CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214094Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214094
PDUFA Goal Date	December 3, 2020
OSE RCM #	2019-2513
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Laura Zendel, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 1, 2020
Subject	Evaluation of Need for a REMS
Established Name	Berotralstat
Trade Name	Orladeyo
Name of Applicant	BioCryst Pharmaceuticals, Inc.
Therapeutic Class	Small molecule plasma kallikrein inhibitor
Formulation(s)	110 mg and 150mg Capsule, oral
Dosing Regimen	Once daily

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity berotralstat is necessary to ensure the benefits outweigh its risks. BioCryst Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 214094 for berotralstat with the proposed indication of prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. The risks associated with berotralstat include the following: gastrointestinal (GI)-related adverse events, transaminase elevations, QT-prolongation, and carcinogenicity in rodent models. The Applicant submitted a proposed routine postmarketing surveillance plan as a risk management strategy but did not include a REMS with this application.

The Division of Risk Management (DRM) and the Division of Pulmonary, Allergy, and Critical Care (DPACC) agree that a REMS is not necessary to ensure the benefits of berotralstat outweigh its risks. Berotralstat demonstrated efficacy in preventing attacks of hereditary angioedema. GI-related adverse events were of mild to moderate severity in a majority of cases. Transaminase elevations were predominantly asymptomatic and correlated with a history of androgen use and recent discontinuation. The Interdisciplinary Review Team for Cardiac Studies (QT-IRT) noted that an increase in QT prolongation can occur at doses higher than the recommended 150 mg once daily dose. After 2 meetings and reanalyzed information from the Applicant, the Executive Carcinogenicity Assessment Committee (Exec CAC) found no risk of carcinogenicity in humans. Recommendations to avoid additional doses or doses above 150 mg will be included in the Warnings and Precautions of the Prescribing Information. The risks associated with berotralstat will be communicated in the labeling and do not require any additional risk management to ensure the benefits outweigh the risks.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) berotralstat is necessary to ensure the benefits outweigh its risks. BioCryst Pharmaceuticals Inc. (BioCryst) submitted a New Drug Application (NDA) 214094 for berotralstat with the proposed indication of prophylaxis to prevent of attacks of hereditary angioedema (HAE) in patients 12 years and older. This application is under review in the Division of Pulmonary, Allergy, and Critical Care (DPACC). The Applicant did not submit a proposed REMS with this application.

2 Background

2.1 PRODUCT INFORMATION

Berotralstat, a new molecular entity, is an inhibitor of plasma kallikrein proposed for prophylaxis to prevent attacks of HAE in patients 12 years and older. Kallikrein is a plasma protease responsible for bradykinin production. Berotralstat binds to plasma kallikrein leading to a decrease in blood levels of bradykinin, which in turn decreases vascular permeability and edema in patients with HAE. Berotralstat is proposed as 110 mg and 150 mg oral capsule to be taken once daily. Berotralstat is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA relevant to this review:

- 11/01/2017: Orphan Drug designation granted.
- 08/02/2019: Fast Track designation granted.
- 05/29/2019: The clinical team informed the Applicant at pre-NDA meeting that a REMS for berotralstat was not needed for the phase 3 study dose and to continue post-marketing surveillance pending final review.
- 12/03/2019: NDA 214094 submission for of prophylaxis to prevent of attacks of hereditary angioedema (HAE) in patients 12 years and older received.
- 03/30/2020: The Agency received the 120-day safety update to the submission.
- 05/21/2020: The Agency and BioCryst hold mid-cycle teleconference.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hereditary angioedema (HAE) is a serious, rare, and potentially life-threatening autosomal-dominant disease characterized by intermittent, unpredictable attacks of angioedema of the skin, pharynx, larynx, the gastrointestinal tract, and extremities. Symptoms include nausea, vomiting, abdominal pain, swelling of affected tissues, and life-threatening airway obstruction. The attacks can be triggered by stress, trauma, or have no known trigger. Attacks usually begin in childhood and worsen during puberty. While the frequency of attacks vary, untreated individuals average one attack every one or two weeks, and last several days each. The majority of cases are caused by mutations of SERPING1, the gene for complement 1 esterase inhibitor (C1-INH), the major regulator of the contact activation pathway. The mutation of the SERPING1 gene causes a deficiency or dysfunction of C1-INH. This leads to the dysregulation of the contact system that activates both the procoagulant intrinsic coagulation pathway and proinflammatory kallikrein-kinin pathways. Due to the deficiency or dysfunction of C1-INH in patients with HAE, the kallikrein activity modulated by C1-INH continues unrestrained, leading to overall excess bradykinin release. Bradykinin then increases vascular permeability that produces the characteristic swelling seen in acute HAE attacks.

