Retrospective analysis of adolescent patients suffering from hereditary angioedema treated with berotralstat in Europe: patients' and treatment characteristics

Case series Observational Plan

Sponsor	BioCryst Ireland Limited (European Headquarters & Marketing Authorisation Holder)
Indication	Hereditary angioedema (HAE)
Exposures of interest	Berotralstat 150 mg once daily as long-term prophylaxis for the prevention of HAE attacks
Planned first patient in	Q2 2025
Planned clinical end	Q2 2026
Principal investigator	Dr Mélisande Bourgoin-Heck, Paris, France
Observational plan version	1.0
Date of Observational Plan	15 March 2025

Observational Plan signatures

Signatures of the Principal Investigator and Sponsor's representative

This retrospective case series is intended to be conducted in compliance with the Observational Plan, Good Clinical Practice and the applicable regulatory requirements.

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1 List of abbreviations

ADR	Adverse drug reaction
BK	Bradykinin
CRF	Case report form
C1-INH	C1 esterase inhibitor
EU	European Union
EMA	European Medicines Agency
HAE	Hereditary angioedema
IEC	Independent Ethics Committee
IRB	Institutional Review Board
QoL	Quality of life
TEAE	Treatment-emergent adverse events

2 Introduction

2.1 Scientific background

HAE is a serious and potentially fatal disease caused by an excessive accumulation of bradykinin (BK)[1,2]. HAE is characterized by recurrent episodes of angioedema affecting various parts of the body[3].

Most cases of HAE are caused by mutations in *SERPING1*, encoding the complement esterase inhibitor 1 (C1-INH), leading to deregulation of BK production[4]. Reduced inhibition of the kallikrein-kinin cascade by C1-INH results in increased cleavage of high molecular weight kininogen (HK) by plasma kallikrein, releasing BK, which is the mediator of angioedema[2,4].

HAE has a reported prevalence between 1 in 30,000–80,000, with no apparent ethnic variation[5]. The frequency of attacks in patients not taking prophylactic medication varies, with 59% of patients reporting at least one attack per month[6]. These attacks can be life-threatening, especially when they involve swelling of the larynx[7]. Even in diagnosed patients with access to care, deaths still occur worldwide due to asphyxia[7].

HAE significantly impacts health status and quality of life (QoL)[6]. Despite the widespread use of modern on-demand treatments for acute attacks, clinically significant anxiety and depression are observed in 38% and 14% of patients, respectively[6]. Quality of life scores show a more severe impact with increasing frequency of attacks, and higher absenteeism with increasing frequency of attacks[8].

Until recently, few treatment options were available in children and adolescents. Only injectable drugs, known to be particularly dread by young patients, were approved,

Berotralstat, a potent small molecule inhibitor of plasma kallikrein, is the first oral agent in its pharmacological class[9]. Berotralstat inhibits plasma kallikrein, compensating for the deficiency of C1-INH and controlling the release of BK, thereby reducing the risk of angioedema attacks[10].

Developed by BioCryst Pharmaceuticals, it has been licensed by the European Medicines Agency (EMA) to BioCryst Ireland Limited with an indication to prevent recurrent HAE-related attacks at a dose of 150 mg once daily[11].

The once-daily oral administration of berotralstat for the prevention of HAE attacks represented a major advance in the management of this serious and life-threatening disease[9].

The APeX-2 study, conducted in 11 countries in North America and Europe, was designed to evaluate the efficacy and safety of two dose levels of berotralstat as an oral medication for attack prevention in patients with HAE aged of at least 12 years[12-14].

Part 1 (randomised, double-blind, placebo-controlled phase Week 1–24) of the study demonstrated a significant reduction in the primary endpoint of attack rate from 2.35 to 1.31 attacks per 28 days (p<0.001) at berotralstat 150 mg (n=40) relative to placebo (n=40)[14]. The most frequently reported treatment-emergent adverse events (TEAEs) were upper respiratory tract infection, nausea, and abdominal pain. The majority of TEAEs were mild to moderate in intensity. No deaths occurred during the study.

The safety, tolerability, and effectiveness of berotralstat were maintained over 48 weeks of treatment in part 2 (blind active phase with 1:1 re-randomisation of placebo patients Week 24–48) of APeX-2[13]. In part 3 (long-term open-label extension phase Week 48–20), berotralstat was generally well tolerated, provided rapid and sustained reductions in HAE attacks, and improved QoL over 96 weeks[12].

The safety of berotralstat was evaluated in a subgroup of 28 adolescent patients aged 12 to <18 years of age and weighing at least 40 kg, with a safety profile similar to that observed in adults.

