**NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY**

# Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting

## APeX-N


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# PASS Information

| | |
|---|---|
| **Title** | Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting |
| **Protocol version identifier** | Final v. 3.0 |
| **Date of last protocol version** | 06 December 2023 |
| **EU PAS Register number** | EUPAS43575 |
| **Active substance** | (*R*)-1-(3-(aminomethyl)phenyl)-*N*-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide |
| **Medicinal product** | berotralstat, ORLADEYO™ |
| **Procedure number** | EMEA/H/C/005138 |
| **Marketing authorisation holder(s)** | BioCryst Ireland Limited |
| **Joint PASS** | No |
| **Research question and objectives** | As the long-term safety of berotralstat cannot be addressed during clinical trials, this non-interventional PASS is designed to further characterize the safety profile of berotralstat.<br>**Primary objective:**<br>• To monitor safety and tolerability of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients during long-term administration in a real-world setting<br>**Secondary objectives:**<br>• To assess growth and development in adolescent patients 12 to 17 years of age<br>• To evaluate the effectiveness of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients in a real-world setting<br>• To assess quality of life during long-term administration of berotralstat in a real-world setting |
| **Country (-ies) of study** | Multiple centres in Europe and the UK |
| **Author** | PPD |

## Marketing Authorisation Holder(s)

| | |
|---|---|
| **Marketing authorisation holder(s)** | BioCryst Ireland Limited<br>Block 4, Harcourt Centre<br>Harcourt Road<br>Dublin 2<br>D02 HW77<br>Ireland |
| **MAH contact person** | PPD<br>Qualified Person for Pharmacovigilance QPPV<br>EUQPPVOffice@BioCryst.com<br>BioCryst Ireland Limited<br>Block 4, Harcourt Centre<br>Harcourt Road<br>Dublin 2<br>D02 HW77<br>Ireland |

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# 2 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AE-QoL | Angioedema Quality of Life Questionnaire |
| AECT | Angioedema Control Test |
| AMS | Advanced Medical Services GmbH (CRO) |
| C1-INH | C1-Inhibitor |
| cATU | French Autorisation Temporaire d'Utilisation de cohorte |
| CDMS | Clinical Data Management System |
| CFR | Code of Federal Regulations |
| CHMP | Committee for Medicinal Products for Human Use |
| CRO | Contract Research Organization |
| EAMS | UK Early Access to Medicines Scheme |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FDA | Food and Drug Administration |
| FPI | First Patient In |
| GAMP | Good Automated Manufacturing Practice |
| GDPR | General Data Protection Regulation |
| GI | Gastrointestinal |
| GPP | Good Pharmacoepidemiological Practices |
| GVP | Good Pharmacovigilance Practice |
| HAE | Hereditary Angioedema |
| IC | Informed Consent |
| ISPE | International Society for Pharmacoepidemiology |
| MAH | Marketing Authorisation Holder |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NI-PASS | Non-interventional Post-Authorisation Safety Study |
| NIS | Non-interventional Study |
| PASS | Post-Authorisation Safety Study |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PT | Preferred Term |
| QPPV | Qualified Person for Pharmacovigilance |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SD | Standard Deviation |
| SE | Standard Error |

| Abbreviation | Definition |
|---|---|
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SSL | Secure Sockets Layer |
| STIAMP | Suspected transmission of infectious agent via medicinal product |
| TEAE | Treatment-Emergent Adverse Event |
| UK | United Kingdom |
| V1 | Visit 1 |
| WHO | World Health Organization |

# 3 RESPONSIBLE PARTIES

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**Coordinating Investigator:**
**Sorena Kiani**
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E-Mail: PPD

# BioCryst Signature Page

**Study Title:** Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting- APeX-N

**Protocol Code:** BCX7353-401

**Protocol Version and Date:** Final v. 3.0, 06th December 2023

**Registry Number:** EUPAS43575

**Sponsor/ Marketing Authorisation Holder (MAH):** BioCryst Ireland Limited

This protocol has been reviewed and approved by:

PPD

11 January 2024 | 07:56:16 EST PPD

Date PPD PPD Signature

PPD

17 January 2024 | 14:18:07 EST

Date PPD PPD PPD Signature

PPD

18 January 2024 | 05:11:33 EST

Date PPD PPD PPD Signature

PPD

# Treating Physician Signature Page

**Study Title:** Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting – APeX-N

**Protocol Code:** BCX7353-401

**Protocol Version and Date:** Final v. 3.0, 06th December 2023

**Registry Number:** EUPAS43575

**Sponsor/ Marketing Authorisation Holder (MAH):** BioCryst Ireland Limited

I have read the above-mentioned protocol and its attachments. I agree to conduct the study in compliance with all stipulations of the protocol, regulations and guidelines.

Name: _____

(Please print)

Affiliation: _____

City: _____

Country: _____

_____ _____

Date Signature

# 4 ABSTRACT

| | |
|---|---|
| **Title** | Non-Interventional Post-Authorisation Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting, APeX-N |
| **Protocol No.** | BCX7353-401 |
| **Observational drug** | Berotralstat, ORLADEYO™ |
| **Indication** | Hereditary Angioedema (HAE) |
| **Rationale and background** | Berotralstat is an oral kallikrein inhibitor indicated for routine prevention of attacks of hereditary angioedema (HAE) in adult patients and adolescent patients aged at least 12 years. Berotralstat is approved by the European Medicines Agency (EMA) (30 April 2021) and the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) (12 May 2021). The purpose of this study is to evaluate long-term safety of berotralstat in a category 3 Post-Authorisation Safety Study (PASS). It is a voluntary commitment in the risk management plan by BioCryst to the EMA to conduct this PASS as an additional pharmacovigilance activity. It is of significant interest to the marketing authorisation holder (MAH) to collect data on routine use of berotralstat in a real-world setting outside of a controlled trial setting and in accordance with EMA- and MHRA-approved labelling. With this non-interventional Post-Authorisation Safety Study (NI-PASS), the MAH plans to collect further long-term data to evaluate safety, tolerability and effectiveness of berotralstat. |
| **Study Design** | A prospective, multicentre, non-interventional PASS (NI-PASS). |
| **Research question and objectives** | The objectives of this study are to further characterize the safety profile of berotralstat, including the long-term impact of berotralstat administration on the growth of adolescents with HAE.<br>Study BCX7353-401 is a non-interventional PASS to evaluate the long-term safety, tolerability, and effectiveness of berotralstat in HAE patients receiving berotralstat prophylaxis over a long-term.<br>**Primary objective:**<br>• To observe safety and tolerability of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients during long-term administration in a real-world setting<br>**Secondary objectives:**<br>• To assess growth and development in adolescent patients 12 to 17 years of age<br>• To evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting<br>• To assess quality of life during long-term administration of berotralstat in a real-world setting |
| **Participating countries** | It is planned to include multiple study sites in Europe and the UK. |
| **Number of study sites** | 30-40 sites |

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| **Population** | It is planned to enrol approximately 150 patients with HAE in this study.<br>The estimated prospective observation period for each patient whilst on berotralstat treatment according to the approved label is anticipated to be up to 60 months or at least 24 months after the last patient was enrolled or until the study is completed.<br>Patient's berotralstat treatment according to the approved label may be documented retrospectively at study inclusion. Limited medical history data as well as treatment with berotralstat according to the approved label prior to informed consent (and e.g., retrospective attack rate, when available) will be documented retrospectively.<br><br>Routine clinical care is at the discretion of the responsible physician. Visit frequency occurs according to routine clinical practice for HAE patients If patient visits occur once a year, one or more additional patient contact which can either be another visit to study site or contact via phone, e-mail etc., are recommended in order to collect and assess any safety event. |
| **Inclusion criteria** | Patients must meet all of the following inclusion criteria to be eligible for participation in this study.<br>• Confirmed diagnosis of hereditary angioedema (HAE).<br>• Adult and adolescent patients who are 12 years of age and older.<br>• Initiation of treatment with berotralstat in accordance with the current EMA- or MHRA-approved labelling. The decision to start treatment with berotralstat must be made before and be independent from enrolment in this study. Patients who received berotralstat via early access programs such as the UK Early Access to Medicines Scheme (EAMS), or the French Autorisation Temporaire d'Utilisation de cohorte (cATU) and who continued treatment with commercial berotralstat are eligible to participate.<br>• Ability to provide informed consent / confirmation of non-opposition to participate in the study as required per country. Adolescent patients must be able to read, understand, and be willing to sign an assent form / confirm their non-opposition to participate in the study. Depending on local requirements, it might be necessary for the legal caregiver(s) to provide informed consent / confirm the non-opposition to the adolescent's participation in the study. |
| **Exclusion criteria** | Patients will not be included in the study if one or more of the following criteria apply:<br>• Contraindication to treatment with berotralstat according to current product labelling.<br>• Current participation in any interventional clinical trial. |

