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HEALTH TECHNOLOGY BRIEFING
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Eptinezumab for prevention of Migraine

NIHRIO ID	8689	**NICE ID**	9871
Developer/Company	Lundbeck Ltd	**UKPS ID**	654593

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

SUMMARY

Eptinezumab is a medicinal product currently in clinical development for the prevention of migraine. A migraine is usually a moderate or severe headache felt as a throbbing pain on one side of the head. Many people also have symptoms such as nausea, vomiting and increased sensitivity to light or sound. Migraines may be with aura (specific warning signs just before the migraine begins, such as seeing flashing lights), although the most common type is without aura (no specific warning signs).

Eptinezumab is a drug, which potentially reduces the occurrence of migraine by blocking the CGRP ligand (a protein) from attaching to, and activating its receptor; a process thought to be involved in migraine. In clinical trials, eptinezumab appears effective and well tolerated in the prevention of migraine. If licenced, eptinezumab will offer an additional option for the preventative treatment of migraine with or without aura in adults.

PROPOSED INDICATION

Prophylaxis of migraine in adults experiencing at least 4 migraine days per month.[1,2]

TECHNOLOGY

DESCRIPTION

Eptinezumab (Vyepti, ALD403) is a humanized monoclonal antibody that binds to human calcitonin gene-related peptide (CGRP).[3] CGRP is present in sensory neurons, including in the trigeminal ganglion and nerve endings as well as dorsal root ganglia and while the mechanism of action is not completely understood, there is evidence that it plays a role in the pathology of migraine. For example, serum CGRP levels are elevated interictally in chronic migraine and to a lesser extent in episodic migraine.[4] By binding to the CGRP ligand, eptinezumab blocks its ability to bind to the receptor, potentially reducing the incidence of migraine.[3]

Eptinezumab is currently in phase III clinical development for the prophylactic treatment of migraine (NCT02985398, NCT02974153 and NCT02559895). The proposed treatment regimen is eptinezumab administered intravenously as 100mg or in some patients 300mg infusions, every 3 months.[1,5]

INNOVATION AND/OR ADVANTAGES

Eptinezumab differs from other CGRP antibodies in development, as it is administered intravenously rather than by subcutaneous injection and it has a 3-month dosing interval, rather than monthly.[6]

Results from the phase 3 trial (Promise 1 and 2) demonstrate that eptinezumab appears effective and well tolerated for the preventive treatment of migraine.[7,8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

In February 2020 the U.S. FDA approved eptinezumab for the preventive treatment of migraine in adults.[3]

Eptinezumab is currently in phase III development for the treatment of acute attack of migraine in adults.[9]

PATIENT GROUP

DISEASE BACKGROUND

A migraine is usually a moderate or severe headache felt as a throbbing pain on one side of the head. Many people also have symptoms such as nausea, vomiting and increased sensitivity to light or sound. Migraines may be with aura (specific warning signs just before the migraine begins, such as seeing flashing lights), although the most common type is without aura (no specific warning signs).[10] Episodic migraine is characterized by those with migraine who have 0 to 14 headache days per month, while chronic migraine is characterized by 15 or more headache days per month.[11]

The exact cause of migraine is unknown, although they are thought to be the result of temporary changes in the chemicals, nerves and blood vessels in the brain.[12] People with migraine often describe

'trigger factors' that increase the likelihood of them having a migraine attack. Examples of triggers include hormonal changes in women (such as changes that occur during the menstrual cycle), exposure to bright light, lack of sleep, hunger or dehydration, and stress.[13] Alternatively, migraine attacks may occur for no apparent reason.[14] Genes may play a role, as around half of people who experience migraine also have a close relative with the condition.[10]

In the hours (or even days) before and after a migraine attack, a person may experience symptoms such as tiredness, difficultly concentrating, or neck stiffness.[15] The disease can interfere significantly with occupational, educational, household, family, and social responsibilities.[16]

