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Health Technology Briefing
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Garadacimab for preventing attacks of hereditary angioedema

Company/Developer	CSL Behring UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27960	NICE TSID: Not applicable	UKPS ID: 657537

Licensing and Market Availability Plans

Garadacimab is currently in phase II/III clinical trials.

Summary

Garadacimab is in clinical development for preventing attacks in people with hereditary angioedema (HAE). HAE is a rare and potentially life-threating type of angioedema, a condition that causes sudden swelling. There are two types of HAE. Type I is more common and occurs because the body has abnormally low levels of proteins that help regulate bodily functions, such as fluids moving in and out of cells. Type II is less common and is caused by the body producing abnormal proteins. People who have HAE have a 50% chance of passing it on to their children. Symptoms of angioedema include swollen skin, mainly around the hands, feet, eyes, lips, and genitals. In people with HAE, symptoms can keep recurring and become more severe. They can experience swelling of the throat or voice-box, which leads to pain, difficulties in swallowing and speaking, and can lead to potentially life-threatening oxygen deprivation.

Garadacimab is delivered through an injection and is designed to target a protein called XIIa. In people with HAE, the body produces too much of a compound in the blood called bradykinin. This causes the lining of blood vessels to become more permeable, which can cause leakage of fluid into bodily tissues. XIIa activates the system that causes bradykinin to form. By targeting XIIa, garadacimab works by stopping the formation of bradykinin and, consequently, helps to prevent HAE attacks. If licensed, garadacimab would provide a novel treatment option for people with HAE.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Preventing attacks in people with C1-inhibitor hereditary angioedema (HAE).[1-3]

Technology

Description

Garadacimab (CSL-312) is an investigational, first-in-class Factor XIIa-inhibitory monoclonal antibody being developed as a preventative treatment for patients with HAE. HAE is a type of bradykinin-mediated angioedema.[4] In HAE, uncontrolled activation of the plasma kallikrein-kinin system and overproduction of bradykinin increases endothelial permeability and causes leakage of fluid into the interstitial tissues. Activation of Factor XII initiates the kallikrein-kinin system, which leads to the formation of bradykinin.[5] Garadacimab works by targeting FXIIa, inhibiting the HAE cascade at its origin by preventing bradykinin formation.[4]

Garadacimab is in clinical development for patients with HAE. In a phase III randomised controlled trial (VANGUARD, NCT04656418), children and adults aged 12 and over with HAE were randomised to either 200 mg of garadacimab after a 400 mg loading dose or matched placebo via subcutaneous (SC) administration.[2,5]

Key Innovation

Currently, approved prophylactic treatments for HAE often require frequent dosing regimens and have shown delays in reaching maximum efficacy at steady-state concentrations. As a result, patients with HAE can still have attacks during the first two months after initiating treatment.[5] A randomised phase III trial suggested that those taking SC garadacimab had significantly fewer HAE attacks than those in the placebo group. In this study, 200 mg of garadacimab was administered subcutaneously one per month after an initial loading dose.[2,5] Furthermore, a randomised phase II clinical trial showed significant reductions in rate of attacks with 200 mg and 600 mg of subcutaneous garadacimab compared with placebo and no serious adverse events.[1,6] If licensed, garadacimab would offer people with HAE another potential option for preventing attacks and could act faster than existing options.

Regulatory & Development Status

Garadacimab does not currently have marketing authorisation in the EU/UK for any indication. Garadacimab has been designated an orphan drug in the EU in 2021 for the treatment of HAE.[7]

Garadacimab is currently in phase III/ II clinical trials for:[8]

- COVID-19
- idiopathic pulmonary fibrosis
- paediatric HAE

Patient Group

Disease Area and Clinical Need

Angioedema is a sudden swelling often caused by an allergic reaction. HAE is a rare and potentially life-threatening type of the condition.[9] There are two main types of HAE. The most common form is HAE type I, which results from abnormally low levels of complex proteins that help regulate bodily functions such as the flow of fluids in and out of cells, called C1 esterase inhibitors, in the blood. These proteins are also known as complements. HAE type II is less common and is the result of the body producing abnormal complement proteins.[10] People with HAE have a 50% chance of passing it on their children. It is thought

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that trauma (including surgery and infection), the oral contraceptive pill and pregnancy might cause HAE to be triggered.[11] Symptoms of angioedema include swollen skin (mainly affecting the hand, feet, eyes, lips, or genitals); hot or painful sensations in the swollen areas; stomach pain; and swelling of the bladder or urethra that can cause difficulties in passing urine.[12] Symptoms of HAE can recur and become more severe, with swelling of the throat or voice-box (laryngeal oedema) resulting in pain, difficulty in swallowing and speaking, and potentially life-threatening asphyxiation.[10]

