

Health Technology Briefing

October 2024

Berotrastat for preventing recurrent attacks of hereditary angioedema in children aged 2 to <12 years

Company/Developer

BioCryst Pharmaceuticals Inc

New Active Substance

Significant Licence Extension (SLE)

NIHRI ID: 35554

NICE ID: Not Applicable

UKPS ID: 674940

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Berotrastat is in development for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to <12 years. HAE is a rare disease, caused by a gene alteration that means an important protein in the immune system, C1 esterase inhibitor (C1-INH), is missing or dysfunctional in these patients. Lack of the C1-INH protein triggers the body's immune system to misfire through a series of downstream signalling pathways that cause excessive production of a protein called bradykinin. Bradykinin acts on blood vessels making them wider and more permeable (leaky) to fluid. Fluid that has leaked from the blood vessels accumulates into surrounding tissues causing rapid swelling (oedema). There are currently no NICE recommended treatments options for preventing recurrent attacks of HAE in children aged under 12 years.

Berotrastat, administered orally, blocks the activity of a protein called kallikrein which is overactive in people with HAE. Overactive kallikrein leads to uncontrolled production of the protein bradykinin, which is involved in the process that causes blood vessels to widen and leak fluid. By blocking the activity of kallikrein, berotrastat will block the downstream signalling pathways that result in swelling and inflammation of HAE attacks. Treatments currently licenced in the UK to prevent attacks of HAE, are given through injections. If recommended, berotrastat would be the first therapy recommended by NICE for prevention of HAE attacks in children aged 2 to <12 years, and the first delivered by an oral route of administration.

Proposed Indication

Prevention of recurrent attacks of hereditary angioedema (HAE) in children aged 2 to < 12 years.¹

Technology

Description

Berotrastat (Orladeyo, BCX7353) is a selective inhibitor of plasma kallikrein used in the prophylaxes of attacks of HAE.^{2,3} Plasma kallikrein is a serine protease that cleaves high-molecular-weight-kinnogen, releasing bradykinin, a potent vasodilator that increases vascular permeability. In patients with HAE due to C1-INH deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired which leads to uncontrolled increases in plasma kallikrein activity and bradykinin release.⁴ Berotrastat works by inhibiting the enzymatic activity of plasma kallikrein in releasing bradykinin, the major biologic peptide that promotes swelling and pain associated with attacks of HAE.²

Berotrastat is currently in clinical development for the routine prevention of recurrent attacks of HAE in children aged 2 to 11 years. In the phase III clinical trial APeX-P (NCT05453968), berotrastat is administered orally once daily at a weight-based dose.¹

Key Innovation

Long-term prophylaxis to prevent recurrent angioedema episodes is a key component of HAE disease management.⁵ Treatment options have been recommended by NICE for the prevention of recurrent attacks in adult and paediatric patients with HAE aged over 12 years.⁶ However, there are currently no NICE recommended treatment options for the prevention of recurrent attacks of HAE in paediatric patients aged less than 12 years.⁷ There are treatment options licensed in the UK/EU to prevent attacks of HAE in children, which are administered by injection.^{8,9} Berotrastat is given through oral administration which may be more acceptable to paediatric patients because they are not associated with pain or fear of needles barriers which may be the case for subcutaneous injections.¹⁰ If licenced, berotrastat will be the first oral medicinal product available to children aged 2 to <12 years for the prevention of recurrent HAE attacks.

Regulatory & Development Status

Berotrastat currently has Marketing Authorisation in the EU/UK for the routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older.⁴

Berotrastat is not currently in late stage clinical trials for any indications besides HAE.¹¹

Patient Group

Disease Area and Clinical Need

HAE is characterised by recurrent episodes of the accumulation of fluids (oedema) outside of the blood vessels, blocking the normal flow of blood or lymphatic fluid and causing rapid swelling of the tissues.¹² HAE is an autosomal dominant disease caused by either a lack of C1-INH protein (type I) or dysfunctional C1-INH protein (type II).¹³ Without enough C1-INH protein, the immune system can misfire through a series of downstream signalling pathways that result in the overactivation of kallikrein, which causes the excessive production of bradykinin. Bradykinin is a protein that acts on blood vessels to make them wider and more permeable, this results in fluid leaking from the blood vessels and accumulating in the tissues which triggers

the symptoms of angioedema.¹⁴ The areas of the body most commonly affected by swelling include the hands, feet, eyelids, lips, and/or genitals. Oedema may also occur in the mucous membranes that line the respiratory and digestive tracts. Certain factors such as injury, surgery, severe pain, viral illness and stress can trigger or worsen the recurring symptoms of HAE.¹⁵