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| **Study duration per patient** | The estimated prospective observation period for each patient is anticipated to be up to 60 months or at least 24 months after the last patient was enrolled, whilst on berotralstat treatment according to the approved label.<br>For patients who are already treated with berotralstat according to the approved label at time of informed consent, treatment data may be collected retrospectively, if available. |
| **Planned study period** | The study duration is 5 years.<br>It is planned to recruit eligible patients for at least 3 years from the date the first patient is consented (First Patient In, FPI).<br>Estimated date first patient enrolled: Q4 2021<br>Estimated end of data collection: Q4 2026<br>The study may be discontinued if ongoing regulatory or institutional review board / ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the conduct of the study. |
| **Study endpoints/ Variables for evaluation** | The following **primary** endpoints are to be assessed within this NI-PASS:<br>• Incidence of adverse drug reactions (ADRs)<br>• Duration of exposure to berotralstat according to the approved label<br><br>The following **secondary** endpoints are to be assessed within this NI-PASS:<br>• Height and weight in patients starting berotralstat treatment according to the approved label. This is applicable to adolescents (12 to < 18 years of age) only<br>• Rate of patient-reported HAE attacks during observation period<br>• Rate of HAE attacks requiring treatment with standard of care medication<br>• Change in severity of disease compared to Visit 1 (V1), measured by the Angioedema Control Test (AECT)<br>• Number of days per month with HAE symptoms<br>• Change of Quality of life compared to V1, measured by the Angioedema Quality of Life Questionnaire (AE-QoL) assessed according to standard of care of the respective participating country.<br><br>**Variables for evaluation**<br>All treatments and measures are up to the investigators' discretion and performed according to standard of care.<br>Visit frequency occurs according to routine clinical practice for HAE patients. If patient visits occur once a year, one or more additional patient contacts, which can either be another visit to study site or contact via phone, e-mail etc., are recommended in order to collect and assess any safety events. |

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| | The following data will be collected during routine visits in the patients' medical records and will be transferred to the electronic Case Report Form (eCRF).<br>• Serious Adverse Events (SAEs)<br>• Non-Serious Adverse Drug Reactions (ADRs)<br>• Height and weight for all patients starting commercial use of berotralstat between the ages of 12 to < 18 years through completion of study. In addition, date of menarche for adolescent females will be collected, if applicable<br>• Variables reported by the patient to the investigator at routine visits based on patient-recorded diary:<br>  ○ Number and location of attacks<br>  ○ Attack severity<br>• Use of standard of care required to treat HAE attacks<br>• AE-QoL<br>• AECT<br>• Concomitant medications and comorbidities<br><br>The following assessments may be performed in accordance with local clinical practice. Results for these assessments should be documented in the patient's medical record but will only be transferred to the eCRF if they meet the criteria of an SAE or a non-serious ADR.<br>• Clinical chemistry and haematology<br>• Electrocardiogram<br>• Physical examination (targeted exams post-baseline)<br>• Vital signs<br><br>Safety and tolerability will be evaluated through assessment of ADRs and SAEs. |
| **Data source** | Data from patient medical records and patient-reported outcomes such as AE-QoL and AECT questionnaires will be analysed. All data obtained during this study are captured electronically in a project-specific programmed Electronic Data Capture (EDC) application, also referred to as eCRF. |
| **Data analysis** | Data will be summarized using descriptive statistics or provided in listings. Adverse drug reaction data and serious adverse event data will be coded using the most current version of Medical Dictionary for Drug Regulatory Affairs (MedDRA). Interim analyses of accumulating data may be done. Growth in paediatric patients will be described. |

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| **Milestones** | Estimated study duration: 60 months<br>Estimated enrolment period: 36 months<br>Estimated prospective observation period: up to 60 months or at least 24 months after the last patient was enrolled.<br>Estimated date first patient enrolled: Q4 2021<br>Estimated date of last patient in: Q4 2024<br>Estimated end of data collection: Q4 2026<br>Estimated final study report: Q2 2027 |

# 5 AMENDMENTS AND UPDATES

| Protocol version | Date | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 1.0 | 19 July 2021 | N/A | N/A | N/A |
| 2.0 (internal version only) | 29 August 2023 | PASS Information / Marketing Authorisation Holder(s)<br>3 Responsible Parties | QPPV:<br>PPD<br>PPD<br>~~FGK Clinical Research GmbH~~<br>~~Heimeranstr. 35~~<br>~~80399 Munich~~<br>~~Germany~~<br>PPD<br>EUQPPVOffice@BioCryst.com<br>BioCryst Ireland Limited<br>Block 4, Harcourt Centre<br>Harcourt Road<br>Dublin 2<br>D02 HW77<br>Ireland<br>Author / Sponsor Project Responsible:<br>PPD | Administrative changes of QPPV and sponsor project responsible person |
| | | 3 Responsible Parties | Responsible Statistician: PPD<br>PPD<br>PPD | Administrative change of responsible statistician |
| | | PASS Information<br>Signature Pages | ~~Not yet registered~~<br>EUPAS43575 | Study was registered before study start |
| | | BioCryst Signature Page | PPD<br>PPD<br>PPD<br>PPD<br>PPD<br>PPD<br>PPD<br>PPD<br>PPD<br>PPD<br>Qualified Person for Pharmacovigilance (QPPV) | Administrative changes |
| | | 2 Abbreviations | Abbreviations deleted from list of abbreviations:<br>~~AGES, BASG, BfArM, GKV, KBV, PEI, PKV, GCP, GMP, ICF, ICH, ICH-GCP, LPI, LPO~~.<br>Abbreviations included in list of abbreviations:<br>ENCePP, IC, PRAC, SADR, STIAMP, TEAE, V1. | In section 10.1 country specific notifications, which included these abbreviations, were deleted<br>Further update of the list of abbreviations |

| Protocol version | Date | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | | | | List of Abbreviations sorted alphabetically |
| | | 4 Abstract | The purpose of this study is to evaluate long-term safety of berotralstat in a category 3 Post-Authorisation Safety Study (PASS) ~~study as requested by EMA/PRAC~~. It is a voluntary commitment in the risk management plan by BioCryst to the EMA to conduct this PASS as an additional pharmacovigilance activity. | Clarification that the PASS is voluntary and not mandated |
| | | 4 Abstract<br>9.2.1 Planned Number of Study Sites | **Participating countries:** It is planned to include multiple study sites in Europe and the UK ~~Germany, France, Austria, Sweden and the UK~~.<br>**Number of study sites:** ~~To be determined~~ 30- 40 sites.<br>The sites will be located in ~~Germany, France, Sweden and the UK~~ Europe and the UK. The planned number of sites ~~is yet to be determined~~ is 30-40 sites in total. | Multiple European countries instead of naming every single country<br>Update of the planned number of study sites |
| | | 4 Abstract<br>9.2.2 Patient Population and Selection Criteria | **Inclusion criterion 4:**<br>Ability to provide ~~written~~ informed consent / confirmation of non-opposition to participate in the study as required per country. Adolescent patients ~~who are aged 12 to 17 years of age~~ must be able to read, understand, and be willing to sign an assent form / confirm their non-opposition to participate in the study ~~in addition to the legal caregiver providing informed consent~~. Depending on local requirements, it might be necessary for the legal caregiver(s) to provide informed consent / confirm the non-opposition to the adolescent's participation in the study. | Changes to inclusion criterion 4 in order to include the country specific requirements for all countries. Rewording is done for the purpose of clarification only; there are no changes to the content |
| | | 6 Milestones | **Registration in the EU PAS Register:** ~~Study is not yet registered~~ 08 October 2021 | Study was registered before study start |
| | | 9.3 Variables | **End of Study:**<br>If premature termination [reasons…., ~~Unsatisfactory efficacy level~~ Discontinuation of treatment with berotralstat, …] | At the end of study visit, the unsatisfactory efficacy level will not be assessed by the discontinuation of berotralstat |
| | | 9.7 Data Analysis | Interim analysis will be performed ~~annually~~ using the data collected so | Interim analysis will be based on the |

