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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Lasmiditan for acute treatment of migraine

NIHRIO ID	6824	**NICE ID**	9687
Developer/Company	Eli Lilly and Company Ltd	**UKPS ID**	654625

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

SUMMARY

Lasmiditan is a medicinal product currently in clinical development for the acute treatment 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).

Lasmiditan presumably exerts its therapeutic action in the treatment of migraine through effects at a specific serotonin receptor called 5-HT1F; however, the precise mechanism is unknown. If licenced, lasmiditan will offer an additional option for first and/or second-line acute treatment of migraine with or without aura in adults.

PROPOSED INDICATION

The acute treatment of migraine with or without aura in adults.[1]

TECHNOLOGY

DESCRIPTION

Lasmiditan (Reyvow, COL-144, LY573144) is a high-affinity, highly selective 5-hydroxytryptamine 1F (5-HT1F) receptor agonist and a first in class ditan.[2] The 5-HT1F receptor subtype is located in the trigeminal ganglion, the trigeminal nucleus caudalis and cephalic blood vessels but does not have vasoconstrictive effects like the 5-HT1B receptor subtype.[3] It is presumed that lasmiditan acts therapeutically on the trigeminal system without causing vasoconstriction due to its low affinity for 5-HT1B receptors.[4] However, the precise mechanism is unknown.[5]

In the phase III clinical trials (NCT02605174, NCT02439320 and NCT03670810) lasmiditan is administered as an oral tablet at 50mg, 100mg or 200mg, taken at the onset of a migraine attack with a second dose allowed for the recurrence of migraine within 24 hours.[1,6,7]

INNOVATION AND/OR ADVANTAGES

Current treatment options include triptans that target 5-HT1B/1D receptors and have vasoconstrictive affects which can cause complications in migraine patients with coexisting cardiovascular disorders.[3] Existing treatment options can be limited due to these contraindications, increasing the burden associated with monitoring, or patient avoidance of side effects. Alongside this, up to 40% of people with migraine do not get adequate responses from their initial triptan showing significant unmet need.[8]

Lasmiditan is the first and only molecule in the alternative ditan class and represents a novel mechanism that targets the underlying pathophysiology of migraine without causing vasoconstriction and a potential treatment option for patients that do not respond to current treatment.[2,9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lasmiditan does not currently have Marketing Authorisation in the EU for any indication.

Lasmiditan is currently in phase III development for acute migraine in adults and in phase I development for migraine in children aged 6 to 17.[10,11,12]

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).[13] The disease can interfere significantly with occupational, educational, household, family, and social responsibilities.[9]

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. Genes may play a role, as around half of people who experience migraine also have a close relative with the condition. Migraine attacks may be associated with certain triggers, which can include starting menses, stress, tiredness, or certain foods or drinks.[13]

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.[13] 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.[14] It is also the second largest cause of years lost to disability.[9]

In 2018/19 there were 29,825 hospital admissions with primary diagnosis of migraine (ICD-10 code: G43), and 37,610 finished consultant episodes (FCEs), resulting in 29,616 FCE bed days and 6,883 day cases.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Acute 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.[16,17]

CURRENT TREATMENT OPTIONS

For adults with migraine (with or without aura) NICE recommends:[18]

- Combination therapy with an oral triptan and a non-steroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, taking into account the person's preference, comorbidities and risk of adverse events.
- For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900mg) or paracetamol, taking into account the person's preference, comorbidities and risk of adverse events.
- For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) are ineffective or not tolerated, offer a non-oral preparation of metoclopramide or prochlorperazine and consider adding a non-oral NSAID or triptan if these have not been tried.

PLACE OF TECHNOLOGY

If licenced, lasmiditan will offer an additional option for the acute treatment of migraine with or without aura in adults.

CLINICAL TRIAL INFORMATION

Trial	NCT03670810, 2018-001661-17; Randomised Controlled Trial of Lasmiditan Over Four Migraine Attacks