The worldwide prevalence of HAE is estimated to be 1 in 10,000 to 50,000. HAE Type I comprises approximately 85% of cases and is caused by low production of normal C1-INH protein. Type ll makes up approximately 15% and is caused by normal production levels of dysfunctional C-INH. Type lll is extremely rare and is most commonly caused by a mutation in the F12 gene. Type III patients are predominantly females with normal levels of C1-INH that functions normally.[1]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Approved treatments to prevent HAE attacks in the United States consist of C1-INH (Cynryze and Haegarda), monoclonal antibody kallikrein inhibitor (Takhzyro) and attenuated androgen (danazol). Androgens are associated with side effects that limit tolerability and C1-INH therapies have a short half-life, making it necessary to administer either intravenously or subcutaneously every three to four days. None of the products approved to prevent HAE attacks have a REMS. A table detailing the currently approved treatments to prevent HAE attacks is included in Section 10.2, Appendix 1.

4 Benefit Assessment

The ongoing pivotal phase 3 study BCX7352-302 (Study 302, NCT 03485911) supporting the safety and efficacy of this application consists of a 3 part, 24-week, double-blind, placebo controlled, parallel-group, multicenter study. Efficacy is supported by Part 1 of Study 302. The safety database is supported by data from Parts 2 and 3 as well as an ongoing open-label Phase 2 extension study, BCX7352-204 (Study 204). As of August 20, 2019, Study 204 treated 100 subjects with 110 mg berotralstat daily and 127 subjects with berotralstat 150 mg daily. The primary endpoint of Study 204 was to obtain long term safety data of berotralstat.

Study 302 Part 1 included 120 adolescent (ages 12 -17) and adult patients with either Type I or Type II HAE who experienced at least two investigator confirmed HAE attacks during the 14-56 day run-in period were randomized 1:1:1 to placebo, berotralstat 110 mg, and berotralstat 150 mg. The primary objective of Part 1 of Study 302 was to determine the efficacy of prophylactic berotralstat 110 mg and 150 mg taken orally once daily for 24 weeks versus placebo. The study's primary efficacy endpoint was the rate of HAE attacks (confirmed by investigator) during the 24 weeks. Secondary efficacy endpoints included the change in baseline Angioedema Quality of Life Questionnaire (AE-QoL) at week 24, number and proportion of days with angioedema symptoms, and rate of investigator confirmed HAE attacks during the period of Day 8 and first dose of Part 2.[2] The primary objective of Parts 2 and 3 of Study 302 was to assess the long term safety with chronic use of berotralstat.

Table 2 below demonstrates that subjects receiving 110 mg berotralstat daily in Part 1 of Study 302 had HAE attack rates decrease by 30% ($p = 0.024$), and subjects receiving berotralstat 150 mg daily had a 44% ($p < 0.001$) decrease in HAE attacks over placebo and a moderately higher reduction in HAE attacks.

Table 1: Primary Endpoint of Investigator-confirmed HAE Attack Rates During Dosing Period

	Berotralstat		Placebo
	110 mg (N = 41)	150 mg (N = 40)	(N = 40)
Estimated rate per 28 days	1.65	1.31	2.35
Attack Rate Ratio (relative to placebo) (95% CI)	0.70 (0.51, 0.95)	0.56 (0.41, 0.77)	Reference
p-value	0.024	<0.001	Reference
Rate difference of active vs placebo: % (95% CI)	-30.0 (-48.7, -4.6)	-44.2 (-59.5, -23.0)	Reference

Source: FDA Statistical Reviewer in ongoing berotralstat review (Accessed on 11/04/2020)

As seen below in Table 2, any changes seen in secondary endpoints were not statistically significant in subjects taking berotralstat at either dose.

