparison to Takhzyro which has the same mode of action as Orladeyo. Unless a comparative efficacy of both products can be shown the benefit of the oral formulation supporting a major contribution to patient care cannot be assessed. The claim that a once a day oral formulation offers a major contribution to patient care in comparison to Takhzyro which is a twice a month subcutaneous injection is not self-evident and further justification will be required.

Further elaboration on parameters such as Quality of Life data as well as any other clinical or healthcare use data could help the COMP establish if the basis for significant benefit is met.

4. COMP list of issues

Prevalence:

The sponsor should provide a more thorough prevalence estimate. The assumptions made at the time of review for the Maintenance of the Orphan Designation appear to be limited.

Significant benefit:

The sponsor is proposing that their product offers a major contribution to patient care. To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products. The sponsor should provide a comparative analysis to Takhzyro which also inhibits kallikrein and discuss the major contribution to patient care as it is delivered as a twice monthly sub cutaneous injection. Further elaboration on parameters such as Quality of Life data as well as any other clinical or healthcare use data could help the COMP establish if the basis for significant benefit is met.