	Phase III **Location(s):** EU (including the UK), USA and other countries.
Trial design	Randomised, parallel assignment, placebo-controlled.
Population	N=1600 (planned); 18 years and older; migraine with or without aura; onset before age 50; history of 3 to 8 migraine attacks per month.
Intervention(s)	High or low dose oral lasmiditan
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Percentage of participants that are pain free 2 hours post-dose during the first attack [Time frame: 2 hours post-dose] • Percentage of participants that are pain free at 2 hours post-dose in at least 2 out of 3 attacks [Time frame: 2 hours post-dose] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**SAMURAI,** NCT02439320; Lasmiditan Compared to Placebo in the Acute Treatment of Migraine **Phase III** **Location(s):** United States
Trial design	Randomised, parallel assignment, double-blind, placebo controlled.
Population	n=2232; 18 yrs and older, migraine onset before 50 yrs, disabling migraine for > year, excluding patients with Coronary Artery Disease (CAD)
Intervention(s)	Oral 100mg or 200mg lasmiditan tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: • Proportion of subjects who are Pain Free at 2 hours post dose [Time frame: 2 hours post dose] • Proportion of subjects who are Most Bothersome Symptom (MBS) free at 2 hours post dose [Time frame: 2 hours post dose] See trial record for full list of other outcomes.
Results (efficacy)	• The percentage of patients with 2-h pain freedom was 28.2% (vs. placebo, $p < 0.001$) in the 100 mg group, 32.2% (vs. placebo, $p < 0.001$) in the 200 mg group and 15.3% in the placebo group. • The percentage of patients with freedom from most bothersome symptom at 2-h was 40.9% (vs. placebo, $p < 0.001$) in the 100 mg group, 40.7% (vs. placebo, $p < 0.001$) in the 200 mg group compared to 29.5% in the placebo group.[3]
Results (safety)	• The most common adverse events were dizziness and paresthesia and both mild to moderate intensity. Dizziness occurred in 11.9% of the 100 mg group and 15.4% of the 200 mg group. Paresthesia occurred in 5.7% of the 100 mg group and 7.6% of the 200 mg group compared to 3.1% and 2.1% in the placebo group. No serious adverse events occurred.[3]

Trial	**SPARTAN, NCT02605174, 2015-005689-40;** A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute Treatment of Migraine **Phase III** **Location(s):** EU (including UK) and USA.
Trial design	Randomised, sequential assignment, double-blind, placebo-controlled.
Population	N=3005, 18 yrs and older, acute migraine with or without aura, onset before 50 yrs, disabling migraine for > year, including CAD patients.
Intervention(s)	Oral 50 mg, 100 mg and 200 mg lasmiditan tablets
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: • Percentage of participants headache pain free at 2 hrs post dose [Time frame: 2 hrs post dose] • Percentage of participants who are MBS free [Time frame: 2 hrs post dose]. See trial record for full list of other outcomes.
Results (efficacy)	• The percentage of patients with 2-h pain freedom was 28.6% (vs. placebo, p = 0.003) in the 50 mg group, 31.4% (vs. placebo, p < 0.001) in the 100 mg group, 38.8% (vs. placebo, p < 0.001) in the 200 mg group and 21.3% in placebo group. • Percentage of patients with freedom from most bothersome symptom at 2-h was 40.8% (vs. placebo, p = 0.009) in the 50 mg group, 44.2% (vs. placebo, p < 0.001) in the 100 mg group, 48.7% (vs. placebo, p < 0.001) in the 200 mg group and 33.5% in the placebo group.[3]
Results (safety)	• Adverse events included dizziness, paresthesia, somnolence, fatigue, nausea and lethargy.[3]

Trial	**GLADIATOR, NCT02565186, 2015-005674-37;** An Open-label, Long-term, Safety Study of Lasmiditan for the Acute Treatment of Migraine **Phase III extension** **Location(s):** EU (including UK) and USA.
Trial design	Randomised, prospective, parallel assignment.
Population	N=2468; 18 yrs and older; Completed COL MIG-301/LAHJ (NCT02439320) or COL MIG-302/LAHK (NCT02605174) within the last 4 wks.
Intervention(s)	Oral 100mg or 200mg lasmiditan tablet
Comparator(s)	-
Outcome(s)	Primary outcome: Safety [Time frame: up to 12 mths] Adverse events will be summarized in terms of the proportion of patients and the proportion of attacks associated with any adverse event and with specific adverse events. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	Interim results:

	• The most frequent treatment-emergent adverse events (TEAEs) (≥2%) were dizziness (18.6%), somnolence (sleepiness or drowsiness; 8.5%), paresthesia (tingling or numb sensation on the skin; 6.8%), fatigue (5.5%), nausea (4.7%) and asthenia (physical weakness or lack of energy; 2.0%).[19]

ESTIMATED COST

The cost of lasmiditan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- 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.[20]
- 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.[17]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *Lasmiditan Compared to Placebo in the Acute Treatment of Migraine: (SAMURAI). Trial ID: NCT02439320*. 2015. Status: Completed Available from: https://clinicaltrials.gov/ct2/show/NCT02439320 [Accessed 28 Nov 2019].

