Health Technology Briefing
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Zavegepant for treating acute migraine

Company/Developer	Pfizer Limited (UK)

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27207	NICE ID: Not available	UKPS ID: 671009

Licensing and Market Availability Plans

Zavegepant is currently in phase II/III clinical development.

Summary

Zavegepant is in clinical development for the acute treatment of migraine. Migraines is a headache that is usually characterised by throbbing in one side of the head. In addition to this, other symptoms include sensitivity to light and sound, nausea and vomiting. The cause of migraines is not known but some triggers include tiredness, anxiety and too much caffeine. Migraines are also thought to be genetic. The two major types are migraine with aura and migraine without aura. Patients experiencing aura can experience problems with sight, numbness and dizziness. Migraine without aura are the most common and usually last 4-72 hours. There remains unmet need in acute migraine treatment such as fast acting relief from pain, and alternatives to oral products that cannot be taken by some patients due to nausea and vomiting.

Zavegepant works by inhibiting the function of a chemical messenger called calcitonin gene-related peptide (CGRP) which is involved in the development of migraines. When zavegepant blocks CGRP it reduces migraine pain and other associated symptoms. Zavegepant is the first CGRP receptor antagonist (type of drug) nasal spray for the acute treatment of migraine in adults. A considerable number of people with migraine are unable to use one or more acute medications due to other conditions. If licenced, zavegepant will offer an additional treatment option for the acute treatment of migraine.

Proposed Indication

Treatment of acute migraine in patients aged 18 years and older.[1]

Technology

Description

Zavegepant (Zavzpret) is a high-affinity, selective, and structurally unique small molecule calcitonin gene-related peptide-receptor (CGRP) antagonist that is formulated as a nasal spray.[2] The pathophysiology of migraine is not fully understood; however, specific vasoactive substances and neurotransmitters such as CGRP, neurokinin A, nitric oxide, and substance P may participate in the neurovascular and cortical spreading depression mechanisms.[3] In acute migraine, the release of CGRP increases vasodilation and modulates neuronal excitability, which facilitates pain responses in structures for migraine pain transmission, such as the trigeminal system.[4] Therefore, CGRP receptor antagonists such as zavegepant inhibit vasodilation mechanisms and desensitize neuronal circuits.[5]

Zavegepant is in development to treat acute migraine. In the pivotal phase III, double-blind, randomised controlled trial (NCT04571060) intranasal formulation of zavegepant was administered at doses of 10mg on occurrence of migraine with moderate or severe intensity.[6,7] In addition, the safety and efficacy of zavegepant was evaluated in an earlier dose-ranging phase II/III clinical trial (NCT03872453) at doses of 5, 10 and 20 mg.[1] Long term safety was assessed at doses of 10mg up to 8 times per month for one year in the phase II/III clinical trial (NCT04408794).[8]

Key Innovation

Zavegepant is the first CGRP receptor antagonist nasal spray for treatment of acute migraine in adults.[2] Zavegepant is administered through an intra-nasal spray that absorbs rapidly. Peak plasma concentration of zavegepant was observed at approximately 30 minutes after a single 10 mg dose of the nasal spray.[9] Therefore, it could be useful as an important attribute in acute migraine treatment is the speed of which it works. It might also be an alternative for patients who cannot take oral treatment due to nausea and vomiting.[10]

A considerable proportion of people with migraine are unable to use one or more acute medications because of medical or behavioural comorbidities. Triptans are contraindicated in people with symptomatic cardiovascular disease , including coronary artery disease, stroke/transient ischemic attack, peripheral vascular disease, and uncontrolled hypertension.[11] Non-steroidal anti-inflammatory drugs (NSAIDs) carry a boxed warning for the increased risk of serious thrombotic cardiovascular events; the warning also calls out the elevated risk for serious GI bleeding among people with a history of bleeding. Both warnings reduce the number of people with migraine who are able to safely use these products..[11] If licensed zavegepant may address this unmet need and offer an additional treatment option for patients experiencing migraine.

Regulatory & Development Status

Zavegepant does not currently have marketing authorisation in the EU/UK for any indication.

Zavegepant is not in phase II/III clinical development for any other indications.

Patient Group

Disease Area and Clinical Need

Migraine is a moderate to severe headache characterised by throbbing pain on one side of the head.[12] Other common symptoms include an increased sensitivity to light, sound and odour, nausea and vomiting.[13] Some symptoms develop before the migraine starts including tiredness, changes in mood, a stiff neck, urinating more frequently, craving certain foods and feeling thirsty. The two major types are migraine with aura and migraine without aura. Aura can include problems with sight, numbness, dizziness, a tingling feeling and difficulty speaking.[12] Migraine without aura are the most common type of migraine and usually last between 4 and 72 hours.[14] The cause of migraine is not known, but the pain is caused by the activation of nerve fibres within the wall of brain blood vessels travelling inside the meninges (three layers of membranes protecting the brain and spinal cord).[13] However, there are multiple migraine triggers including anxiety and depression, stress and tiredness, not eating regularly, too much caffeine, a lack of exercise and the start of a period.[12] Migraines are also genetic and most migraine sufferers have a family history of the disorder. In addition, migraines frequently occur in people who have other medical conditions. Depression, anxiety, bipolar disorder, sleep disorders, and epilepsy are more common in individuals with migraine than in the general population.[13]

