Health Technology Briefing
February 2023

Sebetralstat for treating hereditary angioedema

Company/Developer	KalVista Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29200	NICE ID: 11846	UKPS ID: 667361

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Sebetralstat is currently in clinical development as an on-demand treatment for hereditary angioedema (HAE) type I and type II. HAE is a rare genetic condition that usually develops in childhood or early adulthood. It is caused by a defect in a gene that regulates the blood protein C1-inhibitor. Lack of C1-inhibitor leads to the disruption of a complex cascade of events that regulate inflammation. An enzyme (protein) called plasma kallikrein becomes overactive which can ultimately lead to episodic attacks of swelling (oedema) in the hands, feet, gastrointestinal tract, face, and airway. This swelling can cause severe pain and can be potentially life-threatening. This can have a substantial impact on quality of life, particularly because attacks are often difficult to predict. Most current treatments are injected and are focused on long term treatment to reduce the occurrence of an acute attack.

Sebetralstat is an orally administered drug which works by blocking the activity of plasma kallikrein which is expected to stop the attacks of swelling that occur in patients with hereditary angioedema. If taken at the onset of an attack, sebetralstat may prevent the attack from progressing further which therefore can have a big positive impact on patient clinical outcomes and quality of life. If licensed, sebetralstat would be the first oral on-demand treatment of HAE attacks.

Proposed Indication

Treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.[1]

Technology

Description

Sebetralstat (KVD-900) is an oral plasma kallikrein inhibitor.[2,3] Plasma kallikrein is part of the kallikrein-kinin system, which is overactive in patients with HAE. This is due to inadequate levels or malfunctioning C1-inhibitor, which is a critical mediator of inflammation. This leads the body to produce the vasopeptide bradykinin in excessive amounts, which in turn leads to increased vascular permeability, extravasation of plasma, and sudden onset of angioedema.[4,5] By blocking plasma kallikrein activity, sebetralstat is expected to stop the attacks of swelling that occur in patients with HAE.[6] Sebetralstat was shown to be rapidly absorbed into the systemic circulation (median Tmax of 0.5 hours) and demonstrated absorption, metabolism, and excretion properties that would be beneficial for on-demand treatment of HAE attacks.[7]

Sebetralstat is in clinical development as an on-demand treatment for acute HAE attacks in type I or type II HAE. In phase II and III trials (NCT05505916, NCT04208412, NCT05259917, NCT05511922), sebetralstat is administered orally at a dose of 600mg (2 x 300mg tablets) or 300mg, with a second dose administered after 3 hours if required.[1,8-10]

Key Innovation

There are not many effective on-demand treatments available for treating attacks of HAE. Sebetralstat is an acute therapy intended to reduce the barriers to on-demand treatment as it shows potential to improve treatment outcomes and increase the number of attacks treated on-demand.[11] There is evidence that treatment administered very early in an attack is more effective, and because it precludes the need to attend emergency hospital care, many patients prefer to self-administer their acute treatments at home.[12] Sebetralstat, administered orally as film-coated tablets will enable patients to take their medication as soon as they recognise the signs and symptoms of a HAE attack.

If licenced, sebetralstat would be the first oral on-demand treatment of HAE attacks.

Regulatory & Development Status

Sebetralstat is not currently licensed in the EU/UK for any indications. Sebetralstat has an Orphan Drug Designation in the EU from June 2022 for the treatment of HAE.[6]

Sebetralstat is not currently in clinical development for any other indications.[13]

Patient Group

Disease Area and Clinical Need

HAE is characterised by recurrent, unpredictable, episodes of subcutaneous or mucosal angioedema. The two main types of HAE are caused by mutations in the SERPING1 gene, resulting in quantitative or functional deficiencies in C1-inhibitor activity. Although most cases of HAE with C1-inhibitor deficiency are a result of autosomal dominant inheritance, 25% of cases are thought to result from *de novo* mutations in patients with no family history.[14] Lack of C1-inhibitor leads to uncontrolled activity of plasma kallikrein,

which triggers excessive release of a peptide called bradykinin. This in turn can lead to episodic attacks of oedema in the hands, feet, gastrointestinal tract, face, and larynx. A HAE episode with abdominal or intestinal wall swelling can cause severe pain, nausea, and vomiting. Swelling that attacks the larynx can lead to suffocation and potentially life-threatening situations.[15] The pain and disability caused by attacks may inhibit patients' ability to conduct their normal activities of daily life, including attending work or school. Additionally, the unpredictable nature of attacks, potential for asphyxiation, and possibility of passing the disease on to future generations result in higher levels of depression and anxiety among patients with HAE. Together, these factors contribute to a significant disease burden with reduced quality of life.[14]

HAE affects about 1 in 10,000 to 1 in 50,000 people and is therefore considered to be a rare disease.[16] Applying this patient population to the 2021 population estimates for England, it can be estimated that between 1,130 and 5,649 people would have HAE.[17] Diagnosis and treatment of this condition is important as evidence has shown that the mortality of HAE patients who had not been diagnosed was 29% compared to 3% in those who had been diagnosed.[18] In England 2021-22, there were 821 finished consultant episodes (FCE) and 771 admissions for defects in the complement system (ICD-10 code D84.1) which resulted in 189 FCE bed days and 418 day cases.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) has recommended treatment options for the prevention of HAE attacks, however there are currently no recommended treatment options for acute HAE attacks.[20,21] The British National Formulary (BNF) recommends medicinal products such as icatibant and conestat alfa for acute attacks of HAE, both of which are administered by intravenous injection.[22]