| Protocol version | Date | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | | | far up to the time of the interim analysis. The first interim analysis will be performed once 50 patients have been enrolled, the second one will be performed at 100 patients, and the last one at 150 patients.<br>For annual safety reports, data snapshots will be taken each 3rd December (or if this date falls on a weekend, it will be taken at the next business day). | number of recruited patients rather than annually.<br>Definition of data snapshot time for annual safety reports |
| | | 10.1 Ethical, Legal and Administrative Aspects | ~~Details on registration and notifications are described in a study specific Submission Plan~~<br>~~In Germany this PASS will be notified pursuant to AMG §63f (voluntary PASS) to the BfArM (Federal Institute for Drugs and Medical Devices, Bundesinstitut für Arzneimittel und Medizinprodukte), the National Association of Statutory Health Insurance Physicians (KBV, Kassenärztliche Bundesvereinigung), the Confederation of Statutory Health Insurance Providers (GKV, Spitzenverband der Krankenversicherungen) and the Association of Private Health Insurers (PKV, Verband der privaten Krankenversicherungen) by the MAH. The names and unique lifetime IDs of participating investigator will be submitted to KBV, PKV and GKV. Fees paid to participating investigator will be reported (quarterly and annually) to KBV, and GKV. Moreover, after completion of the study, a final list indicating the number of enrolled patients and the sum of fees paid per investigator will be provided to KBV, PKV and GKV.~~<br>~~In Austria every non-interventional study (NIS) has to be notified electronically to the Austrian Federal Office for Safety in Healthcare (Bundesamt für Sicherheit im Gesundheitswesen, BASG) according to the Ordinance on the Conduct of Non-Interventional Studies (Federal Law Gazette II No. 180/2010) and registered in the Austrian Agency for Health and Food Safety Ltd. (AGES) NIS registry. After completion of the NIS, a final report as well as a shortened lay summary of the final report must be submitted electronically to the BASG NIS register according to §11 of the NIS MeldeVO within 12~~ | No need to mention submission in single countries, as multiple European countries are to be included and submissions are performed according to local legal obligations |

| Protocol version | Date | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | | | ~~months after completion of the data collection at the latest. The shortened version of the final report is published electronically by BASG~~ | |
| | | 10.2 Patient Information and Informed Consent | Informed consent will be obtained from all patients in accordance with local legislation and guidelines. Patients and for adolescent patients ~~(12 - 17 years of age)~~ also their legal caregivers must sign and date the most recent informed consent form that has been previously assessed by an independent EC, before any study-specific data will be collected. Informed consent will be obtained from the patient him/herself. The investigator or a delegate will inform the patients and legal caregivers (for adolescent patients ~~12 - 17 years of age~~) that they are completely free to refuse to enter the study or to withdraw from it at any time, and that they are not obliged to state their reasons. After withdrawal of consent, no additional data can be collected. Data already collected prior to withdrawal must be deleted at the patient's request. […] All patients and legal caregivers (for adolescent patients ~~12 - 17 years of age~~) should be given sufficient time to request further details about the study before signing the informed consent form. Patients and for adolescent patients ~~(12 - 17 years of age)~~ also their legal caregivers will personally sign and date the informed consent form. The informed consent will be documented in the source data. […] Patients and for adolescent patients ~~(12 - 17 years of age)~~ also their legal caregivers give informed consent to direct access to their original records for the purpose of monitoring, audits and regulatory inspections. […] | '12-17 years of age' removed in order to meet all country specific requirements. |
| | | 10.3 Confidentiality of Study Documents and Patient Records | With his/her consent the patient and legal caregivers (for adolescent patients ~~12 - 17 years of age~~) gives his/her/their agreement to the documentation of clinical data in the bounds of the study and to their transmission to the sponsor. […] | '12-17 years of age' removed in order to meet all country specific requirements |
| | | 11.1.3 Special Situations | In this study, the following are considered special situations: off-label use (e.g., unapproved indication or age group), overdose, abuse, misuse, medication error, product technical complaints, lack of therapeutic efficacy, drug exposure | Further specifications of special situations |

| Protocol version | Date | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | | | during pregnancy or lactation, drug exposure via father, occupational or accidental exposure, falsified medicinal product suspected transmission of infectious agent via medicinal product (STIAMP), drug interaction | |
| | | 11.3.2 Pregnancy / Drug Exposure via Parent | E-mail address updated and second e-mail address added: PM_Safety@biocryst.com; cc APeX-N-Safety@ams-europe.com | Update of e-mail addresses for the reporting of pregnancy / drug exposure via parent |
| | | Various sections | Correction of typos | Consistency |
| 3.0 | 14 December 2023 | Abstract | The estimated prospective observation period for each patient whilst on berotralstat treatment according to the approved label is anticipated ~~for~~ to be up to 60 months or ~~and~~ at least 24 months ~~from the time~~ after the last patient was enrolled or until the study is completed.<br><br>Estimated prospective observation period: up to 60 months or at least 24 months after the last patient was enrolled. | Addition of **'prospective'** prior to observation period to clarify that each patient will be observed prospectively for up to 60 months or at least 24 months after the last patient was enrolled |
| | | Section 9.1.1 | The planned study duration is 5 years, starting in Q4 2021 (estimated First Patient In, FPI) with a recruitment period of up to 36 months and ~~an~~ prospective observation period whilst on berotralstat treatment according to the approved label of up to 60 months or at least 24 months after the last patient was enrolled.<br><br>Each patient will be prospectively observed for up to 60 months or at least 24 months after the last patient was enrolled whilst on berotralstat treatment according to the approved label.<br><br>Figure 1 adapted to changes mentioned above | Addition of **'prospective'** prior to observation period to clarify that each patient will be observed prospectively for up to 60 months or at least 24 months after the last patient was enrolled |
| | | PASS Information | QPPV<br>PPD<br>EUQPPVOffice@BioCryst.com<br>PPD | Contact e-mail address revised |
| | | 3 Responsible Parties | Responsible Statistician: PPD<br>PPD | Administrative change |

| Protocol version | Date | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | | 11.1.5 Pre-existing Medical Conditions | (…) However, baseline medical conditions, other than the disease under study, that worsen in severity or frequency during the study and suspected to be due to Orladeyo use ~~assessed as~~ should be recorded and reported as ~~SAE~~ an ADR. | Correction that any worsening of baseline conditions shall only be recorded and reported if suspected due to Orladeyo use and therefore constitute an ADR. |
| | | 11.2.3 Classification of Causality | All SAEs and ~~O~~only related AEs not meeting seriousness criteria defined as ADRs and ~~all SAEs~~ are to be recorded in the eCRF AE Form. | Sentence structure revised |
| | | 11.3 Reporting of Drug Safety Information | E-mail: APeX-N-Safety@ams-europe.com ~~BioCryst.Pharmacovigilance@propharmagroup.com~~ | Contact E-Mail address revised |
| | | 11.3.2 Pregnancy | E-mail: PM_Safety@biocryst.com; cc APeX-N-Safety@ams-europe.com ~~BioCryst.Pharmacovigilance@propharmagroup.com~~ | Contact E-Mail address revised |

# 6 MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | *Q4 2021* |
| End of data collection | *Q4 2026* |
| Registration in the EU PAS Register | *08 October 2021* |
| Final report of study results | *Q2 2027* |

# 7 RATIONALE AND BACKGROUND

Hereditary angioedema (HAE) with C1 esterase inhibitor (C1-INH) deficiency is an autosomal dominant disorder characterized by recurrent episodes of swelling of the skin, pharynx, larynx, gastrointestinal (GI) tract, genitals, and extremities (Longhurst and Cicardi 2012). The reported prevalence of HAE varies widely, from 1:50,000 to 1:100,000. The frequency of attacks varies among patients, from rarely in some patients to every few days in others. Angioedema attacks may or may not be precipitated by a stimulus (such as stress, trauma, or increased estrogen) and are typically rapid in onset, with symptoms subsiding gradually over the following 3 to 5 days in the absence of treatment (Zuraw and Christiansen 2011). Oropharyngeal swelling can be life-threatening (Bork, Hardt et al. 2012), whilst attacks in other sites, including limbs, genitalia, face, and intestines, can be painful, disabling, and disfiguring, and have a significant impact on functionality and quality of life (Lumry, Castaldo et al. 2010). Although mortality risk from asphyxiation is much higher in undiagnosed patients with HAE, deaths still occur in patients who have been diagnosed with HAE and have access to healthcare at centres of excellence (Bork, Hardt et al. 2012).

Berotralstat (ORLADEYO™) is a potent, synthetic, small molecule inhibitor of plasma kallikrein. In contrast to parenterally administered options commercially available for treatment of HAE attacks, inhibition of kallikrein with an orally bioavailable small molecule such as berotralstat offers the advantage of oral administration. Inhibition of plasma kallikrein with berotralstat has significant benefits for patients with HAE by reducing the duration and/or severity of attacks.

In previous clinical studies, the efficacy and safety of berotralstat was demonstrated in patients with HAE type I or II. A Phase 2 study (APeX-1; NCT02870972) confirmed a significantly lower rate of angioedema attacks during berotralstat treatment compared to placebo for 75 randomized patients. Mild GI symptoms were the principal adverse event (AE). (Aygoren-Pursun et al. 2018). A Phase 3 study (APeX-2, NCT03485911) was performed in 11 countries and enrolled 121 patients. A total of 120 patients were randomized to either 110 mg (n = 41), 150 mg (n = 40), or placebo (n = 39). Berotralstat demonstrated a significant reduction in attack rate at both 110 mg (1.65 attacks/month; p = .024) and 150 mg (1.31 attacks/month; p < .001) relative to placebo (2.35 attacks/month). The most frequent treatment-emergent adverse events (TEAEs) that occurred more with berotralstat than with placebo were abdominal pain, vomiting, diarrhoea, and back pain. No drug-related serious treatment-emergent AEs occurred (Zuraw et al. 2020).