Table 2: Secondary endpoint of AE-QoL Scores at Week 24 (ITT Population)

	Berotralstat		Placebo
	110 mg (N = 41)	150 mg (N = 40)	(N = 40)
N	40	38	36
LSM AE-QoL total score (SE)	-12.46 (2.530)	-14.59 (2.592)	-9.69 (2.643)
LSM difference from placebo (95% CI)	-2.77 (-10.08, 4.53)	-4.90 (-12.23, 2.43)	Reference
p-value	0.453	0.188	Reference

Source: FDA Statistical Reviewer in ongoing berotralstat review (Accessed on 11/04/2020)
Abbreviations: ITT, intent to treat; LSM, least-square mean; AE-Qol, angioedema quality of life; SE, standard error

Study 204 was primarily for safety, however, it provided some supportive evidence of efficacy. Due to the study design, baseline HAE attack rates were not calculated. However, after the first month of berotralstat 150 mg treatment, the mean (SD) attack rate was 1.64 (1.83) attacks per month. This decreased to 1.38 (1.73) and 0.77 (1.00) attacks per month by months 6 and 12 of 150 mg berotralstat daily. After the first month of berotralstat 110 mg treatment, the mean (SD) attack rate was 1.39 (1.55), and 1.05 (1.27) and 0.16 (1.04) at 6 and 12 months of treatment, respectively. These rates may have been affected by subjects who discontinued due to lack of perceived efficacy. The total days with angioedema symptoms were similar in the 110 and 150 mg treatment groups, with month 1 median days (median percentage of days) with symptoms being 2.0 (7.1%) for both dosage groups, 1.0 (3.6%) days for both treatment groups at month 6, and 0 (0%) at month 12 for each group. Seventeen subjects in the berotralstat 110 mg dose group and 11 subjects taking 150 mg discontinued the study due to lack of perceived efficacy. Twenty of the twenty-eight discontinued prior to week 12.[2]

In the clinical review that is in progress, the clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness and supported the Applicant's recommended dose of 150 mg daily as well as an alternate dose of 110 mg daily for patients who could not tolerate the adverse events or had (b) (4) moderate liver impairment.

5 Risk Assessment & Safe-Use Conditions

The safety database is comprised of 347 subjects with berotralstat exposure in Study 302 and Study 204. The clinical reviewer states in the ongoing clinical review that the safety database of berotralstat is of sufficient in both size and duration for assessment for a chronically administered drug in a rare disease. The most commonly (>10%) seen adverse events (AEs) were gastrointestinal (GI) disorders (abdominal pain, nausea, vomiting, and diarrhea), nasopharyngitis and upper respiratory infections, injury/poisoning/procedural complications, headache, back pain, musculoskeletal and connective tissue disorders. In subjects taking 110 mg berotralstat, 49% had GI AEs, as did 50% of the subjects taking 150 mg berotralstat. Most of the GI AEs were categorized as mild to moderate severity, and it is noteworthy that 41% of subjects taking a placebo also reported a GI AE as well. Although food had no significant impact on berotralstat pharmacokinetics, berotralstat was administered with food in the phase 3 study to avoid GI AEs. Berotralstat labeling will include a recommendation to administer with food.

No deaths occurred in Part 1 of Study 302 or in Study 204, however 34 subjects experienced a serious adverse event (SAEs).[3] Three SAEs occurred in subjects taking a placebo, including a transient ischemic attack and diverticular intestinal hemorrhage in one subject, and one event each of pneumonia and leiomyoma. One subject in the placebo group discontinued due to an episode of depression. One patient in the 110 mg group developed myeloma (see Section 5.2). Eighteen subjects in the 110 mg group and 12 subjects in the 150 mg group had SAEs. Twelve of the thirty subjects with SAEs were hereditary angioedema attacks (10 in 110 mg group and 2 in the 150 mg group). The rest of the SAEs from 110 mg berotralstat included 1 episode of increased liver enzymes, 2 medical observation investigations, and 1 report each of viral gastroenteritis, anal abscess, abdominal pain, enteritis,

gastroenteritis, lower limb fracture, myocardial infarction, facial paralysis, and asthma. The 150 mg group added 1 SAE each of splenic hamartoma, abnormal liver function test, medical observation, anxiety, suicide attempt, foot deformity, intervertebral disc protrusion, pneumonia, pyelonephritis, chest pain, acute myelomonocytic leukemia, vomiting, diarrhea, and biliary colic. Five subjects discontinued berotralstat due to an adverse event. One subject in the 150 mg treatment group developed grade 4 ALT elevation (see Section 5.1), a subject in the 110 mg treatment group discontinued due to nausea/dyspepsia/vomiting, another 110 mg subject discontinued after developing a purpuric rash, and the last patient to discontinue early was the afore mentioned patient with multiple myeloma.