2.2 Rationale for conducting the retrospective case series in adolescents

HAE has a mean age of onset of 11 years old and approximately two thirds of individuals with HAE experience symptoms by the age of 15 years old, meaning that treatment initiation usually occurs early in life[15]. The treatment of adolescents with long-term therapy poses some unique challenges compared with treating adults, including compliance[16].

Since 30 April 2021, berotralstat has been licensed for long-term prophylaxis of HAE attacks in patients over 12 years of age by the EMA, based on its positive risk:benefit profile. However, few adolescent patients were included in clinical trials of berotralstat compared with those aged 18 years and over[12,13]. In APeX-S, a subgroup analysis of 14 patients aged 12–17 years old showed sustained low attack rates in patients treated with 150 mg berotralstat and suggested that berotralstat was generally well-tolerated throughout the 48 weeks of study treatment[17].

Due to the low number of adolescent patients treated in clinical trials it is important to increase knowledge about berotralstat therapy in this specific patient population in a real-life setting.

This retrospective case series has been designed to provide insights on the characteristics of adolescent HAE patients treated by berotralstat in Europe, to describe the evolution of disease under treatment and to provide more information on safety in this specific population.

2.3 Summary

This case series is an international, retrospective, multicenter, observational project run by BioCryst Ireland Limited. Data collection is scheduled to start in Q2 2025 and will run over a 12-month period. Its objective is to describe the patient population and provide information on treatment-related outcomes in adolescent European HAE patients treated with berotralstat.

Version	Date	Remarks and changes
v 1.0	15 March 2025	First official version

3 Responsible parties

3.1 Sponsor

The Sponsor of the study is BioCryst Ireland Limited. Responsibilities of the Sponsor are:

- Decision on the Observational Plan
- Decision on the data to be captured as outlined in the case report form
- Selection and invitation of participating sites
- Clinical data management, cleaning, and validation
- Review and interpretation of consolidated results
- Writing, and supporting the investigators in producing, publications and abstracts

The Sponsor can be contacted at the following address:

BioCryst Ireland Limited (European Headquarters & Marketing Authorisation Holder)
Block 4, Harcourt Centre, Harcourt Road, Dublin 2, D02 HW77, Republic of Ireland

3.2 Principal Investigator

The Principal Investigator of the study is Dr Mélisande Bourgoin-Heck, contactable at the following address:

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Centre de référence Angioedèmes bradykiniques (CREAK)
Hôpital St Antoine
France

3.3 Financial disclosure

BioCryst Ireland Ltd (Ireland) is funding the study.

4 Objectives and endpoints

4.1 Objective

The primary objective of this retrospective study is to describe the clinical profile of adolescent European HAE patients treated with berotralstat in order to characterize this population with particular attention to their baseline features and clinical context.

Secondary objectives include:

- Description of treatment characteristics (e.g., dose, adherence, modifications),

- Description of the disease trajectory under berotralstat treatment, including changes in attack frequency, severity, and patient-reported outcomes over time,

- Description of adverse events.

4.2 Endpoints

Collected data related to effectiveness will include:

- Patients' demographic characteristics (age and sex)
- History and description of HAE (date of diagnosis, HAE type, biology, familial or sporadic form)
- Description of the disease prior to berotralstat initiation (attack frequency, triggers for HAE attacks, affected body location(s) , average duration of HAE attacks (hours), average severity of attacks (mild: no impact on daily life; moderate: moderate impact; severe: laryngeal attack/abdominal attack or attack with major impact on daily life), number of hospitalizations/hospital visits within last 6 months, acute treatment of attacks, school absenteeism related to HAE, prophylactic treatment of attacks if any

- Rationale for prescribing berotralstat as orally administered LTP
- Description of berotralstat treatment (date of initiation, dose, concomitant therapies, adherence to treatment, as rated by physician
- Description of the disease within 6 months after berotralstat initiation (attack frequency, triggers for HAE attacks, affected body location(s) , average duration of HAE attacks (hours), average severity of attacks (mild: no impact on daily life; moderate: moderate impact; severe: laryngeal attack/abdominal attack or attack with major impact on daily life), number of hospitalizations/hospital visits, acute treatment of attacks, school absenteeism related to HAE
- Physician's global evaluation of disease evolution
- Adverse events considered related to berotralstat from berotralstat initiation to the last follow-up visit at the time of case report completion, whether they were reported to local authorities, their timing relative to berotralstat initiation, severity, imputability, and management, collected in a specific form

Any concomitant treatment with other HAE long-term prophylaxis or non-HAE medications, data on patient demographics, HAE diagnosis, clinical course of HAE, concurrent medications, comorbidities, and transition to berotralstat will also be collected.