In another Phase 3 study with a similar design (APeX-J, NCT03873116) conducted in Japan, 19 HAE patients were randomized to receive once-daily berotralstat 110 mg (n = 6) or 150 mg

(n = 7) or placebo (n = 6). Treatment with berotralstat 150 mg significantly reduced HAE attacks relative to placebo (1.11 vs. 2.18 attacks/month, p = .003). The most frequently reported treatment-emergent adverse events (TEAEs) in berotralstat-treated patients (n = 13) were nasopharyngitis (n = 4, 31%), abdominal pain, cough, diarrhoea, and pyrexia (n = 2 each, 15%) (Ohsawa et al. 2020).

Berotralstat was first approved in the USA (03 December 2020) for prophylaxis to prevent attacks of HAE in adults and paediatric patients aged 12 years or older (Lee 2021). On 22 January 2021 the Japanese Pharmaceuticals and Medical Devices Agency approved berotralstat for the suppression of the onset of acute hereditary angioedema attacks in adults and children aged 12 years and older (PMDA 2021).

On 25 February 2021, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending marketing authorisation for berotralstat for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older (CHMP 2021). This was approved by the European Commission on 30 April 2021. On 12 May 2021 the UK's Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisation for oral, once-daily berotralstat for the routine prevention of recurrent HAE attacks in HAE patients aged 12 years and older. A category 3 non-interventional Post-Authorisation Safety Study (NI-PASS) was recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to further evaluate the long-term safety of berotralstat in paediatric patients as an additional pharmacovigilance activity.

As soon as berotralstat becomes commercially available in the respective country and these patients decide to start berotralstat or continue berotralstat treatment from the existing early access programs, these patients will be invited to participate in this NI-PASS which aims to monitor long-term safety and tolerability as well as effectiveness of berotralstat in a real-world setting.

# 8 RESEARCH QUESTION AND OBJECTIVES

This study (BCX7353-401) aims to collect long-term data on the safety, tolerability, and effectiveness of berotralstat in HAE patients receiving berotralstat for long-term prophylaxis in a real-world setting. In addition, the long-term effects of berotralstat administration on the growth of adolescent patients is of particular interest.

The **primary objective** of this NI-PASS is:

- To observe the safety and tolerability of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients during long-term administration in a real-world setting

**Secondary objectives** are:

- To assess growth and development in adolescent patients 12 to 17 years of age
- To evaluate the effectiveness of berotralstat for routine prevention of attacks of HAE in adult and adolescent patients in a real-world setting
- To assess quality of life during long-term administration of berotralstat in a real-world setting

# 9 RESEARCH METHODS

## 9.1 Study Design

This study is designed as a prospective, multicentre NI-PASS.

The planned study duration is 5 years, starting in Q4 2021 (estimated First Patient In, FPI) with a recruitment period of up to 36 months and a prospective observation period whilst on berotralstat treatment according to the approved label of up to 60 months or at least 24 months after the last patient was enrolled. The estimated end of data collection is in Q4 2026.

The study may be discontinued if ongoing regulatory or institutional review board/ethics committee approval is withdrawn, or in the event that technical or logistical factors prevent the conduct of the study.

A patient's berotralstat treatment according to the approved label can be documented retrospectively at study inclusion.

The first date on berotralstat treatment according to the approved label, which can either be within an early access program or at the start of commercial use, is defined as Visit 1 (V1).

Each patient will be prospectively observed for up to 60 months or at least 24 months after the last patient was enrolled whilst on berotralstat treatment according to the approved label (Fig. 1).

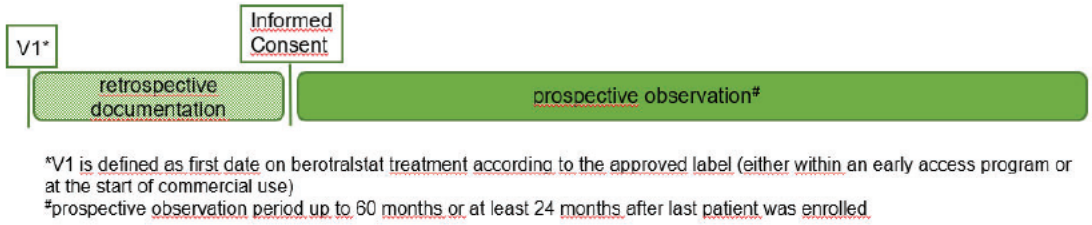


***Figure 1:*** *Study Design*

As this is a NI-PASS no stipulations regarding patient treatment, or monitoring will be provided by this protocol. Investigators will treat patients in accordance with their medical judgment and standard of care. Any treatments and tests have to be administered at the discretion of the treating physician and treatments have to be in accordance with the approved Summary of Product Characteristics (SmPC).

The participating sites will offer participation in this study to all patients, who receive berotralstat treatment as part of routine clinical practice according to the current SmPC. Of patients who were in early access programs (such as EAMS, cATU) prior to this NI-PASS and who continued treatment with commercially available berotralstat prior to signing informed consent, treatment data may be collected retrospectively.

### 9.1.1 Endpoints

The **primary endpoints** are:

- Incidence of adverse drug reactions (ADRs)
- Duration of exposure to berotralstat

The **secondary endpoints** are:

- Height and weight in patients starting berotralstat treatment according to the approved label. This is applicable to adolescents (12 to < 18 years of age) only
- Rate of patient-reported HAE attacks during observation period
- Rate of HAE attacks requiring treatment with standard of care medication
- Change in severity of disease compared to V1, measured by the Angioedema Control Test (AECT)
- Number of days per month with HAE symptoms
- Change of Quality of life compared to V1, measured by the Angioedema Quality of Life Questionnaire (AE-QoL), assessed according to standard of care of the respective participating country

The described tests/assessments will only be performed if they represent standard of care for HAE patients in the respective participating country.

The AE-QoL questionnaire used in this study is validated for adult patients (> 18 years) but will also be used for adolescent patients in this NI-PASS.

## 9.2 Study Setting

### 9.2.1 Planned Number of Study Sites

The sites will be located in Europe and the UK. The planned number of sites is 30 - 40 sites in total.

### 9.2.2 Patient Population and Selection Criteria

It is planned that approximately 150 patients diagnosed with HAE will be observed in this NI-PASS. If a patient fulfils all of the inclusion criteria and none of the exclusion criteria, he/she will be enrolled.

The investigator will verify that all inclusion criteria are met and no exclusion criterion is met and all other requirements of the study protocol are fulfilled. He/she will confirm that according to his/her judgment the respective patient is eligible for participation in the study.

**Inclusion Criteria**

Patients have to meet all of the following criteria to be included:

- Confirmed diagnosis of hereditary angioedema (HAE).
- Adult and adolescent patients who are 12 years of age and older.
- Initiation of treatment with berotralstat in accordance with the current EMA- or MHRA-approved labelling. The decision to start treatment with berotralstat must be made before and be independent from enrolment in this study. Patients who received berotralstat via early access programs such as the UK Early Access to Medicines Scheme (EAMS), or the French Autorisation Temporaire d'Utilisation de cohorte (cATU) and who continued treatment with commercial berotralstat are eligible to participate.
- Ability to provide informed consent / confirmation of non-opposition to participate in the study as required per country. Adolescent patients must be able to read, understand, and be willing to sign an assent form / confirm their non-opposition to participate in the study. Depending on local requirements, it might be necessary for the legal caregiver(s) to provide informed consent / confirm the non-opposition to the adolescent's participation in the study.

**Exclusion Criteria**

Patients will be excluded from the study if they meet any of the following criteria:

- Contraindication to treatment with berotralstat according to current product labelling.
- Current participation in any interventional clinical trial.

## 9.3 Variables

The variables listed in this section will be recorded during routine visits for all included patients. All treatments and measures are up to the physicians' discretion and performed according to standard of care. Data will be collected during routine visits in the patient's medical record and will be transferred to the electronic Case Report Form (eCRF). Visit frequency occurs according to routine clinical practice for HAE patients. If patient visits occur once a year, one or more additional patient contact which can either be another visit to study site or contact via phone, e-mail etc., are recommended in order to collect and assess any safety event.