An estimated 190,000 migraine attacks are experienced every day in England with prevalence of 5-25% in women and 2-10% in men.[15] In England, 2022-23, there were 1,539 finished consultant episodes (FCE) and 1,458 admissions for migraine without aura (ICD-10 code G43.0) which resulted in 402 FCE bed days and 1,152 day cases. There were also 5,883 FCE and 4,628 admissions for migraine with aura (ICD-10 code G43.1) which resulted in 5,514 FCE bed days and 1,168 day cases.[16]

Recommended Treatment Options

NICE recommended treatments for adults with acute migraine include:

- Rimegepant is recommended as an option for the acute treatment of migraine with or without aura in adults, with restrictions.[17]
- Combination therapy of oral triptan with an NSAID or paracetamol.[18]
- Monotherapy with an oral triptan, NSAID, asprin, or paracetamol.[18]

Clinical Trial Information

Trial	NCT04571060; Double-Blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3500 (Zavegepant) Intranasal for the Acute Treatment of Migraine **Phase III –** Completed **Location(s):** USA **Actual study completion date:** October 2021
Trial Design	Randomised, parallel assignment, double blind
Population	N=1978; participants with at least 1 year history of migraine (with or without aura); aged 18 and older
Intervention(s)	10mg intranasal dose of zavegepant

Comparator(s)	Placebo
Outcome(s)	Primary outcomes: - Percentage of participants with freedom from pain at 2 hours post-dose [time frame: 2 hours post-dose] - Percentage of participants with freedom from most bothersome symptom at 2 hours post-dose [time frame: 2 hours post-dose] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	NCT03872453; Phase II/III: Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine **Phase II/III –** Completed **Location(s):** USA **Actual study completion date:** November 2019
Trial Design	Randomised, parallel assignment, double blind, placebo-controlled
Population	N=2154; participants have at least 1-year history of migraine; aged 18 years and older
Intervention(s)	Single 5, 10 and 20 mg intranasal dose of zavegepant
Comparator(s)	Placebo
Outcome(s)	Primary outcomes: - Percentage of participants with freedom from pain at 2 hours post-dose [time frame: 2 hours post-dose] - Percentage of participants with freedom from most bothersome symptom at 2 hours post-dose [time frame: 2 hours post-dose] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	NCT04408794; A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (Zavegepant*) Intranasal (IN) for the Acute Treatment of Migraine **Phase II/III –** Completed **Location(s):** USA **Actual study completion date:** December 2021
Trial Design	Open label, single group assignment
Population	N=974; participants with acute migraine; ages 18 and older
Intervention(s)	10mg intranasal dose of zavegepant up to 8 times per month, up to 1 year

Comparator(s)	No comparator
Outcome(s)	Primary outcomes: - Number of participants with adverse events (AEs), serious adverse events and AEs leading to discontinuation [time frame: from study drug dosing up to the end of the study (up to 52 weeks)] - Number of participants with clinically significant laboratory abnormalities [time frame: from study drug dosing up to the end of the study (up to 52 weeks)] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of zavegepant is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Rimegepant for treating migraine (TA919). October 2023.
- NICE clinical guideline. Headaches in over 12s: diagnosis and management (CG150). December 2021.
- NICE quality standard. Headaches in over 12s (QS42). August 2013.
- NICE interventional procedure guidance. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (IPG740). October 2022.
- NICE interventional procedure guidance. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (IPG559). May 2016.
- NICE interventional procedure guidance. Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). March 2016.
- NICE interventional procedure guidance. Transcranial magnetic stimulation for treating and preventing migraine (IPG477). January 2014.
- NICE interventional procedure guidance. Percutaneous closure of patent foramen ovale for recurrent migraine (IPG370). December 2010.

NHS England (Policy/Commissioning) Guidance

- NHS England. NHS Standard Contract for Specialised Pain. D08/S/a.
- NHS England. NHS Standard Contract for Neurosurgery. D03/S/a.
- NHS England. Clinical Commissioning Policy: Occipital Nerve Stimulation for Adults with Intractable Chronic Migraine and Medically Refractory Chronic Cluster Headaches. D08/P/c. July 2015.

Other Guidance

- Scottish Intercollegiate Guidelines Network. Pharmacological management of migraine. 2023.[19]
- British Association for the Study of Headache. National Headache Management System for Adults. 2019.[20]

- Berkshire West Integrated Care System. Migraine: Acute Therapy Guidelines. 2015.[21]

Additional Information

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