Clinical Trial Information

Trial	**KONFIDENT, NCT05259917; EudraCT 2021-001226-21**; A Phase III, Crossover Trial Evaluating the Efficacy and Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) **Phase III** – recruiting **Locations:** UK, US, 12 EU countries, Canada, and other countries **Primary completion date:** October 2023
Trial Design	Randomised, double-blind, placebo-controlled, three-way crossover.
Population	N=114 (estimated); aged 12 years and older, with a confirmed diagnosis of HAE type I or II at any time in the medical history.
Intervention(s)	Sebetralstat 300mg film coated tablet • Sebetralstat 300 mg film coated tablet • Sebetralstat 2x300 mg film coated tablet • If required, a second dose of sebetralstat after 3 hours
Comparator(s)	Placebo
Outcome(s)	Primary outcome measure: • Time to beginning of symptom relief Patient Global Impression of Change (PGI-C) [Time frame: within 12 hours of the first investigational medicinal product (IMP) administration]

	See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	**KONFIDENT-S, NCT05505916; EudraCT 2021-001176-42**; An Open-label Extension Trial to Evaluate the Long-term Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) **Phase III** – recruiting **Locations:** US, UK, 13 EU countries, Canada, and other countries **Primary completion date:** January 2026
Trial Design	Open label, multicentre extension, single group assignment.
Population	N=150 (estimated); aged 12 years and older, with a confirmed diagnosis of HAE type I or II at any time in the medical history and has had at least 2 documented HAE attacks within 3 months prior to the Enrolment Visit.
Intervention(s)	Sebetralstat 2x300mg Film Coated Tablet. If required, a second dose of sebetralstat after 3 hours.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • The proportion of patients with at least one AE in adolescent and adult patients with HAE type I or II who have taken at least one dose of Investigational medicinal product (IMP). [Time frame: AEs will be recorded from the first dose of IMP in the KVD900-302 trial up to and including the end of study (EOS) visit, a maximum of 2 years for each patient] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	**KONFIDENT-S, NCT05511922**; PK Subtrial in Adolescent Patients With HAE Type I or II Participating in the KVD900-302 Trial **Phase III** – recruiting **Locations:** US, 4 EU countries, Japan, Israel and Australia **Primary completion date:** January 2026
Trial Design	Open label, multicentre single group assignment.
Population	N=12 (estimated); aged 12 to 17 years old, who are currently participating in trial NCT05505916.
Intervention(s)	Sebetralstat 2x300mg film coated tablet

Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Pharmacokinetics – Cmax [Time frame: Up to 6 hours after IMP administration] • Pharmacokinetics – Tmax [Time frame: Up to 6 hours after IMP administration] Pharmacokinetics – AUC [Time frame: Up to 6 hours after IMP administration]
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	NCT04208412; **EudraCT** 2018-004489-32; A Phase II, Cross-over Clinical Trial Evaluating the Efficacy and Safety of KVD900 in the On-demand Treatment of Angioedema Attacks in Adult Subjects With Hereditary Angioedema Type I or II **Phase II** – completed **Locations**: UK, US, 9 EU countries and Macedonia **Primary completion date**: December 2020
Trial Design	Randomised, double-blind, placebo-controlled crossover assignment.
Population	N=68 (actual); aged 18 years and older, with a confirmed diagnosis of HAE type I or II and at least 3 documented HAE attacks in the past 93 days, as supported by medical history.
Intervention(s)	Sebetralstat 600mg tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Time to use of conventional attack treatment [Time frame: 12 hours] See trial record for full list of other outcomes.
Results (efficacy)	Attacks treated with KVD900 significantly reduced use of rescue (p=0.001), with 15% of KVD900 treated attacks rescued compared to 30% on placebo at 12 hours. This efficacy benefit of KVD900 was maintained at 24 hours (p=0.0005). KVD900 significantly reduced time to onset of symptom relief (p=<0.0001) on a Patient Global Impression of Change scale (PGI-C), with a median time of 1.6 hours versus 9 hours for attacks treated with placebo. KVD900 treated attacks achieved symptom relief more quickly than placebo treated attacks (p<0.0001) when assessed using a composite Visual Analogue Scale (VAS) score. Within 12 hours of oral administration, KVD900 significantly increased the number of stabilized or improved attacks when assessed by a Patient Global Impression of Severity scale (PGI-S) or use of rescue (p<0.0001). Additional exploratory endpoints were also statistically significant and favoured KVD900 treatment over placebo.[23]
Results (safety)	There were no serious adverse events reported in the trial and no patients withdrew due to adverse events (AEs). In the open-label phase, 8 on-treatment drug-related treatment emergent adverse event (TEAE) were experienced by 5 patients. In the crossover phase of the trial, 3 on-treatment drug-related TEAEs were experienced by 3 patients (5.2%) following administration of KVD900, and 2 on-treatment drug-

	related TEAEs were experienced by 2 patients (3.6%) following administration of placebo.[23]

Estimated Cost

The cost of sebetralstat is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema (Adult). NHSCB/B09/P/b. April 2013.

Other Guidance

- World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI). The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. 2022.[24]
- United States Hereditary Angioedema Association (US HAEA) Medical Advisory Board. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. 2020.[25]

Additional Information

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