For the day of **patient enrolment in NI-PASS** the following variables will be documented

- Eligibility according to SmPC/ in- and exclusion criteria
- Written informed consent

**Demographic data**

- Age [years]
- Sex [male/female]
    - If female: Pregnancy [test results, if available] / lactation
- Ethnicity [Caucasian, Asian, African, Other]
- Height [cm], weight [kg]; BMI [kg/m$^2$ calculated on backend by EDC]; in all adolescent patients starting berotralstat treatment according to the approved label; and menarche in adolescent females [Yes/No, if Yes, date of onset]

**Medical history and HAE specific variables**

- Diagnosis: HAE
- C1-Inhibitor concentration [g/L]
- C1 functional activity [%]
- Drugs with narrow therapeutic range metabolised by CYP2D6 (e.g., pimazide), CYP3A4 (e.g., ciclosporin, fentanyl), CYP2C19 (e.g., desogestrel) or p-glycoprotein substrates (e.g., digoxin) [if Yes, to be specified]
- Age at diagnosis [age in years]
- Family history of HAE [Yes/No]
- Prior preventive treatments [if Yes, treatment name and duration in months]
- Time since last attack [days]
- Number of HAE attacks in the last 6 months [#]
- AECT score [score]
- AE-QoL score [score]
- Comorbidities [if Yes, to be specified]
- Concomitant medications [if Yes, to be specified]

**Visit 1:**

The following variables will be documented for **Visit 1 (V1),** which is defined as the first date on berotralstat treatment according to the approved label.

**Safety variables:**

- Berotralstat treatment regime [to be specified]

**Patient characteristics**

- Height [cm], weight [kg]; BMI [kg/m$^2$ calculated on backend by EDC]; in all adolescent patients starting berotralstat treatment according to the approved label; and menarche in adolescent females [Yes/No, if Yes since when]

**HAE specific variables**

- Time since last attack [days]
- Number of attacks in the last 6 months [#]
- Number of on-demand treatments use in the last 6 months [#]
- AECT score [score]
- AE-QoL score [score]

**Observation Period:**

The following variables will be assessed at every routine visit during the **observation period**.

**Safety variables:**

- Adverse Drug Reactions (ADRs) [if Yes, to be specified in Adverse event Form in eCRF]
- Serious adverse events (SAEs) [if Yes, to be specified in Adverse event Form in eCRF]
- Berotralstat treatment [if changes, to be specified]
- Height [cm], weight [kg], BMI [kg/m$^2$ calculated on backend by Electronic Data Capture (EDC)]; in all adolescent patients starting berotralstat treatment according to the approved label; and menarche in adolescent females [if not answered with Yes before; Yes/No, if Yes date of onset]. To be assessed until adulthood (18 years of age)

**Effectiveness variables:**

- Disease severity measured by AECT [score]
- HAE attacks [if Yes; duration, location, severity, risk factors, standard of care treatment, hospitalisation; time to resolution of the attack]

**Variables pertaining to quality of life:**

- Quality of life as measured by the AE-QoL [score]

**Further variables:**

- Change in comorbidities [if Yes, to be specified]
- Change in concomitant medications [if Yes, to be specified]

- If any vital signs, laboratory values (i.e., clinical chemistry or haematology values), electrocardiogram results or physician examination results performed as part of routine care meet the criteria of an SAE or a non-serious ADR, they should be documented on the SAE/ADR form in the eCRF.

**Treatment Discontinuation**

In case of **treatment discontinuation**, the same variables will be assessed as during the observation period and in addition the following

- Last administration [Date]
- Reason for treatment discontinuation [to be specified; ADR, Unsatisfactory efficacy level, Pregnancy, Death, Medical decision, Other (specify choice)]
- Death [Date, Cause, Causal relationship to berotralstat treatment]

**End of Study**

At the **end of study**, the same variables will be assessed as during the observation period and in addition the following

- End of study [Date]
- Premature or regular termination [to be specified; Yes/No]
    - If premature termination [reason to be specified; ADR, Discontinuation of treatment with berotralstat, Lost to follow-up, Pregnancy, Withdrawal of consent, Death, Medical decision, Other (specify choice)]

### 9.3.1 Schedule of Data Collection (According to Standard of Care)

Visits are not scheduled by the study but will follow routine clinical care based on medical necessity. The documentation does not influence the individual course of treatment (Tab.1).

***Table 1:*** *Schedule of Data Collection*

| **Study Phase** | **Patient Enrolment in NI-PASS** | **Visit 1[1]** | **Visits during Observation period[2]** | **Treatment discontinuation** | **End of study** |
|---|---|---|---|---|---|
| Eligibility according to SmPC / in- and exclusion criteria | x | | | | |
| Written informed consent | x | | | | |
| Demographic data | x | | | | |
| Pregnancy test results, if available | x | | | | |
| Diagnosis of HAE / Age at diagnosis | x | | | | |
| Medical history and family history of HAE | x | | | | |
| Drugs with narrow therapeutic range | x | | | | |
| Time since last HAE attack,<br>Number of attacks in the last 6 months | x | x | | | |
| Number of on-demand treatments use in the last 6 months | | x | | | |
| C1 functional activity | x | | | | |
| Prior preventive treatments | x | | | | |
| Comorbidities / concomitant medications | x | | | | |
| C1-INH concentration | x | | | | |
| Growth parameters for adolescent patients# | x | x | x | x | x |
| ADRs / SAEs / Special Situations | | | x^ | x | x |
| Treatment with berotralstat according to the approved label | | x | x | x | x |
| Disease severity (by AECT) | x | x | x | x | x |
| HAE attacks | | | x | x | x |

| Study Phase | Patient Enrolment in NI-PASS | Visit 1[1] | Visits during Observation period[2] | Treatment discontinuation | End of study |
|---|---|---|---|---|---|
| Quality of life score (by AE-QoL) | x | x | x | x | x |
| Change in concomitant medications and comorbidities | | | x | x | x |
| Vital signs+ | | | x | x | x |
| Clinical chemistry and haematology+ | | | x | x | x |
| Electrocardiogram+ | | | x | x | x |
| Physical examination+ | | | x | x | x |
| End of study date; if premature termination, reason to be specified | | | | | x |
| Reason for treatment discontinuation / Date of last administration | | | | x | |

[1]Visit 1 (V1) is defined as first date on berotralstat treatment according to the approved label
[2]Data collection at every routine visit at the study site (or at additional patient contacts) and retrospectively for patients being treated with berotralstat according to approved label prior signing Informed Consent (IC)
#Height, weight, onset of menarche
+Will only be documented if clinically significant and meeting criteria of an SAE or non-serious ADR on the SAE/ADR form
^ADRs / SAEs / Special Situations will be documented from the date of Informed Consent onwards
Abbreviations: ADR, Adverse Drug Reaction; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; C1-INH, C1-Inhibitor; HAE, Hereditary Angioedema; NI-PASS, Non-interventional Post-Authorisation Safety Study; SAE, Serious Adverse Event; SmPC, Summary of Product Characteristics.

## 9.4 Data Sources

In this non-interventional study, the main data source is the patient's medical record. Patient-reported outcomes such as patient questionnaires (AE-QoLs) serve as a second type of data source. At routine visits to the study site patients will report on HAE attacks and respective treatments, based on their entries in patient-recorded diaries. This information is to be entered in the patient's medical record by the investigator.

Data from medical records and questionnaires have to be recorded on electronic Case Report Forms (eCRFs) by the investigator and/or authorised site staff as soon as they become available. Questionnaires are to be used in local language, but the eCRF is in English only. Therefore, the investigator and/or authorised site staff will need to translate the patient-reported outcomes when transferring to eCRF.

No visits or measurements will be made mandatory by this protocol. The assignment of patients to berotralstat falls within current practice. Prescription of berotralstat occurred before and independently from the decision to include the patient in the study.

Collected ADRs and SAEs will be coded according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) and medications will be coded according to the World Health Organization (WHO) Drug Dictionary using the most current versions.

## 9.5 Study Size

All patients with HAE disease who meet the eligibility criteria may participate in the study. It is estimated that approximately 150 patients will be enrolled in the study. As no statistical hypotheses will be tested the sample size is based on feasibility considerations.

## 9.6 Data Management

Data management will be done in accordance with the Standard Operating Procedures (SOPs) of the Contract Research Organization (CRO) Advanced Medical Services GmbH ***(AMS)***. All data obtained during this study will be captured electronically in a project-specific programmed Electronic Data Capture (EDC) application, also referred to as the eCRF. The eCRF is specifically designed for the collection of the data detailed in this study protocol. The EDC application used for this study is the Clinical Data Management System (CDMS) Clincase® (supplied by Quadratek Data Solutions Ltd.), which is fully validated according to Good Automated Manufacturing Practice (GAMP) 5 and compliant with United States Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) part 11.

The project-specific eCRF will be validated according to ***AMS*** SOPs and the above-mentioned regulations prior to going live. Only authorised staff will have access to the EDC system via a secure website (Secure Sockets Layer [SSL] encryption), using unique username and password. Data will be entered into eCRFs by the investigator and/or authorised site staff in accordance with instructions provided by ***AMS***.

Data from patient's routine visits, AE-QoL and AECT questionnaires and patient reports on HAE attacks and respective treatments, based on their entries in diaries will be transferred into the eCRF by the investigator and/or authorised site staff. Moreover, it is the responsibility of

the investigator to thoroughly check patient-reported outcomes for any potential ADRs and SAEs and to document reportable events in the eCRF in accordance with this protocol.

Each investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner and are assigned to the correct patient. The investigator confirms this by electronically signing the documentation, equivalent to a traditional handwritten signature. The eCRFs should be electronically signed on all required pages by the investigator after completion.