CLINICAL NEED AND BURDEN OF DISEASE

Migraine is a common health condition, affecting around one in every five women and around one in every 15 men. They usually begin in early adulthood.[10] Research suggests that 3,000 attacks occur every day per 1,000,000 population, equating to over 190,000 migraine attacks every day in the UK. It is estimated that the UK population loses 25 million days from work or school each year because of migraine, costing £2.25 billion per year. Migraine is estimated to cost the NHS in the UK £150 million per year, mostly from the costs of prescription drugs and GP visits.[17] It is also the second largest cause of years lost to disability.[16]

In 2018/19 there were 29,825 hospital admissions with primary diagnosis of migraine (ICD-10: G43), and 37,610 finished consultant episodes (FCEs), resulting in 29,616 FCE bed days and 6,883 day cases.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Migraine can be diagnosed by a GP using a table of headache features. Patients may be offered acute treatment (to be taken at onset of a migraine) or prophylactic treatment (used to reduce the number of attacks). Non-drug interventions including physical therapy, dental treatment or psychological therapy may also be useful.[19,20]

Examples of interventional procedures include: transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine, transcranial magnetic stimulation for treating and preventing migraine and occipital nerve stimulation for intractable chronic migraine.[21] If pharmaceutical prophylactics are unsuitable or ineffective, a course of up to 10 sessions of acupuncture over 5–8 weeks can also be considered.[21]

CURRENT TREATMENT OPTIONS

For the prophylactic treatment of migraine NICE recommends the following, with the choice of treatment being dependent on the person's preference, comorbidities and risk of adverse events:[19]

- Propranolol
- Topiramate
- Amitriptyline
- Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine) that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.

- The food supplement, riboflavin (400 mg[3] once a day) may be effective in reducing migraine frequency and intensity for some people and it can be suggested to people with migraine.

PLACE OF TECHNOLOGY

If licenced, eptinezumab will offer an additional option for the prophylactic treatment of migraine in adults.

CLINICAL TRIAL INFORMATION

Trial	**PREVAIL, NCT02985398;** An Open Label Phase 3 Trial to Evaluate the Safety of ALD403 Administered Intravenously in Patients With Chronic Migraines **Phase III - Completed** **Location:** United States
Trial design	Single group assignment, open-label study
Population	N = 128, aged 18 to 65 years, diagnosed with migraines at ≤ 50 years of age, and have a history of chronic migraine for ≥ 12 months before screening.
Intervention(s)	Eptinezumab intravenously at a 300mg dose.
Comparator(s)	None
Outcome(s)	Primary outcomes: • Laboratory variables & ECG [Time frame: 104 weeks] • Adverse Events [Time frame: 104 weeks] See trial record for full list of other outcomes.
Results (efficacy)	• Mean Headache Impact Test (HIT-6) total scores decreased from 65.2 at baseline to 57.1 (-8.0) at month 1, with reductions generally similar through months 3 through 12 (month 12 mean, 56.9 [±8.69]; change from baseline, -8.3), all of which were statistically significant (*P* <.001).[22] • Migraine Disability Assessment (MIDAS) mean total score at baseline was 56.8, which decreased to 20 (mean change -36.3) at month 3, and continued to decrease through months 6 and 9. Changes were generally maintained at month 12, with all reductions from baseline statistically significant (P <.001).[22]
Results (safety)	-

Trial	**PROMISE 2, NCT02974153,** 2016-001306-41; A Parallel Group, Double-Blind, Randomized, Placebo Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients With Chronic Migraine **Phase III - Completed** **Location:** EU countries (inc UK), United States and other countries.
Trial design	Parallel group, double blind, randomised, placebo controlled.
Population	N = 1,121, aged 18 to 65 years, diagnosed with migraines at ≤ 50 years of age, and have a history of chronic migraine for ≥ 12 months before screening, headaches occurring on ≥ 15 to ≤ 26 days of which at least 8 must be migraine days in screening period.
Intervention(s)	Eptinezumab intravenously at a dose of 100mg or 300mg.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome:

