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HEALTH TECHNOLOGY BRIEFING
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BCX7353 for prevention of acute attacks of angioedema in hereditary angioedema

NIHRIO ID	13078	**NICE ID**	9984
Developer/Company	BioCryst Pharmaceuticals Inc.	**UKPS ID**	649857

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

BCX7353 is in clinical development for routine prevention of angioedema attacks in patients with hereditary angioedema (HAE). HAE is a rare genetic disorder of blood vessels characterised by recurrent episodes of severe swelling (angioedema) below the skin which often affect the face, throat, stomach, genitals, hands or feet, causing discomfort and pain. HAE may be life threatening when the swelling occurs in the throat as it can obstruct the airways and impede breathing. HAE has no known cure and the goal of treatment is to minimise the burden of illness on patients and enable them to lead normal lives. Long-term preventive treatments are used routinely to reduce the need for treatment of acute attacks. Currently available treatments are given by injection.

BCX7353 is an oral treatment that works by blocking the activity the specific pathway that becomes overactive in patients with angioedema. By blocking this pathway, BCX7353 is expected to reduce the number of angioedema attacks. Early studies of BCX7353 has shown that it helped to prevent swelling and inflammation in HAE. In addition, BCX7353 has the distinct advantage over current treatment of being administered orally, making it easier to use for routine prevention of HAE attacks.

PROPOSED INDICATION

Routine prevention of attacks of angioedema in patients 12 years and older with hereditary angioedema (HAE).[a]

TECHNOLOGY

DESCRIPTION

BCX7353 is a potent oral synthetic inhibitor of plasma kallikrein (pKal) with a pharmacokinetic and pharmacodynamic profile that prevents angioedema attacks in hereditary angioedema (HAE). HAE is caused by mutations in the gene encoding C1 inhibitor (also called C1 esterase inhibitor) that lead to over activation of the kallikrein–bradykinin cascade.[1] The primary function of C1 inhibitor is to regulate the activation of the complement and contact system pathways. Deficiency of C1-inhibitor permits pKal activation, which leads to the production of the vasoactive protein fragment (peptide) bradykinin.[2] Without the proper levels of functional C1 inhibitor, excessive amounts of bradykinin are generated. Bradykinin promotes inflammation by increasing the leakage of fluid through the walls of blood vessels into body tissues. Excessive accumulation of fluids in body tissues causes the episodes of swelling.[3] It is thus postulated that inhibiting pKal with BCX7353 should be a prophylactic measure against HAE.[4]

BCX7353 is in clinical development for the routine prevention of angioedema attacks in patients, aged 12 years and older with Type I and Type II HAE. In the phase III clinical trial (APeX-2; NCT03485911, EudraCT-2017-003966-29), BCX7353 is administered as an oral capsule at a dose of 110mg or 150mg once daily for 24 weeks, with a long term safety extension up to 96 weeks.[5,6]

INNOVATION AND/OR ADVANTAGES

Subcutaneous or intravenous (IV) forms of plasma-derived purified C1 inhibitors and a fully humanised IgG1 monoclonal antibody targeting plasma kallikrein for the treatment of hereditary angioedema are already approved in the EU.[7,8]

The only available effective drugs for oral prophylaxis against angioedema attacks are attenuated androgens that present a number of unacceptable adverse effects and several contraindications (e.g. in growing children and pregnant women), which limits their clinical use.[1]

BCX7353 targets the specific disease pathway involved in HAE and has the potential to offer a distinct advantage of oral administration for routine prophylaxis against angioedema attacks [1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

BCX7353 does not currently have Marketing Authorisation in the EU/UK for any indication.

BCX7353 was granted an orphan designation in the EU in June 2018 for the treatment of HAE.[7]

BCX7353 has been granted a Medicines and Healthcare products Regulatory Agency (MHRA) Promising Innovative Medicines (PIM) designation.[9]

[a] Information provided by Biocryst Pharmaceuticals Inc.

PATIENT GROUP

DISEASE BACKGROUND

Hereditary angioedema (HAE) is a group of rare, potentially life-threatening, and frequently debilitating diseases characterised by recurrent, and often with an unpredictable onset, of swelling attacks. HAE is heterogeneous, with considerable differences between its subtypes, patients, and even within the same patient over time.[10]

It is currently classified into three types (I, II and III), according to the deficiency or absence of C1 inhibitor. Types I and II are caused by mutations in the C1NH gene (also called the SERPING1 gene), which provides instructions for making the C1 inhibitor protein. Type I is due to deficiency of C1 inhibitor, and type II is due to dysfunction of C1 inhibitor. These types are also characterised by abnormal complement protein levels. Inheritance of types I and II is autosomal dominant, but not all people with a SERPING1 gene mutation will develop symptoms of HAE. A third type is called HAE with normal C1 inhibitor. This type is characterised by normal C1 inhibitor and normal complement protein levels, and usually begins in adulthood. While some cases of type III are due to mutations in the F12, plasminogen or angiopoietin I genes, in other cases the cause is not yet known.[11,12]