Each initial entry, each data modification (incl. reason for change), as well as all actions in the eCRF are tracked in an audit trail, including username, date and time. Patients' personal data will be gathered, stored and processed exclusively in a pseudonymous form according to national data protection laws.

Further details will be described in a project-specific Data Management Plan.

## 9.7 Data Analysis

All safety and effectiveness variables collected in this study will be analysed descriptively. For continuous data, the mean, sample size (n), standard deviation (SD), standard error (SE), median, minimum, maximum, 25$^{th}$ percentile (Q1) and 75$^{th}$ percentile (Q3) will be provided. Categorical data will be displayed by absolute and relative frequencies (percentages). For means or proportions, 95% confidence intervals will be provided where appropriate.

The incidence of ADRs and SAEs will be summarized according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) primary system organ classification (SOC) and preferred term (PT). Medications will be coded according to the WHO Drug Dictionary. Growth in paediatric patients will be described.

The analyses will be performed as observed-case analyses for all eligible patients included in the study who gave their informed consent.

Details / further analyses will be specified in a Statistical Analysis Plan (SAP), which will be approved prior to performance of any analyses. Statistical tests (if any) will be performed in exploratory fashion without adjustment for multiplicity.

Interim analyses will be performed using the data collected so far up to the time of the interim analysis. The first interim analysis will be performed once 50 patients have been enrolled, the second one will be performed at 100 patients, and the last one at 150 patients.

For annual safety reports, data snapshots will be taken each 3$^{rd}$ December (or if this date falls on a weekend, it will be taken at the next business day).

It is planned to organize a Data Review Meeting prior to database lock for the final analysis. This pre-analysis review will include review of data from patients who did not fulfil all inclusion and exclusion criteria or had no berotralstat treatment documented. Other topics may be discussed as well. Based on this review, the analysis defined in the SAP may need to be adapted, e.g., further sensitivity analyses or subgroup analyses may be defined. All decisions will be documented in the meeting minutes; the signed minutes can serve as an SAP amendment.

Analyses will be performed using Statistical Analysis System (SAS) 9.4 for Windows or higher.

## 9.8 Quality Control

### 9.8.1 Applicable Guidelines

This study will be performed in compliance with the guideline on good pharmacovigilance practices (GVP) module VIII by the European Medicines Agency (EMA) and the Guidelines for Good Pharmacoepidemiological Practices (GPP) by the International Society for Pharmacoepidemiology (ISPE).

The study protocol is developed according to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance on protocol development and the NI-PASS was registered in the EU PAS Register.

The study will be conducted and reported in accordance with the protocol, the applicable regulatory requirements and the applicable Standard Operating Procedures (SOPs) of **BioCryst** and ***AMS***.

The investigator will assure that he/she will conduct the study in accordance with the guidelines mentioned above and the prevailing local laws and that he/she accepts and observes all provisions of this study protocol. The study investigators should ensure that all the requirements of their professional code of conduct are met according to local regulatory requirements.

### 9.8.2 Study Monitoring

The investigator will permit a sponsor's representative (i.e., a 'study monitor') designated by the sponsor to monitor the study according to the relevant SOPs and to a separate study-specific Site Management Manual as frequently as deemed necessary by the sponsor to verify the correct entry of data and the conduct of the study in accordance with the protocol and with regard to factors such as the study design and site enrolment rate.

Monitors of the appointed CRO ***AMS*** will perform on-site initiation visits (including eCRF training). The site staff will be trained with special emphasis on collecting and reporting of adverse events

During the course of the study ***AMS*** will perform remote monitoring in each study site starting after recruitment of the first patient. This will be complemented with scheduled on-site monitoring visits. Please refer to Site Management Manual for precise information on monitoring frequencies.

The investigator must ensure that eCRFs are completed in a timely manner and must allow the study monitor access to patient records and all study-related material as well as internet access for the review of eCRFs during monitoring visits. During each monitoring visit the monitor will check the entries made in the eCRFs and compare these entries with the source data, e.g., the patient's medical records or patient questionnaires. The scope of this source data verification will be defined in the Site Management Manual.

The monitor will check the data for plausibility and completeness in collaboration with the investigator or his/her authorised site staff. It is understood that the investigator and his/her personnel will assist the monitor in every respect and provide them with all relevant study data.

### 9.8.3 Investigator's Files / Retention of Documents

The investigator must retain all study records required by BioCryst and by the applicable regulations in a secure and safe facility. The investigator must consult a BioCryst representative before disposal of any study records, and must notify BioCryst of any change in the location, disposition, or custody of the study files. The investigator/Institution must take measures to prevent accidental or premature destruction of essential documents such as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., patient charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The investigator/Institution should retain patient files and other source data in accordance with the country specific regulatory requirements for data retention. BioCryst must be notified and will assist with retention should the investigator/Institution be unable to continue maintenance of patient files for the term required. BioCryst is responsible for informing the investigator/Institution as to when these documents no longer need to be retained.

### 9.8.4 Audits and Inspections

For quality assurance reasons the sponsor or a third party on behalf of the sponsor may conduct quality assurance audits at any time during or following the study. Regulatory agencies may conduct inspections. The investigator must agree to allow auditors and inspectors direct access to all study-related documents including source documents, and must agree to allocate his/her time and the time of his/her study staff to the auditors/inspectors in order to discuss findings, issues and potential remedies. All persons involved are bound to maintain strict confidentiality concerning the identification of the patients.

### 9.8.5 Completion of Study

The completion of the study is defined as "last patient out of the study". The sponsor reserves the right at any time to discontinue inclusion of additional patients into the study, at any site or to discontinue the study for any reasons.

### 9.8.6 Control of Data Entered in the eCRF

During the electronic data entry in the eCRF, data are automatically checked for plausibility by programmed edit checks. Incomplete data fields in the eCRF are clearly labelled as incomplete (red symbols). Other discrepancies may be clarified by addressing manual queries to the site within the eCRF.

There will be a regular reconciliation between the adverse events documented in the study database and in the safety database. Due to the non-interventional nature of the study, missing values and/or implausibility may persist and will not be corrected.

## 9.9 Limitations of the Research Methods

Like any observational research, this study may be subject to the risk of various biases. A major potential bias is the selection bias, i.e., selective recruitment into the study of patients that are not representative of the exposure or outcome pattern in the source population. The target population of this study comprises patients diagnosed with HAE in a real-life setting in European countries and the UK. The inclusion of a large number of patients for a rare disease (approximately 150) is assumed to draw a representative sample of the target population. Patients are identified and recruited by their treating physicians/investigator.

The study will be non-comparative. The lack of an internal reference therapy is a limitation of this study and should be kept in mind when interpreting the data.

Information bias is caused by the collection of incorrect information about exposure or outcome or covariates. This bias as well as the limitation of missing data is supposed to be minimised as far as possible in a non-interventional study (NIS) by the planned measures of quality assurance (specifically study monitoring, see section 9.8.2). However, due to the non-interventional character of the study, missing values and/or implausibilities may persist at the end of the study.

In addition, data reporting / collection will be conducted in a consistent way to avoid bias in the data collection process (see section 9.6).

In non-interventional studies, the amount of data cleaning is limited. Therefore, missing values and/or implausible values are to be expected. The Statistical Analysis Plan will provide a detailed description on how to handle those values.

# 10 PROTECTION OF PATIENTS

## 10.1 Ethical, Legal and Administrative Aspects

This study is a Post-Authorisation Safety Study (PASS) according to European legal definition in GVP module VIII. The study will be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

**Independent Ethics Committee**

Prior to study start, the protocol, patient information, informed consent forms (for adults, legal caregivers and adolescents) and any information presented to potential study participants will be submitted to an independent ethics committee (EC) for assessment.

Each participating investigator may seek advice from her/his EC according to his/her code of medical ethics. For this purpose, the protocol, patient information, informed consent form and the assessment by the first EC may be disclosed.

**Notifications / Registration**

This voluntary NI-PASS will be conducted in several member states of the European Union and the UK and will therefore be notified to the Pharmacovigilance Risk Assessment Committee (PRAC). This study was listed in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register, see section 6 MILESTONES).

In the European countries participating in this NIS, registration of the study and required notifications will follow the local legal obligations.

## 10.2 Patient Information and Informed Consent

Informed consent will be obtained from all patients in accordance with local legislation and guidelines. Patients, and for adolescent patients also their legal caregivers, must sign and date the most recent informed consent form that has been previously assessed by an independent EC, before any study-specific data will be collected. Informed consent will be obtained from the patient him/herself.

The investigator or a delegate will inform the patients and legal caregivers (for adolescent patients) that they are completely free to refuse to enter the study or to withdraw from it at any time, and that they are not obliged to state their reasons. After withdrawal of consent, no additional data can be collected. Data already collected prior to withdrawal must be deleted at the patient's request.