Clinical development of berotralstat allowed patients with mild to moderate renal impairment (>30 to <90 mL/min CL_{CR}) to enroll in studies, and the safety profile is similar to the overall study population. No dosage adjustment is necessary for renal impairment. Berotralstat exposure is increased in subjects with moderate and severe (Child-Pugh Classes B and C) hepatic impairment as seen in single-dose, open-label pharmacokinetic Study 108. These patients should be given the 110 mg dose, and labeling will reflect this. Berotralstat is a P-gp and BCRP substrate. With the addition of cyclosporin, a known P-gp, OATP, and BCRP inhibitor to berotralstat, a single dose of berotralstat's exposure increased (C_{max} by 25% and AUC by 69%). The Agency recommends berotralstat dose adjustment to 110 mg daily if used in combination with P-gp or BCRP inhibitors, and to avoid use with P-gp inducers and berotralstat labeling will reflect this.

5.1 TRANSAMINASE ELEVATIONS

One subject in the 150 mg group of Study 302 developed grade 3 alanine aminotransferase (ALT) elevation (238 U/L) on day 14, and grade 4 elevation (430 U/L) on day 22. Subject discontinued berotralstat on day 17 but remained in the study receiving assessments per protocol. The subject remained asymptomatic and had no other laboratory abnormalities. By day 75, the subject's ALT had normalized (30 U/L), but on day 127, developed a grade 2 ALT elevation at day 127 and ALT was still at a grade 1 elevation on day 169 (study completion). The subject had a prior history of androgen use from 2013 – 2017 but had not used androgen for over a year from study entrance and had normal liver enzymes at baseline. The subject subsequently prematurely discontinued treatment in Study 302. Four subjects in the placebo arm, 2 subjects in the 110 mg berotralstat arm, and 3 subjects in the 150 mg berotralstat arm had mild elevations of ALT up to 3 times the upper limit of normal (ULN). The were no potential Hy's Law cases in the studies. The ongoing clinical review finds a correlation between recent androgen use in the majority of mild transaminase elevations.

In Study 204, ALT elevations occurred more frequently in the 110 mg treatment group (9%) versus the 150 mg treatment group (4.7%), while ALT elevations >5 times the ULN affected 3% of both groups. One subject in the 150 mg group had >10 times the ULN elevation and discontinued the study. In the ongoing clinical review, the clinical reviewer states that the increases in AST and ALT were generally asymptomatic and not dose dependent, but did correlate with a history of androgen use and recent discontinuation of androgen therapy.

5.2 CARCINOGENICITY IN RAT MODELS

One subject taking 110 mg berotralstat daily developed myeloma. Upon retrospective review, this subject had elevated serum protein on intake labs, and myeloma is suspected to be present prior to drug administration.

Two-year carcinogenicity studies in rats were evaluated by the Agency's Executive Carcinogenicity Assessment Committee (Exec CAC) on March 10 and July 20, 2020. The March evaluation concluded that while it appeared berotralstat at 20 mg/kg/day caused increases in hemangiosarcoma in the mesenteric lymph nodes of male rats, the relevance in humans was unknown. The Applicant argued that the findings were species-specific and assembled a pathology expert working group to re-evaluate the microscopic changes in the lymph system of male and female rats. The Applicant submitted an amended report on July 9, 2020 stating the updated data demonstrated no carcinogenicity in rats. The Exec CAC evaluated the amended report and agreed with the Applicant. The lack of causality of the singular myeloma case with berotralstat supports the Exec CAC findings.[4,5] In the ongoing clinical review, the clinical reviewer states that there is minimal safety risk to patients taking berotralstat.

5.3 INCREASE IN QT IN SUPRATHERAPEUTIC DOSES

Only a single subject in the placebo group of Study 302 had an abnormal electrocardiogram finding. However, prior studies of berotralstat did find prolonged QT at dosages higher than used in the pivotal studies. A QT-IRT (QT-Integrated Review Team) consult was performed. The consult found that at the recommended 150 mg daily dose, berotralstat does not prolong the QT interval to a clinically relevant extent.[6] In the ongoing clinical review, the clinical reviewer agreed with the QT-IRT determination that there was minimal concern for patient safety at the recommended dose. The risk of QT prolongation at higher than recommended doses will be mitigated in labeling as a Warning and Precaution.