C1 inhibitor is a key regulator of the complement, coagulation, and kallikrein–kinin cascades. In HAE with C1 inhibitor deficiency, activation of the kallikrein–kinin cascade leads to uncontrolled generation of plasma kallikrein and consequent proteolysis of HMWK. This results in excessive bradykinin production, which causes vasodilatation, vascular leakage, and subsequent angioedema and pain.[13]

Symptoms include abdominal swelling that can cause severe pain and potentially intestinal obstruction, incapacitating the patient during the attack; swelling of the extremities that can impede patients from walking or using their hands, and swelling with airway involvement that is potentially life-threatening. The pain and disability caused by attacks may inhibit patients' ability to conduct their normal activities of daily life, including attending work or school.

Attacks are unpredictable, making it difficult for patients to plan for travel or other life events, and often cause anxiety about future attacks. Since C1 deficiency HAE is an autosomal dominant disorder, parents with the condition may have concerns about having children or passing it on to their children. There is frequently a delay in the time between symptom onset and confirmed diagnosis in patients. Without a proper diagnosis, patients may spend years without appropriate therapy and are at risk for a potentially life-threatening airway attack. Patients may also have inadequate or suboptimal therapy because of the rarity of the disease.[14]

The crises of HAE can be triggered by trauma, pressure, emotional stress and the use of medications, especially inhibitors of angiotensin-converting enzyme (ACE) and oestrogens, which may induce and/or exacerbate quiescent disease in all types of HAE. In relation to pregnancy, patients with HAE usually improve, especially from the second quarter. The trauma of delivery does not precipitate the crisis, but these may recur after the first week of the puerperium.[15]

CLINICAL NEED AND BURDEN OF DISEASE

The NHS in England estimates HAE to affect 1 in 50,000 to 100,000 people of any ethnic group and of either gender.[16] Applying the 2017 mid-year population estimates for England, between 1112 and 556 people would have HAE.[17] Type I HAE is estimated to occur in 80% to 85% of patients while type II HAE occurs in the remaining 15% to 20% of patients.[18]

Most patients with symptomatic untreated HAE experience at least 1 acute exacerbation per month,[17] each attack typically lasts a few days before spontaneously subsiding. It is estimated that individual patients can be debilitated by their symptoms for 20 to 100 days per year. Seventy-five percent of patients with HAE have cutaneous angioedema of an extremity as the first presenting sign of the disease.[18]

Subcutaneous swelling, occurs in 91% of patients, submucosal swelling causing abdominal pain in 74% of patients, and laryngeal swelling occurring in 47% of patients. Swelling of the airways during an attack is potentially life-threatening, with a 30% risk of death due to asphyxiation if untreated.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the absence of a cure, the goal of treatment of HAE is to minimise the burden of illness on patients and enable them to lead normal lives.[14] Education and counselling of patients and their family members, family physicians, and consultant specialists including paediatricians with respect to diagnosis and therapy of HAE is the cornerstone of successful management of HAE in all age groups.[20]

Broadly, there are 3 approaches to managing HAE: avoidance of precipitating factors (e.g. minor trauma, hormone replacement therapy), acute treatments and preventive (prophylactic) treatments of acute attacks. Short-term preventive treatments aim to prevent an attack before known triggers which include, for example, dental work or surgery, whereas long-term preventative treatments are used routinely to reduce the need for treatment of acute attacks.[21]

Prophylaxis therapy should be discussed as a potential treatment option for each patient. The decision to use prophylaxis medication will depend on the patient's individual needs and the course of their symptoms. Clinical aspects of disease activity, such as attack frequency and severity and history of severe debilitating or life-threatening attacks, may be considered, as well as access to urgent care in case one of these severe attacks occurs. However, other components of disease burden may also be considered. The benefit risk profile and treatment burden of available therapies should be considered in the decision for prophylaxis. Patients who are not receiving long-term prophylaxis should receive short-term prophylaxis before events or circumstances that are expected to trigger an attack, such as surgery or invasive dental work, and some may also consider it before or during stressful life events.[14]

Individuals known to have HAE will be managed in specialist centres. For potentially life-threatening attacks involving the airway the patient would require management in an emergency setting where they would be treated for acute symptoms as required. Individuals may have treatment doses of C1 inhibitor or icatibant at home which can (with appropriate training from the specialist centres) be self-administered for clinically significant attacks.