HAE is a rare disease that affects between 1 in 25,000 and 1 in 50,000 of the population.¹⁶ Applying this prevalence to the mid-year 2022 population estimate for children in England aged 2 to 12 years, it can be estimated that the patient population would be between 139 and 279 people in England.¹⁷ In England, 2022-23, there were 731 finished consultant episodes (FCE) and 683 admissions for defects in the complement system (ICD-10 code D84.1), which includes hereditary angioedema. This resulted in 323 FCE bed days and 433 day cases.¹⁸

Recommended Treatment Options

The following treatment options are approved in the UK/EU within their licenced indications for the prevention of routine recurrent attacks of HAE:

- C1-esterase inhibitor (Cinryze) has Marketing Authorisation in the EU for the routine prevention of angioedema attacks in adults, adolescents and children (6 years and above) with severe attacks of HAE, who are intolerant or insufficiently protected by oral prevention treatments.⁸
- Lanadelumab (Takhzyro) has Marketing Authorisation in the EU for the routine prevention of recurrent attacks of HAE in patients aged 2 years and older.⁹

C1-INH and icatibant are the only approved on-demand treatments for children with HAE.¹⁹

Clinical Trial Information

Trial	<p>APeX-P, NCT05453968, 2021-005932-50; A Phase III Study to Evaluate the Safety and Pharmacokinetics of Berotralstat Prophylaxis in Children With Hereditary Angioedema Who Are 2 to 11 Years of Age</p> <p>Phase III: Active, not recruiting</p> <p>Locations: 7 EU countries, UK, Canada and Israel</p> <p>Primary completion date: July 2025</p>
Trial Design	Open-label, single group assignment
Population	N=29 (actual); clinical diagnosis of HAE; children aged 2 to 11 years;
Intervention(s)	Berotralstat administered orally once daily at a weight-based dose
Comparator(s)	No comparator
Outcome(s)	<p>All primary outcomes were measured at pre-dose and at multiple timepoints up to 24 hours post-dose, they were:</p> <ul style="list-style-type: none"> • Pharmacokinetics: C_{max} (maximum plasma concentration of berotralstat) • Pharmacokinetics: AUC_{0-tau} (area under the plasma concentration berotralstat time curve from time 0 to end of dosing (tau)). • Pharmacokinetics: CL/F (apparent oral clearance of berotralstat) <p>See trial record for full list of other outcomes</p>
Results (efficacy)	-

Results (safety)

-

Estimated Cost

Berotrastat is already marketed in the UK for the prevention of recurrent attacks of HAE in people aged over 12 years. The NHS price for 28 capsules of Orladeyo (150mg) is £10,205.²⁰

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Plasma derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II. July 2016.

Other Guidance

- World Allergy Organisation (WAO) / European Academy of Allergy and Clinical Immunology (EAACI). The international WA/EAACI guideline for the management of hereditary angioedema. 2022.¹⁹
- University Hospitals of Leicester NHS Trust. Hereditary Angioedema (HAE) Children's Guideline. 2022.²¹

Additional Information

The company anticipate a paediatric formulation of berotrastat (granules) being available at the time of regulatory approval.