5 Study design

5.1 Research design

This is a retrospective observational case series, consisting of analysis of data retrieved from medical files in adolescent patients diagnosed with HAE who were started on treatment with berotralstat between the age of 12 and 17 years old inclusive. Patients will have undergone clinical assessments and will have received standard medical care, as determined by the treating physician. Patients will not have received experimental intervention or treatment as a consequence of their participation in the case series. This case series does not provide a specific therapy protocol.

5.2 Case series sites and locations

The study will enroll patients from approximately 5–8 sites throughout Europe. Participation in the case series will be upon invitation by BioCryst Pharmaceuticals. Study sites will be selected from among those known to treat adolescent patients with HAE. Participating sites will commit

to applicable local regulations, including vote from the local Institutional Review Board (IRB) or Independent Ethics Committee (IEC), if required. Sites are also required to uphold applicable data protection policies.

5.3 Number of patients and enrollment

Enrollment will be open for 12 months. An estimated maximum of 30 patients in total is foreseen. The enrollment duration can be extended by the study Sponsor for a maximum of another 12 months in case of slow accrual.

5.4 Milestones and timelines

Enrollment and data collection is scheduled to take place from Q2 2025 to Q2 2026. Data collation and analysis is expected to take place in Q3 2026.

5.5 Study visits

As per the retrospective nature of the study, no visit schedule is defined in the Observational Plan. Clinical visits were held as per the discretion of the treating physician and determined by the healthcare needs of the patients.

5.5.1 Documentation of medical treatment

Changes in HAE-specific medical treatment will be recorded retrospectively in the case report form (CRF) based on the patient files.

6 Patient selection

Patients with HAE receiving berotralstat and meeting the inclusion/exclusion criteria listed below are eligible for inclusion into the case series.

6.1 Inclusion criteria

Patients eligible for inclusion into the retrospective case series must meet all the following criteria:

- Confirmed diagnosis of HAE
- Aged 12–17 years old (inclusive) and weighing at least 40 kg at time of berotralstat initiation
- Ongoing treatment with berotralstat, started after April 2021 in line with the SmPC for at least 6 months with stable dosing and without treatment interruption being advised by the

treating healthcare professional Click or tap here to enter text.

- Patient or parent/legal guardian willing and able to provide informed consent as applicable (informed consent signed)

6.2 Exclusion criteria

- Patients prescribed berotralstat outside its licensed indication (including, but not limited to, patients less than 12 years old and patients less than 40 kg).

6.3 Consent procedure

Each patient or their parent/legal guardian will provide written informed consent for their participation in the case series. The informed consent will be provided in the language of the country in which the participating site is located. Minors under the legal age but old enough to be able to comprehend the concept and implications of this study are given the opportunity to give consent alongside their parents/legal guardians.

Patients or their parents/legal guardians are free to withdraw their data from the study and those who withdraw their informed consent will have their data removed from the database.

7 Data analysis and statistical methods

The data analysis of the case series and its presentation will be purely descriptive and exploratory in nature.

The measurement and documentation of all study variables, including schedule, method, and responsible person for data entry will be at the discretion of the sites' principal investigators. No formal training of site staff will be required and conducted.

7.1 Primary outcome analysis

Not applicable, see section 4.1.

7.2 Secondary outcome analysis

Not applicable, see section 4.1.

7.3 Safety analyses

During the chart review, the investigator will record adverse reactions to berotralstat noted in the medical records. Because of the retrospective nature of the data collection, no individual

cases will be collected for expedited reporting to regulatory authorities as the duty to report lays with the treating physicians at the time the reaction was observed or reported. The only exception is for serious or severe ADRs as they may represent potentially important safety information.

All AEs will be assessed (graded) for severity and classified using the general DMID criteria (not event specific) for grading AEs (Publish date November, 2007).

Mild: *(Grade 1): Transient or mild symptoms; no limitation in activity; no intervention required. The AE does not interfere with the participant's normal functioning level. It may be an annoyance.*

Moderate: *(Grade 2): Symptom results in mild to moderate limitation in activity; no or minimal intervention required. The AE produces some impairment of functioning, but it is not hazardous to health. It is uncomfortable or an*

embarrassment.

Severe: *(Grade 3): Symptom results in significant limitation in activity; medical intervention may be required. The AE produces significant impairment of functioning or incapacitation.*

Life- threatening:*(Grade 4): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required to prevent death, hospitalization; or hospice care probable*[18]*.*

Note: any serious or severe adverse reactions, explicitly related to berotralstat therapy, identified during the course of the review will be reported under the responsibility of the investigator to BioCryst Post-marketing Safety Operations Group via email (pm_safety@biocryst.com) within 1 business day to support aggregate assessment and signal detection. All other safety information collected for the study should be recorded and summarized in the final study report according to section 11.