Oral prophylaxis should be the first line of treatment for individuals at risk of attack. However, for people with HAE who continue to experience two or more clinically significant attacks per week, or who are contraindicated for oral prophylaxis (e.g. pregnant women), and who are under the care of a specialist team, long-term prophylactic C1-inhibitor injections can be considered as an option following discussion within their immunology network multi-disciplinary team. Training of eligible patients or their infusion partner would take on average two visits to a day-care unit experienced in training patients for self-administration of medication.[16]

CURRENT TREATMENT OPTIONS

The newly updated 2017 World Allergy Organisation in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI) HAE guidelines recommend the following treatment for the short and long term prophylaxis of HAE type I and type II:[22]

- Preprocedural or short-term prophylaxis with C1-INH concentrate is recommended for all medical, surgical, and dental procedures associated with any mechanical impact to the upper aero-digestive tract.
- Plasma-derived C1-INH is currently the preferred long-term prophylaxis for the prevention of HAE attacks and should be offered as first-line option;
- Androgens should be offered as second-line long-term prophylaxis provided careful surveillance is granted due to their recognized side effects;
- Antifibrinolytics are not recommended for long-term prophylaxis.

PLACE OF TECHNOLOGY

If licensed, BCX7353 will offer a treatment option as the first oral targeted therapy for routine prevention of attacks of angioedema in patients 12 years and older with hereditary angioedema type I and type II.

CLINICAL TRIAL INFORMATION

Trial	**APeX-2, BCX7353-302, NCT03485911**, EudraCT-2017-003966-29, aged 12 years and older; BCX7353 vs placebo; phase III
Sponsor	BioCryst Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[5,6]
Location	8 EU countries, incl UK, USA, Canada and Macedonia
Design	Randomised, double-blind, placebo-controlled, parallel assignment
Participants	N=96; aged 12 years and older; clinical diagnosis of hereditary angioedema type I or Type II, defined as having a C1-INH functional level and a C4 level below the lower limit of the normal (LLN) reference range, as assessed during the Screening period.
Schedule	Randomised to: • BCX7353 110mg oral capsules administered once daily, or • BCX7353 150mg oral capsules administered once daily, or • Matching placebo administered as oral capsules once daily.
Follow-up	Part 1: 24 weeks; Part 2: 24-96 weeks
Primary Outcomes	The rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Day 1 to Day 168) [Time Frame: 24 weeks]
Secondary Outcomes	Time Frame: Day 1 - Week 96 • The safety of oral BCX7353 capsules Time Frame: Day 8 to 24 weeks • Rate of investigator-confirmed HAE attacks during dosing in the effective treatment period Time Frame: 24 weeks • Change from baseline in Angioedema Quality of Life questionnaire at Week 24 (total score)

	• Proportion of days with angioedema symptoms through 24 weeks Time Frame: Weeks 24-48 • Rate of investigator-confirmed HAE attacks • Durability of response (attack rate trend over time) • Durability in Angioedema Quality of Life questionnaire score • Proportion of days with angioedema symptoms Time Frame: Weeks 48-96 • Rate of HAE attacks during dosing • Durability of response (attack rate trend over time) • Durability in Angioedema Quality of Life questionnaire score • Proportion of days with angioedema symptoms
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as October 2020

Trial	**APeX-S, BCX7353-204, NCT03472040**, EudraCT-2017-003281-27, aged 12 years and older; phase II & III
Sponsor	BioCryst Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[23,24]
Location	11 EU countries, incl UK, USA, Canada, countries in Africa, NE Asia and western Pacific and European region.
Design	Long-term, open label non-randomised, parallel assignment
Participants	N=225 (planned); aged 12 years and older; subjects with HAE Type I or II who either have participated in a previous BCX7353 study or, in selected countries, in the opinion of the Investigator are expected to derive benefit from an oral treatment for the prevention of angioedema attacks
Schedule	Allocated to: • BCX7353 110mg oral capsules administered once daily, or • BCX7353 150mg oral capsules administered once daily
Follow-up	96 weeks
Primary Outcomes	The long term safety of oral BCX7353 capsules [Time Frame: 96 weeks]
Secondary Outcomes	Time Frame: 96 weeks • The rate of acute attacks of angioedema during treatment • The durability of response to treatment • Patient reported quality of life (QoL) during treatment

	• Patient's satisfaction with medication during long term administration of BCX7353
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as February 2021

ESTIMATED COST

The cost of BCX7353 is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Lanadelumab for preventing recurrent attacks of hereditary angioedema (ID1268). Expected publication date, August 2019.

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. 16045/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Immunology (all ages). B09/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Allergy Services (all ages). B09/S/b.

OTHER GUIDANCE

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