NDA 214094
IND 135058

WRITTEN REQUEST – AMENDMENT #1

BioCryst Pharmaceuticals, Inc.
Attention: Caroline Monkiewicz
Associate Director, Regulatory Affairs Strategy
4505 Emperor Boulevard
Nottingham Hall, Suite 200
Durham, NC 27703

Dear Caroline Monkiewicz:

Please refer to your correspondence dated June 13, 2024, requesting changes to FDA's November 21, 2023, Written Request for pediatric studies for Orladeyo (berotralstat).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on November 21, 2023, remain the same. (Text deleted is strikethrough.)

BACKGROUND:

Hereditary angioedema is a rare, genetic disorder caused by mutations in the C1 inhibitor (C1-INH) *SERPING* gene, leading to absent or reduced or dysfunctional C1-INH plasma protein. HAE is clinically characterized by episodic, spontaneous attacks of angioedema, typically involving the skin or submucosal surfaces of the face, gastrointestinal tract, limbs and/or upper respiratory tract. The attacks can be life-threatening when the swelling involves the upper respiratory tract. The median age of symptom onset is between 6 to 11 years of age.

Studies are not requested in patients less than 2 years of age, including neonates, because the rarity of HAE in patients under 2 years of age make studies in the youngest pediatric patients, including neonates, infeasible.

Berotralstat is currently approved for pediatric patients 12 years and older, thus the adolescent age group will not be included in this Written Request (WR).

The Division has determined the pathophysiology of HAE in pediatric patients 2 to <12 years of age is sufficiently similar to the pathophysiology of HAE in adults and adolescents to allow for extrapolation of efficacy from the adult and adolescent clinical trial to pediatric patients. As berotralstat is an oral kallikrein inhibitor (i.e. inhibitor of the enzyme that generates bradykinin), pediatric patients 2 to <12 years of age with HAE

are expected to respond similarly to adults and adolescents treated with berotralstat if they achieve similar drug exposures.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on berotralstat, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study*:

  Based on review of the available nonclinical toxicology data (including a juvenile toxicity study of berotralstat in rats), no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

  Study 1: An open-label safety, pharmacokinetic (PK), and clinical outcome study in pediatric patients 2 to <12 years of age with Type I or II hereditary angioedema. The protocol must be agreed upon by FDA prior to enrolling patients.

  - *Study Objectives:* To evaluate the safety, PK, and efficacy of berotralstat in pediatric patients 2 to <12 years of age with HAE.

  - *Patients to be Studied:*

    - *Age groups to be studied:* 2 to <12 years of age

    - *Number of patients to be studied:* PK must be collected from a minimum of 20 patients, and a minimum of 15 patients must complete 1 year of treatment. Adequate numbers of pediatric patients must be evaluated to characterize the PK and identify an appropriate dose in each weight group (weight ranges listed below):
      - ≥40 kg
      - 32 to <40 kg
      - 24 to <32 kg
      - 12 to <24 kg

- *Study endpoints:*

  - ☐ Pharmacokinetic~~/Pharmacodynamic~~ endpoints must include the following:
    - Plasma concentrations of berotralstat over the 1-year treatment period by weight group as agreed upon in the protocol
    - PK parameters by weight group estimated using modeling and simulation and agreed upon in the protocol
    - ~~Change from baseline in plasma kallikrein activity over the 1-year treatment period by weight group as agreed upon in the protocol~~

  - ☐ Clinical effectiveness outcomes must include:
    - Number of HAE attacks during the 1-year treatment period
    - The location, duration, and severity of the HAE attacks
    - Number of HAE attacks requiring use of on-demand rescue medication
    - Number of hospitalization and clinic visits for HAE attacks

- *Safety Endpoints/Monitoring:*

  - ☐ Safety monitoring that must be included in the protocol: Adverse events, vital signs, laboratory parameters (hematology, chemistry including LFTs, coagulation), growth parameters (height, weight, BMI), EKG (PR and QTc intervals).

  - ☐ Monitoring of the following adverse events of special interest must be included in the protocol and the study report must include a summary of these adverse events:
    - Hypersensitivity reactions
    - QTc Prolongation

    The protocol must include a plan for monitoring of all adverse events until symptom resolution or until the condition stabilizes.

- *Statistical Plan* – Clinical effectiveness outcomes (listed above) will be analyzed using descriptive statistics.

- *A Data Monitoring Committee (DMC) must be included for all studies.*

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form:* oral capsule or granules
  - *route of administration:* oral
  - *regimen:* per protocol

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  (3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided

for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that berotralstat is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports evaluating a one-year treatment duration (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before June 30, 2025. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated November 21, 2023, as amended by this letter, must be submitted to the Agency on or before June 30, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your

[2] https://www.fda.gov/media/154109/download

submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
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If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648 or phuong.ton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Director
Office of Immunology and Inflammation (OII)
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Written Request as Amended

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

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If you have any questions, contact Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648 or phuong.ton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Director
Office of Immunology and Inflammation (OII)
Office of New Drugs
Center for Drug Evaluation and Research

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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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/

NIKOLAY P NIKOLOV
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