7.4 Health economic analyses

Not applicable.

7.5 Determination of sample size

It is anticipated that the study will comprise of 5–8 participating sites with an estimated maximum of 30 patients overall, although no limit will be imposed. The study is not statistically powered.

7.6 Interim analyses

No interim analysis is planned.

7.7 Data sources

Data entered in the CRF by investigators from the patient records.

8 Data management, security, and ownership

8.1 Data entry

A specifically designed Microsoft Excel® spreadsheet will be used for data entry by each site and consolidated into a single spreadsheet.

8.2 Data access and security

Access to the patient database will be restricted to authorized users only.

After study completion, the data will be stored by BioCryst Ireland Limited (European Headquarters) for at least 10 years. Only authorized users will have access rights to the data.

8.3 Patient identification

Each patient is fully pseudonymized with a center and patient identifier. No personal identifiers (e.g., name, exact date of birth, place of residence) will be collected. No information enabling the identification of individuals will be communicated to third parties other than those legally authorized to hold this information (and who are bound by professional duty).

All patients' personal data collected and processed as part of the study will be collated by the doctor with appropriate precautions to ensure confidentiality. The database set up for the analysis will not contain any data that could be used to identify a patient.

In all presentations of the results of this study at meetings or in publications, the identity of the patients will remain confidential.

8.4 Responsibility for data entry

The site enrolling a patient into the study will be solely responsible for data entry for this patient.

8.5 Data ownership

The case series is a multi-site project. Sites participating in this project own the data contributed from patients at their site. The consolidated data, rendered pseudonymous, from all participating sites are the property of BioCryst..

8.6 Quality control

Quality of data entered into the CRF will be the responsibility of the participating study sites. Questions arising during data review and analysis will be queried with the participating sites.

8.7 Limitations of the research methods

Treatments received by patients at the time of inclusion into the study and throughout the study will not be directed in any way by the Observational Plan. All interventions and treatments will be at the discretion of the treating physician. Unmeasured confounders retain a risk for bias. Follow-up consultations and documentation of patient data will have been done in line with standard clinical practice which may impact data completeness and quality.

8.8 Protection of human patients and data confidentiality

The case series will not involve any investigational or interventional procedures that are not part of the routine clinical practice at any of the participating sites. Participation in the study will not affect patients' medical care.

Data collected will be kept strictly confidential.

Patient participation is voluntary. For every patient, appropriate patient consent will be obtained before data are entered into the case series. Patients are free to withdraw their consent at any time for any reason.

8.9 Institutional Review Board and Independent Ethics Committee

Depending on the local regulations and the participating physician's institutional policies, approval for participation in the study by an IRB/IEC may be required and the participating site/physician may have to submit the Observational Plan, a sample patient consent form and other relevant information to an IRB/IEC. In such case, approval from the IRB/IEC must be obtained before entering data into the CRF. Having appropriate approval from the IRB/IEC and

local regulatory bodies in place before study start according to the applicable requirements is the responsibility of the participating site.

9 Potential benefits and risks

There are no direct benefits to patients for participating in this study due to its retrospective nature. However, data collected may contribute to improving the management of adolescent patients with HAE in the future. Patients participating in this case series will continue to be treated according to the discretion of their treating physician independent of their participation in the case series. The most likely risk posed to participants would be a breach of confidentiality if a person outside the research team obtained access to the data. Standard cybersecurity measures and compliance with regulatory standards for data protection will be in place.

10 Adverse event reporting

Due to the retrospective nature of this study, with a design based on secondary use of data previously collected (medical charts maintained by healthcare providers) submission of adverse events in the form of Individual Case Safety Reports is not a requirement. Safety information identified during the course of the review will be handled by BioCryst. according to section

11 Plans for result dissemination and publication

A narrative synthesis will be produced at the minimum. Results may be presented at specialized congresses and published in peer-reviewed journals. Decisions will be made jointly with the investigators on publication of data, and the investigators will have the final decision on all publications of the data from their center. The final report will include a summary of any safety information identified during the course of the study to support aggregate assessment of the benefit risk profile and will be provided to BioCryst Global Drug Safety and Pharmacovigilance (GDSP) team upon completion of the study.

12 Observational plan amendments and changes in study conduct

12.1 Observational plan amendments

Neither the investigator nor the Sponsor will modify this Observational Plan without a formal amendment by the Sponsor. All amendments must be issued by the Sponsor and must not be implemented without prior IEC/IRB approval where this is required.

12.2 Changes to the case report form

If there are new developments or areas of interest to the majority of the participating sites that are not addressed in the current CRF, improvements may be implemented accordingly.

13 Literature cited

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