It is estimated that between 1 in 10,000 to 50,000 people are affected by HAE worldwide,[13] while in the United Kingdom it is estimated that 1 in 59,000 people will have HAE.[14] It has been estimated that the death rate for those with laryngeal oedema worldwide is 1 in 20,[15] while an audit in the UK stated there were 55 deaths from HAE across 33 families.[16]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently do not have published clinical guidelines on preventing attacks in people with HAE but have published technology assessments recommending berotralstat and lanadelumab for preventing HAE attacks.[17,18] The National Health Service (NHS) recommends danazol and tranexamic acid for preventing attacks associated with HAE and C1-inhibitors for preventing attacks caused by surgical trauma.[19]

Clinical Trial Information

Trial	NCT04739059, EudraCT-2020-003918-12; An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema **Phase III** - Active, not recruiting **Location(s):** 5 EU countries, USA, Canada, and other countries **Study completion date (estimated):** November 2025
Trial Design	Single group assignment, non-randomised, open-label
Population	N = 171; children and adults aged 12 and over with clinically-confirmed C1-inhibitor HAE who have experienced three or more HAE attacks in the three months prior to screening, participated in the run-in period for at least one month and experienced an average of one HAE attack per month during the run-in period
Intervention(s)	Garadacimab
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Number of subjects with treatment emergent adverse events (TEAEs) [Time Frame: Up to 45 months] • Percentage of subjects with TEAEs [Time Frame: Up to 45 months] • TEAEs rates per injection [Time Frame: Up to 45 months] • TEAEs rates per subject year [Time Frame: Up to 45 months] See trial record for full list of other outcomes.
Results (efficacy)	-

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Results (safety)	-

Trial	**VANGUARD;** NCT04656418, EudraCT-2020-000570-25; A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema **Phase III** – Completed **Location(s):** 3 EU countries, USA, Canada, and other countries **Study completion date:** June 2022
Trial Design	Randomised, parallel-assignment, double-blind,[5] placebo-controlled
Population	N = 64 (actual), children and adults aged 12 and over with a clinical diagnosis of C1-inhibitor HAE and have experienced three or more attacks during the three months before screening.
Intervention(s)	Garadacimab delivered as a 400 mg loading dose of two 200 mg SC injections in month one, then one monthly 200 mg SC injections from months two to six.
Comparator(s)	Matched placebo loading dose as SC injection in month one, followed by matched placebo SC injections once per month from months two to six.
Outcome(s)	Primary outcome measure: • Time-normalised number of HAE attacks per month during treatment period [Time Frame: First injection up to 6 months] See trial record for full list of other outcomes.
Results (efficacy)	During the 6-month treatment period (day 1 to day 182), the mean number of investigator-confirmed hereditary angioedema attacks per month was significantly lower in the garadacimab group (0.27, 95% CI 0.05 to 0.49) than in the placebo group (2.01, 1.44 to 2.57; p<0.0001), corresponding to a percentage difference in means of −87% (95% CI −96 to −58; p<0.0001). The median number of hereditary angioedema attacks per month was 0 (IQR 0.00–0.31) for garadacimab and 1.35 (1.00–3.20) for placebo.[5]
Results (safety)	The most common treatment-emergent adverse events were upper-respiratory tract infections, nasopharyngitis, and headaches. FXIIa inhibition was not associated with an increased risk of bleeding or thromboembolic events.[5]

Trial	NCT03712228, EudraCT- 2018-000605-24; A Multicenter, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in Subjects With Hereditary Angioedema **Phase II** – Completed **Location(s):** Germany, USA, Canada, and Israel

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	Study completion date: October 2021
Trial Design	Randomised, parallel-assignment, double-blind,[6] placebo-controlled
Population	N = 32 (actual)[a], adults aged between 18 and 65 with a diagnosis of C1 inhibitor HAE or FXII/PLG HAE
Intervention(s)	75 mg, 200 mg or 600 mg garadacimab[6]
Comparator(s)	Placebo
Outcome(s)	Primary outcome measure: • Mean time normalised number of HAE attacks per month in subjects with C1-inhibitor HAE during treatment period 1 [Time Frame: 13 weeks] See trial record for full list of other outcomes.
Results (efficacy)	The median number of monthly attacks during the 12-week subcutaneous treatment period was 4.6 (IQR 3.1–5.0) with placebo, 0.0 (0.0–0.4) with 75 mg garadacimab, 0.0 (0.0–0.0) with 200 mg garadacimab, and 0.3 (0.0–0.7) with 600 mg garadacimab. Compared with placebo, the rate of attacks was significantly reduced with garadacimab at 200 mg (reduced by 100% [95% CI 98–101]; p=0.0002) and 600 mg (reduced by 93% [54–110]; p=0.0003).[6]
Results (safety)	No serious adverse events, deaths, or adverse events of special interest (anaphylaxis, thromboembolic events, and bleeding events) were observed.[6]

Estimated Cost

The cost of garadacimab is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over (GID-TA11334). Expected date of issue to be confirmed.
- NICE technology appraisal. Berotralstat for preventing recurrent attacks of hereditary angioedema (TA738). October 2021.
- NICE technology appraisal. Lanadelumab for preventing recurrent attacks of hereditary angioedema (TA606). October 2019.

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

[a] Information provided by CSL Behring UK Ltd

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