If the patient withdraws his/her consent, no new study data will be collected about him/her. Data collected after withdrawal of consent must be deleted. The pseudonymised data collected until withdrawal of consent are necessary for scientific research and the withdrawal does not automatically lead to their deletion because this would make the objectives of data processing impossible or seriously impair them.

All patients and legal caregivers (for adolescent patients) should be given sufficient time to request further details about the study before signing the informed consent form. Patients, and for adolescent patients also their legal caregivers, will personally sign and date the informed consent form. The informed consent will be documented in the source data.

One copy of the consent form signed and dated by the patient and by the investigator who informed the patient will be kept at the study site; a second copy will be handed over to the patient. Each patient must receive a patient information sheet written in local language.

In case of new relevant information, all concerned patients should be informed and asked again for their consent in a timely manner, if applicable.

Patients, and for adolescent patients also their legal caregivers, give informed consent to direct access to their original records for the purpose of monitoring, audits and regulatory inspections. They also give informed consent to documentation of clinical data for the NI-PASS and to transmission of clinical data to the sponsor and applicable authorities.

In case a patient withdraws from the study, the treating investigator must document the discontinuation of study participation in the eCRF.

## 10.3 Confidentiality of Study Documents and Patient Records

With his/her consent the patient and legal caregivers (for adolescent patients) gives his/her/their agreement to the documentation of clinical data in the bounds of the study and to their transmission to the sponsor. They will, together with completed consent forms, be maintained by the investigator in strict confidence.

Neither the names of the patients nor any other records that may identify the patients will be made publicly available by the investigator or by the sponsor. The data collected as part of the study are subject to the provisions of the European General Data Protection Regulation (EU GDPR) 2016/679 and to applicable national laws.

The investigator must ensure that each patient's pseudonymity will be strictly maintained. On eCRFs or other documents submitted to the sponsor, patients must not be identified by their names, initials, addresses, complete dates of birth or any other information that may identify the patient, but by an unambiguous identification code consisting of the patient number. If patient names are included on copies of documents submitted to the sponsor, the names must be redacted and the assigned patient number must be added to the documents instead.

The investigator has to keep a separate patient identification list with patient numbers and patient names along with the completed informed consent forms. Documents, which contain the names associated with the patient numbers must not be submitted to the sponsor. They will be maintained by the investigator in strict confidence.

## 10.4 Substantial Changes to the Protocol

Any substantial change to the protocol can only be made in the form of a written amendment to the study protocol. Such amendments have to be signed by all roles who signed the previous protocol version and submitted to an EC prior to implementation.

Amendments, which might have an impact on the patients, have effects on the informed consent procedure and require the signature of the revised informed consent form by all patients enrolled in the study who are affected by the amendment.

# 11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Assessment of all adverse events will be performed throughout the course of the study from the time of patient's signature of Informed Consent (IC) onwards.

## 11.1 Definitions

### 11.1.1 Adverse Event (AE) and Adverse Drug Reaction (ADR)

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs are undesirable events not present prior to the observed medical treatment or an already present event that worsens either in intensity or frequency following the treatment.

An ADR is a response to a medicinal product which is noxious and unintended. An ADR, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

### 11.1.2 Serious Adverse Event (SAE) and Serious Adverse Drug Reaction (SADR)

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is any untoward medical occurrence or effect that at any dose:

- **results in death** (i.e., the AE/ADR causes or contributes to the death).
  Death cases due to the underlying disease are NOT considered as SAEs.
- **is life-threatening** (i.e., an AE/ADR in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- **requires inpatient hospitalisation or prolongation of existing hospitalisation** (i.e., the AE/ADR requires at least a 24-hour inpatient hospitalisation or prolongs a hospitalisation beyond the expected length).
  Hospital admissions planned before informed consent (where the condition requiring the hospitalisation has not changed post-medicinal treatment administration), for respite care, for social reasons or for normal disease management (administration of medicinal treatment or insertion of access for administration of medicinal treatment) are NOT to be considered as serious.
- **results in persistent or significant disability or incapacity** (i.e., the AE/ADR resulted in a substantial disruption of the patient's ability to conduct normal activities).
- **is a congenital anomaly or birth defect** (i.e., an adverse outcome in a child or fetus of a patient exposed to the Medicinal Product before conception or during pregnancy).
- **is a medically important condition** (medical and scientific judgment should be exercised in deciding whether an AE/ADR is serious in other situations. Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered as serious).

### 11.1.3 Special Situations

In this study, the following are considered special situations: off-label use (e.g., unapproved indication or age group), overdose, abuse, misuse, medication error, product technical complaints, lack of therapeutic efficacy, drug exposure during pregnancy or lactation, drug exposure via father, occupational or accidental exposure, falsified medicinal product, suspected transmission of infectious agent via medicinal product (STIAMP), drug interaction. All special situations should be recorded regardless of association with an adverse reaction.

Lack of therapeutic efficacy should only be captured when it was judged as such by the investigator. If lack of therapeutic efficacy is documented as special situation, batch number/expiry date should be documented in the eCRF.

If the investigator suspects drug interaction between drugs as cause of ADR or abnormal laboratory findings, this should be documented in the eCRF.

### 11.1.4 Abnormal Laboratory Findings and Other Objective Measurements

Abnormal laboratory findings and other objective measurements should not be routinely captured and reported as ADRs unless they are judged by the investigator to represent clinically significant changes from baseline values and are suspected of being causally related to Orladeyo use. If a routine laboratory value is abnormal, it is up to the investigator to determine whether the value constitutes an AE or ADR.

When reporting an abnormal laboratory finding on the AE section of the eCRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if this is available (for example, "anaemia" rather than "decreased red blood cell count" or "haemoglobin = 10.5 g/dL").

### 11.1.5 Pre-existing Medical Conditions

Medical conditions present at the start of observation that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are not to be considered AEs. These medical conditions should be adequately documented on the medical history section of the eCRF. Any edema and signs and symptoms that are clear manifestations of the underlying disease should not be recorded as an AE except meeting any seriousness criteria or judged to be related to berotralstat (e.g., lack of effectiveness).

However, baseline medical conditions, other than the disease under study, that worsen in severity or frequency during the study and suspected to be due to Orladeyo use should be recorded and reported as an ADR.

## 11.2 Recording of Safety Data

### 11.2.1 Eliciting Adverse Events

Data on AEs will be obtained at all visits, based on the constant survey of the patient's health status by the investigator and on information spontaneously provided by the patient and/or through questioning of the patient.

If a patient is seen by an investigator not involved in the study in relation to an AE, the study investigator should make every effort to contact the treating investigator in a timely manner in order to obtain all information necessary for appropriate reporting of the event.

### 11.2.2 Recording Adverse Events

Within this study, the following types of events are recorded in the eCRF

- any adverse drug reactions (ADRs)
- all serious adverse events (SAEs), regardless of their relationship to the observational drug
- special situations

Pregnancies are to be recorded on paper forms provided to the study sites.

The investigator should use the AE and ADR definitions provided in the above sections and should observe the following guidelines when completing the AE sections of the eCRF:

- Whenever possible, recognized medical terms should be used to describe an event rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.
- Events should be described using a specific clinical diagnosis, if this is available, rather than a set of signs and symptoms (for example, 'congestive heart failure' rather than 'dyspnoea, rales and cyanosis.')
- However, signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual event.
- Provisional diagnosis (e.g., "suspected myocardial infarction") are acceptable but should be followed up to a definite diagnosis if finally available.
- Events occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary event, if clearly identifiable, generally represents the most accurate clinical term to record. The investigator should be invited to provide his/her opinion of which is the primary event, or "Reporter's highlighted term".
- In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

It is important that each report includes a description of the event, whether it is considered serious (and if so, the criterion satisfied), its duration (onset and resolution dates), its relationship to the observational drug, any other potential causality factors, any treatment given or other action taken (including dose modification or discontinuation of the observational drug) and its outcome.

**ADRs** must be recorded on an ongoing basis from the day of written informed consent until discontinuation of study, withdrawal of consent or end of study.

**SAEs** must be recorded on an ongoing basis from the day of written informed consent until discontinuation of study, withdrawal of consent or end of study.

If ADRs / SAEs still persist at the end of the study, the events should be followed up with reasonable effort until they have resolved or, if resolution is unlikely, until they have stabilized. The length of follow-up depends on the severity and the progression of an SAE. If a patient is lost to follow-up, ongoing SAEs cannot be followed up.

**Rationale for non-collection of safety data in this study.**

AEs not meeting seriousness criteria that do not have a causal relationship with berotralstat will not be collected on the eCRF and subsequently captured in the EDC. The collection of non-serious, not related AEs is not required for the berotralstat NI-PASS. The characterization of very common (≥1/10) and common (≥1/100 to <1/10) non-serious reactions including gastrointestinal disorders, skin and subcutaneous disorders (rash) and headache is documented in the EU SmPC. The safety profile of berotralstat remained consistent across the pivotal clinical trials and the long-term safety study, across different regions and demographics. The sponsor concludes that the collection of non-serious ADRs and serious adverse events

(SAEs) for subsequent causality assessment to be sufficient to further elucidate the safety profile of berotralstat.