6 Expected Postmarket Use

Berotralstat is likely to be prescribed by allergists and will be used by patients on an outpatient basis. Hereditary angioedema is a rare and potentially fatal disease, and treatments do exist for these patients that have adverse events that must be monitored by prescribers, so being alert to adverse events of berotralstat should be no different.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for berotralstat beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Berotralstat met its primary efficacy goal of decreasing the HAE attack rate in patients with HAE without exposing patients to undue risks. In the ongoing clinical review,the clinical reviewer recommends approval of berotralstat on the basis of the efficacy and safety information currently available and considers berotralstat effective while the safety population and duration were acceptable for a drug that will be chronically administered to patients with a rare and potential life-threatening disease.

DRM and DPACC considered the benefit of berotralstat, an oral HAE preventative medication and its risks of liver transaminase elevations, QT prolongation at supratherapeutic levels, drug-drug interactions and common gastrointestinal adverse events. The necessity of a REMS to ensure the benefit of berotralstat outweighed its risks was also discussed. Necessary dosage adjustments due to drug-drug interactions are routinely conveyed through labeling. The interactions of berotralstat with P-gp inhibitors and inducers and BCRP inhibitors are not novel and will be included in the Dosing and Administration and Drug Interactions sections of labeling. Gastrointestinal adverse events and elevation of liver transaminases will be listed in labeling as adverse events that are possible with berotralstat. QT prolongation at supratherapeutic doses will be described in Warnings and Precautions. We expect prescribers to know how to monitor and treat these risks. A Patient Package Insert will provide patient-friendly language explaining the risks of berotralstat, and when to notify prescribers.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of berotralstat outweigh the risks of gastrointestinal adverse events and liver transaminase elevations and QT prolongation at supratherapeutic doses. These risks, as well as dose adjustments in moderate and severe hepatic impairment and with concomitant use of P-gp or BCRP inhibitors will be communicated in labeling via Warnings and Precautions, drug interactions, and dosage and administration instructions.

Should DPACC have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1. National Institutes of Health Genetics Home Reference "Hereditary Angioedema". https://ghr.nlm.nih.gov/condition/hereditary-angioedema#statistics. Updated July 7, 2020. Accessed July 10, 2020.
2. BioCryst Pharmaceuticals, Inc. Summary of Clinical Efficacy of Berotralstat 2020.
3. BioCryst Pharmaceuticals, Inc. Summary of Clincal Safety of Berotralstat 2020.
4. Aziz R. Exec CAC Final Meeting Minutes March 10, 2020.
5. Aziz R. Exec CAC Final Study Minutes Meeting via Email Communication July 10, 2020.
6. Bende G. Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review.

10.2 CURRENTLY APPROVED TREATMENTS TO PREVENT HAE ATTACKS

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Danazol 1976	Prevention of HAE attacks of angioedema of all types; treatment of endometriosis	Starting Dose: 200 mg 2 – 3 times daily. Continuing dose may be titrated down by <50% every 1-3 months. Dosage may be increased up to 200 mg daily in event of attack.	-Multiple androgenic and anabolic adverse effects -Teratogenic effects, thrombotic events, peliosis hepatitis, benign hepatic adenoma, benign intracranial hypertension -Contraindicated in pregnancy	Boxed Warning
Cinryze IV (c1-esterase inhibitor (human)) 2008	Routine prophylaxis against angioedema attacks in patients 6 years of age and over with HAE	-Adult (12 years of age and older) Dose: 1,000 units intravenously every 3 – 4 days -Pediatric Dose: 500 units intravenously every 3-4 days	-Severe hypersensitivity reactions, thrombotic events, potential risk of transmitting infectious agents	
Haegarda SC (c1-esterase inhibitor (human)) 2017	Routine prophylaxis to prevent HAE attacks in adolescent and adult patients	60 International Units per kg body weight subcutaneously twice weekly (every 3 – 4 days)	-Severe hypersensitivity reactions -Potential thrombotic event risk due to events seen in IV use -Potential risk of transmitting infectious agents	

Takhzyro SC (lanadelumab-flyo) (2018)	Prophylaxis to prevent attacks of HAE in patients 12 years and older	300 mg subcutaneously every 2 weeks	-Hypersensitivity reactions, hepatic dysfunction	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COURTNEY A CUNNINGHAM
12/01/2020 10:35:46 AM

LAURA A ZENDEL
12/01/2020 10:47:32 AM

CYNTHIA L LACIVITA
12/01/2020 10:55:13 AM