2 NeurologyLive. *Lasmiditan Approved for Acute Migraine Treatment in Adults.* 2019. Available from: https://www.neurologylive.com/clinical-focus/lasmiditan-approved-for-migraine-treatment-in-adults [Accessed 03 Jan 2020].

3 Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? *The journal of headache and pain*. 2019;20(1):37. Available from: https://doi.org/10.1186/s10194-019-0974-3.

4 Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine. *Neurology*. 2018;91(24):e2222. Available from: https://n.neurology.org/content/91/24/e2222.

5 Lilly. *Lilly's REYVOW™ (lasmiditan), The First and Only Medicine in a New Class of Acute Treatment for Migraine, Receives FDA Approval.* 2019. Available from: http://lilly.mediaroom.com/2019-10-11-Lillys-REYVOW-TM-lasmiditan-The-First-and-Only-Medicine-in-a-New-Class-of-Acute-Treatment-for-Migraine-Receives-FDA-Approval [Accessed 28 Nov 2019].

6 Clinicaltrials.gov. *Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute Treatment of Migraine (SPARTAN). Trial ID: NCT02605174*. 2015. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02605174 [Accessed 28 Nov 2019].

7 Clinicaltrials.gov. *A Study of Lasmiditan (LY573144) Over Four Migraine Attacks. Trial ID: NCT03670810*. 2018. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03670810 [Accessed 28 Nov 2019].

8 Färkkilä M, Olesen J, Dahlöf C, Stovner L, ter Bruggen J, Rasmussen S, et al. Eletriptan for the Treatment of Migraine in Patients with Previous Poor Response or Tolerance to Oral Sumatriptan. *Cephalalgia*. 2003;23(6):463-71. Available from: https://doi.org/10.1046/j.1468-2982.2003.00554.x.

9 Shapiro RE, Hochstetler HM, Dennehy EB, Khanna R, Doty EG, Berg PH, et al. Lasmiditan for acute treatment of migraine in patients with cardiovascular risk factors: post-hoc analysis of pooled results from 2 randomized, double-blind, placebo-controlled, phase 3 trials. *The journal of headache and pain*. 2019;20(1):90. Available from: https://doi.org/10.1186/s10194-019-1044-6.

10 European Medicines Agency. *EMEA-002166-PIP01-17-M02*. 2019. Available from: https://www.ema.europa.eu/en/medicines/human/paediatric-investigation-plans/emea-002166-pip01-17-m02 [Accessed 29 Nov 2019].

11 Clinicaltrials.gov. *Search: "Lasmiditan" "Phase 2, 3"*. 2019. Available from: https://clinicaltrials.gov/ct2/results?term=Lasmiditan&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 03 Jan 2020].

12 Clinicaltrials.gov. *A Study of Lasmiditan (LY573144) in Children Aged 6 to 17 With Migraine. Trial ID: NCT03988088*. 2019. Status: Recruiting. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03988088 [Accessed 15 Jan 2020].

13 National Health Service. *Migraine.* 2019. Available from: https://www.nhs.uk/conditions/migraine/ [Accessed 25 Nov 2019].

14 The Migraine Trust. *Key facts and figures about migraine.* Available from: https://www.migrainetrust.org/about-migraine/migraine-what-is-it/facts-figures/ [Accessed 25 Nov 2019].

15 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

16 National Institute for Health and Care Excellence. *Headaches in over 12s: diagnosis and management*. 2015. Available from: https://www.nice.org.uk/guidance/cg150/chapter/recommendations#diagnosis [Accessed 25 Nov 2019].

17 British Association for the Study of Headache. *Diagnosis and management of Migraine.* 2010. Available from: https://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf [Accessed 28 Nov 2019].

18 National Institute for Health and Care Excellence. *Management of migraine (with or without aura)* Last Update Date: 2015. Available from: https://pathways.nice.org.uk/pathways/headaches#path=view%3A/pathways/headaches/management-of-migraine-with-or-without-aura.xml&content=view-node%3Anodes-acute-treatment [Accessed 25 Nov 2019].

19 Lilly. *AAN 2019: Two New Analyses of Lasmiditan Phase 3 Studies Measured Onset of Effect and the Effect of Lasmiditan in Patients with Prior Triptan Experience.* 2019. Available from: http://lilly.mediaroom.com/index.php?s=9042&item=137900 [Accessed 09 Nov 2019].

20 Scottish Intercollegiate Guidelines Network. *Pharmacological management of migraine* (*SIGN 155).* Last Update Date: Available from: https://www.sign.ac.uk/assets/sign155.pdf [Accessed 03 Jan 2020].

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