### 11.2.3 Classification of Causality

Every effort must be made by the investigator to categorize each AE according to its relationship to the study treatment by considering the following items:

- Temporal relationship of the onset of the AE to the initiation of the treatment.
- Discontinuation or reintroduction of treatment affecting the course of the AE.
- Known association of the AE with the treatment.
- Risk factors present in the study patient known to increase the occurrence of the AE.
- Non-treatment related factors known to be associated with the occurrence of the AE.

The following definitions apply:

Not related:
A causal relationship between the treatment with berotralstat and the AE is not a reasonable possibility. Reasons for this determination may include the presence of other factors such as the patient's clinical state, therapeutic interventions or concomitant products administered to the patient. The AE also does not follow a known response pattern to berotralstat.

Related:
A causal relationship between the treatment with the observational drug and the AE is a reasonable possibility.

All SAEs and only related AEs not meeting seriousness criteria defined as ADRs are to be recorded in the eCRF AE Form.

### 11.2.4 Grading of Severity

All AEs will be classified as

Mild:
The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate:
The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe:
Significant impairment of functioning: the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). This has to be clearly distinguished from the term "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligation.

### 11.2.5 Outcome of ADRs / SAEs

Outcome will be classified as

- Fatal (incl. date of death, cause of death)
- Recovered/Resolved (incl. recovery date)
- Recovering/Resolved with sequelae
- Not recovered/Not resolved
- Unknown

## 11.3 Reporting of Drug Safety Information

Any ADR; SAE, special situation; and/or clinically physical exam finding, vital sign result, electrocardiogram tracing, or laboratory result qualifying as an SAE or a non-serious ADR occurring during the course of the study must be reported to the sponsor by the investigator via the EDC system:

- SAEs within 24 hours of becoming aware
- all other events must be reported within 3 calendar days of becoming aware.

The investigator/reporter must provide as much detailed information as possible and complete associated relevant sections [e.g., concomitant medication, medical history, etc.]. It is important that each report includes a description of the event, whether it is considered serious, its duration [onset and resolution dates], its relationship to the observational drug, any other potential causality factors, any treatment given or other action taken [including dose modification or discontinuation of the observational drug] and its outcome.

In addition, the investigator/reporter must respond to any request for follow-up information or questions the sponsor may have regarding the safety information within the same timelines as for initial reports.

The investigator/reporter must ensure that the patient's pseudonymity will be maintained. The patient's name (and other information that may identify the patient) must be replaced by the patient number.

Paper AE and Special Situation reporting forms will be available as back-up in case of non-availability of eCRF for an extended period. If paper forms are used, they need to be faxed or emailed using the following contact:

- E-mail: APeX-N-Safety@ams-europe.com

As soon as the eCRF is accessible again, the site needs to subsequently document the ADR, SAE or special situation in the eCRF.

Only requested supporting documentation (e.g., discharge summary, laboratory results, autopsy report) should be sent to the same AE reporting contact. The investigator must ensure that the patient's pseudonymity will be maintained in these additional documents (e.g., blacking all sections that could enable identification of the patient).

ADRs will be reported by the sponsor to the competent authorities according the local and regional law. The format of these reports will follow the local and regional requirements.

### 11.3.1 Reporting Period

ADRs, SAEs and special situations will be recorded on an ongoing basis and independent of the visits throughout the patient's participation in the study. The collection starts from the time of patient's signature of Informed Consent and includes all ADRs, SAEs and special situations occurring since patient's consent to study participation.

In case of ongoing ADRs / SAEs at study termination, the events should be followed up with reasonable effort until they have resolved or until the degree of a permanent disability can be assessed. If a patient is documented as lost to follow-up, ongoing/unknown outcome of ADR / SAE will not be followed up.

If there is an ADR / SAE or special situation after completion of the observational period for the patient, which the investigator considers to be related to the observational drug, this should be reported as spontaneous case to the following contact:

- E-mail: PM_Safety@biocryst.com

### 11.3.2 Pregnancy / Drug Exposure via Parent

Only pregnancies considered related to study treatment by the investigator (i.e., resulting from a drug interaction with a contraceptive medication) are considered as ADRs. However, all pregnancies occurring from the date of informed consent signature until at least until end of observation must be recorded an a 'Pregnancy/Drug Exposure via Parent Data Collection Form', which is not part of the eCRF. Pregnancy outcomes are not recorded in the eCRF unless considered ADRs.

The investigator must notify the sponsor in an expedited manner of any pregnancy occurring during the above-mentioned period, by completing the first sections of the 'Pregnancy/Drug Exposure via Parent Data Collection Form'.

The completed 'Pregnancy/Drug Exposure via Parent Data Collection Form' should be emailed within 5 calendar days to the sponsor using the following contact:

- E-mail: PM_Safety@biocryst.com; cc APeX-N-Safety@ams-europe.com

The same reporting modalities apply in case the partner of a male study patient becomes pregnant at any time during the whole course of the study.

Investigators must actively follow-up, document and report the outcome of all these pregnancies to the sponsor, even if the patient was withdrawn from the study.

# 12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data and results of this study are the sole property of the sponsor and may be used world-wide for product documentation and publications. By conducting this study, the investigator affirms to the sponsor that he/she will maintain, in strict confidence, information provided to him/her by the sponsor, including data generated from this study, except as exempted for regulatory purposes.

In accordance with generally recognized principles of scientific collaboration, co-authorship with any personnel involved in this study will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

Design, progress and results of this study are planned to be presented at scientific conferences.

The final study report - all personal data redacted and regardless of outcome – will be published on the publicly accessible website of the respective competent authority in each participating country in accordance with the applicable laws and regulations.

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# ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

# ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

## ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title:
Non-Interventional Post-Authorization Study to Evaluate the Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting -ApeX-N

**EU PAS Register® number:** Study is not yet registered
**Study reference number (if applicable):** BCX7353-401

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim report(s) | ☐ | ☒ | ☐ | Mentioned in section 9.7 |
| 1.1.5 Registration in the EU PAS Register® | ☐ | ☒ | ☐ | Not yet registered |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | |

Comments:

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 8 |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 8 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8 |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

| Section 2: Research question | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 8 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

| Section 3: Study design | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 9.1.1 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☐ | ☐ | ☒ | |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

| Section 4: Source and study populations | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.1 |
| 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.2.2 |
| 4.2.3 Country of origin | ☐ | ☐ | ☒ | |
| 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 9.2.2 |
| 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.1 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.2 |

Comments:

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.1 | Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.1.1/ 9.3 |
| 5.2 | Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 5.3 | Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 9.1.1/ 9.3 |
| 5.4 | Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.1.1/ 9.3 |
| 5.5 | Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | |
| 5.6 | Is (are) (an) appropriate comparator(s) identified? | ☐ | ☐ | ☒ | |

Comments:

| **Section 6: Outcome definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 6.1 | Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 9.1.1 |
| 6.2 | Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3 |
| 6.3 | Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 6.4 | Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☒ | ☐ | ☐ | 9.1.1 |

Comments:

| **Section 7: Bias** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 7.1 | Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☒ | ☐ | ☐ | 9.9 |
| 7.2 | Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.3 | Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.9 |

Comments:

| Section 8: Effect measure modification | | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| 8.1 | Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☐ | ☐ | ☒ | |

Comments:

| Section 9: Data sources | | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| 9.1 | Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| | 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.3 / 9.4 |
| | 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3 / 9.4 |
| | 9.1.3 Covariates and other characteristics? | ☐ | ☐ | ☒ | |
| 9.2 | Does the protocol describe the information available from the data source(s) on: | | | | |
| | 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.3 / 9.4 |
| | 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3 / 9.4 |
| | 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.4 |
| 9.3 | Is a coding system described for: | | | | |
| | 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.4 |
| | 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.4 |
| | 9.3.3 Covariates and other characteristics? | ☐ | ☐ | ☒ | |
| 9.4 | Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 10.3 |

Comments:

| Section 10: Analysis plan | | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| 10.1 | Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 | Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5 |

| Section 10: Analysis plan | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.4 Are stratified analyses included? | ☐ | ☐ | ☒ | |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☐ | ☒ | |
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☐ | ☒ | |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☐ | ☒ | |

Comments:

SAP will be written and approved before any analysis

| Section 11: Data management and quality control | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.6/ 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

| Section 12: Limitations | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | ☐ | ☐ | ☒ | |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☐ | ☐ | ☒ | |

Comments:

| Section 13: Ethical/data protection issues | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 10.1 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |

| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10.3 |

Comments:

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 10.1 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

Name of the main author of the protocol: PPD

Date:19/July/2021

Signature: _____

ENCePP Checklist for Study Protocols (Revision 4) Page 6/6

# ANNEX 3. ADDITIONAL INFORMATION

None

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