References

- 1 Clinicaltrials.gov. *Berotrastat Treatment in Children With Hereditary Angioedema (APeX-P)*. Trial ID: NCT0543968. 2022. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/study/NCT0543968> [Accessed 28 August 2024].
- 2 DrugBank. *Berotrastat*. 2020. Available from: <https://go.drugbank.com/drugs/DB15982> [Accessed 28 August 2024].
- 3 US Food and Drug Administration (FDA). *ORLADEYO (berotrastat) capsules for oral use*. 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214094s000lbl.pdf [Accessed 27 September 2024].
- 4 Electronic Medicines Compendium (EMC). *Orladeyo 150mg capsule* 2024. Available from: <https://www.medicines.org.uk/emc/product/12883/smpc#gref> [Accessed 28 August 2024].
- 5 Srinivasan C, Ritchie B, Adatia A. Berotrastat in hereditary angioedema due to C1 inhibitor deficiency: first real-world evidence from a Canadian center. *Frontiers in Immunology*. 2024;15. Available from: <https://doi.org/10.3389/fimmu.2024.1339421>.
- 6 National Institute for Health and Care Excellence (NICE). *Berotrastat for preventing recurrent attacks of hereditary angioedema (TA738)*. Last Update Date: 20 October 2021. Available from: <https://www.nice.org.uk/guidance/ta738> [Accessed 28 August 2024].

- 7 National Institute for Health and Care Excellence (NICE). Search for Hereditary Angioedema Guidance 2024. <https://www.nice.org.uk/search?q=hereditary+angioedema>.
- 8 Electronic Medicines Compendium (EMC). *Cinryze 500 IU powder and solvent for solution for injection* 2024. Available from: <https://www.medicines.org.uk/emc/product/2808/smpc#gref> [Accessed 17 October 2024].
- 9 Electronic Medicines Compendium (EMC). *TAKHZYRO 300 mg solution for injection in pre-filled syringe*. 2024. Available from: <https://www.medicines.org.uk/emc/product/12051/smpc#gref> [Accessed 17 October 2024].
- 10 Taddio A, McMurtry CM, Logeman C, Gudzak V, de Boer A, Constantin K, et al. Prevalence of pain and fear as barriers to vaccination in children – Systematic review and meta-analysis. *Vaccine*. 2022;40(52):7526-37. Available from: <https://doi.org/https://doi.org/10.1016/j.vaccine.2022.10.026>.
- 11 Clinicaltrials.gov. Search for *Berotrastat Studies: Phase II and III*. 2024. Available from: <https://clinicaltrials.gov/search?aggFilters=phase:2%203&intr=berotrastat> [Accessed 28 August 2024].
- 12 National Organization for Rare Disorders (NORD). *Hereditary Angioedema*. 2021. Available from: <https://rarediseases.org/rare-diseases/hereditary-angioedema/> [Accessed 28 August 2024].
- 13 Abdulkarim A, Craig TJ. *Hereditary Angioedema*. Treasure Island, Florida: 2024.
- 14 NHS Inform. *Angioedema*. 2023. Available from: <https://www.nhsinform.scot/illnesses-and-conditions/skin-hair-and-nails/angioedema/#causes-of-angioedema> [Accessed 28 August 2024].
- 15 National Organization for Rare Disorders (NORD). *Hereditary Angioedema: Signs and Symptoms*. 2021. Available from: <https://rarediseases.org/rare-diseases/hereditary-angioedema/#symptoms> [Accessed 28 August 2024].
- 16 HAE UK. *What Causes HAE*. 2024. Available from: <https://www.haeuk.org/what-is-hae/what-causes-hae/> [Accessed 28 August 2024].
- 17 Office for National Statistics (ONS). *Estimates of the population for England and Wales*. 2024. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/estimatesofthepopulationforenglandandwales> [Downloaded 15 July 2024].
- 18 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23> [Downloaded 21 September 2023].
- 19 Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961-90. Available from: <https://doi.org/10.1111/all.15214>.
- 20 National Institute for Health and Care Excellence (NICE). *Berotrastat*. 2024. Available from: <https://bnf.nice.org.uk/drugs/berotrastat/#indications-and-dose> [Accessed 28 August 2024].
- 21 NHS Trust: University Hospitals of Leicester. *Hereditary Angioedema (HAE) UHL Children's Guideline*. 2022. Available from: [https://secure.library.leicestershospitals.nhs.uk/PAGL/Shared%20Documents/Hereditary%200Angioedema%20\(HAE\)%20UHL%20Childrens%20Guideline.pdf](https://secure.library.leicestershospitals.nhs.uk/PAGL/Shared%20Documents/Hereditary%200Angioedema%20(HAE)%20UHL%20Childrens%20Guideline.pdf) [Accessed 28 August 2024].

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