	• Change in frequency of migraine days [Time frame: 12 weeks] See trial record for full list of other outcomes.
Results (efficacy)	• Mean migraine frequency at baseline was approximately 16.1 migraine days per month and was similar across treatment groups. • Mean change from baseline in mean Monthly Migraine Days (MMD) compared with placebo months 1-3: -7.7 days for 100 mg (p<0.001), -8.2 days for 300 mg (p<0.001), and -5.6 days for placebo. • Percent responders with at least 50% reduction in MMD in months 1-3 compared with placebo: 57.6% for 100 mg (p<0.001), 61.4% for 300 mg (p<0.001), and 39.3% for placebo. • Percent responders with at least 75% reduction in MMD in months 1-3: 26.7% for 100 mg (p<0.001), 33.1% for 300 mg (p<0.001), and 15.0% for placebo. • An approximate 50% reduction in migraine at day 1 after the infusion was seen for 100 mg and 300 mg, respectively. • Greater percentage of placebo-treated patients had migraine on each individual day during the first 7 days of treatment compared to eptinezumab-treated patients.[3,8]
Results (safety)	• The most common (incidence at least 2% and at least 2% greater than placebo) adverse reactions was nasopharyngitis. Other adverse events included: upper respiratory tract infections, sinusitis, migraine, urinary tract infection, nausea and fatigue. • Less than 1 % at placebo or 100 mg and 1.2 % at 300 mg discontinued because of adverse reactions.[8]

Trial	**PROMISE 1, NCT02559895;** A Parallel Group, Double-Blind, Randomized, Placebo Controlled, Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients With Frequent Episodic Migraines **Phase III - Completed** **Location:** United States and Georgia
Trial design	Parallel group, double blind, randomised, placebo controlled.
Population	N = 900, aged 18 years to 75 years, diagnosis of migraine at ≤ 50 years of age, historic of migraine ≥ 12 months with ≤ 14 headache days of which at least 4 have to be migraine days in each 28 day period.
Intervention(s)	Eptinezumab intravenously at a dose of 30mg, 100mg or 300mg.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Change in frequency of migraine days (MMD) [Time frame: 12 weeks] See trial record for full list of other outcomes.
Results (efficacy)	• Mean migraine frequency at baseline was approximately 8.6 migraine days per month and was similar across treatment groups.[23] • Mean change from baseline in mean MMD compared with placebo months 1-3: -3.9 days for 100 mg (p=0.018), -4.3 days for 300 mg (p<0.001), and -3.2 days for placebo.

	• Percent responders with at least 50% reduction in MMD in months 1-3 compared with placebo: 49.8% for 100 mg (p=0.009), 56.3% for 300 mg (p<0.001), and 37.4% for placebo. • An approximately 50 % reduction in migraine at day 1 after the infusion was seen for 100 mg and 300 mg, respectively. • Percent responders with at least 75% reduction in MMD in months 1-3: 22.2%for 100 mg (not statistically significant), 29.7% for 300 mg (p<0.001), and 16.2% for placebo.[7,23]
Results (safety)	• The most common (incidence at least 2% and at least 2% greater than placebo) adverse reactions were upper respiratory tract infection, nasopharyngitis and fatigue. • Adverse effect leading to withdrawal: 2.7 % in the placebo group, 5.5% in the eptinezumab 30 mg group, 2.7% in the eptinezumab 100 mg group, and 2.2% in the eptinezumab 300 mg group.[7]

ESTIMATED COST

The cost of eptinezumab is unknown.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Erenumab for preventing migraine (GID-TA10302). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Fremanezumab for preventing migraine (GID-TA10339). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Galcanezumab for preventing migraine (GID-TA10454). Expected: October 2020.
- NICE technology appraisal guidance. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260). June 2012.
- NICE clinical guideline. Headaches in over 12s: diagnosis and management (CG150). September 2012.
- 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 (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.

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 Migraines and Medically Refractory Chronic Cluster Headaches. D08/P/c. July 2015.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network. Pharmacological management of migraine (SIGN 155). 2018.[24]
- British Association for the Study of Headache. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache, Medication-Overuse Headache. 3rd Edition. 2010.[20]

ADDITIONAL INFORMATION

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