

Health Technology Briefing

February 2022

Atogepant for prevention of migraine

Company/Developer

Allergan Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 13635

NICE ID: 9504

UKPS ID: 664194

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Atogepant is currently in clinical development for the prevention of migraine. Migraines can occur with or without aura. Migraine without aura is a recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraine with aura consists of recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. Preventative (prophylactic) treatment of migraine is used to reduce the number of migraines a patient experiences. However, currently available treatment options involve injections underneath the skin (subcutaneous injection), which can cause unwanted side-effects. There remains an unmet need for prophylactic treatment options to prevent migraine that can be given to patients without the need for subcutaneous injection.

Atogepant is a new type of medicinal product which works by attaching to and blocking the activity of the calcitonin gene-related peptide (CGRP) receptor. Increased amounts of CGRP have been detected in the blood during migraine attacks and elevated levels are thought to contribute to the development of migraines. Atogepant is taken as an oral tablet, providing a novel method of administration which is less likely to cause adverse reactions. If licenced, atogepant would offer an additional preventative treatment option for migraine patients.

Proposed Indication

Prophylaxis of migraine in adults.¹

Technology

Description

Atogepant (Qulipta, AGN-241689) is a calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a 37-amino acid peptide thought to be important in the pathogenesis of migraine and increased concentrations of CGRP have been detected in the cranial circulation during migraine attacks.² Serum CGRP levels are elevated interictally in chronic migraine and to a lesser extent in episodic migraine.³

Atogepant is currently in phase III clinical development for the prevention of migraines (NCT03855137, NCT04686136 and NCT04740827). The proposed treatment regimen is either a 30mg oral tablet administered twice a day, or a 60mg oral tablet administered once a day.^{1,4,5}

Key Innovation

Atogepant is the first and only oral CGRP receptor antagonist specifically developed for the preventative treatment of migraine.⁶ Current standard of care CGRP receptor antagonists are administered as subcutaneous injections which can result in adverse events, the most common of which being injection site reactions, including pain. CGRP related therapies such as atogepant are designed to act on the trigeminal pain system, making them more specific with little or no adverse effects. The development of atogepant as an orally administered CGRP receptor antagonist is advantageous for patients because, if approved, it would provide a new route of administration which will not cause injection site reactions.⁷

Regulatory & Development Status

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

In September 2021 the US FDA approved atogepant for the preventative treatment of episodic migraine in adults.⁸

Patient Group

Disease Area and Clinical Need

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 feeling sick, being sick and increased sensitivity to light or sound. Migraines without aura are the most common type, where the migraine happens without warning signs such as seeing flashing lights.⁹ This type of migraine manifests in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraines with aura consist of recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.¹⁰ The exact cause of migraines is unknown, but they are thought to be the result of abnormal brain activity temporarily affecting nerve signals, chemicals and blood vessels in the brain. It's not clear what causes this change in brain activity, but it is possible that a patient's genes make them more likely to experience migraines as a result of a specific trigger. There are many possible migraine triggers including: hormonal changes; emotional triggers such as

stress or anxiety; physical triggers such as tiredness and shoulder tension; dietary triggers; and environmental triggers such as bright lights and certain medicines.¹¹

Migraine occurs in 15% of the UK adult population.¹² The disease is more common in women, around 1 in every 5 women are affected compared to around 1 in every 15 men.^{9,13} In England (2020/21), there were 27,290 hospital admissions with primary diagnosis of migraine (ICD-10: G43), and 34,814 finished consultant episodes (FCEs), resulting in 25,807 FCE bed days and 4,867 day cases.¹⁴

Recommended Treatment Options

Prophylactic treatment of migraine is used to reduce the number of migraines the patient experiences.¹⁵ Depending on the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life, the National Institute for Health and Care Excellence (NICE) currently recommends the following prophylactic treatment options for adult patients with migraines:

- Erenumab and galcanezumab are recommended for preventing migraine in adults if the patient has at least 4 migraine days a month and at least 3 preventative drug treatments have previously failed.^{16,17}
- Fremanezumab and botulinum toxin type A are recommended for preventing chronic migraine in adults if the patient has chronic migraines (15 or more headache days a month, with at least 8 of those days having features of migraine) and at least 3 preventative drug treatments have previously failed.^{18,19}
- Fremanezumab is also recommended as an option for preventing episodic migraine in adults if: they have 4 or more migraine days a month, at least 3 preventative drug treatments have failed, and the company provides it according to the commercial arrangement.¹⁹

Clinical Trial Information

Trial	NCT02848326 ; A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study To Evaluate The Efficacy, Safety, And Tolerability Of Multiple Dosing Regimens Of Oral Atogepant In Episodic Migraine Prevention Phase III – Completed Location: US Study completion date: April 2018
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=834; adults aged 18 to 75 years; at least a 1 year history of migraine with or without aura; history of 4 to 14 migraine days per month on average in the 3 months prior to visit 1
Intervention(s)	Atogepant (oral capsule)
Comparator(s)	Matched placebo (oral capsule)
Outcome(s)	Primary outcome: Change From Baseline in Mean Monthly Migraine Days (Migraine/Probable Migraine Headache Days) Across the 12-Week Treatment Period [Time Frame: Baseline (First 28 Days of Screening/Baseline Period) to Week 12] See trial record for full list of other outcomes
Results (efficacy)	See trial record

Results (safety)	See trial record
Trial	NCT03700320 ; A Phase 3, Multicenter, Randomized, Open-label Study to Evaluate the Long-term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine Phase III – Completed Location(s): US Study completion date: May 2020
Trial Design	Randomised, parallel assignment, open-label
Population	N=744; adults aged 18 to 80 years; at least a 1 year history of migraine with or without aura; history of 4 to 14 migraine days per month on average in the 3 months prior to visit 1
Intervention(s)	Atogepant 60mg (oral tablet) once daily
Comparator(s)	Oral standard of care migraine preventative medication
Outcome(s)	Primary outcome: Percentage of Participants With at Least 1 Treatment Emergent Adverse Event (TEAE) [Time Frame: From first dose up to the end of study (median treatment of 52 weeks) + 4 weeks follow-up] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	ADVANCE, NCT03777059 ; A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine Phase III – Completed Location(s): US Study completion date: June 2020	NCT03939312 ; A Phase 3, Multicenter, Open-Label 40-week Extension Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine Phase III – Completed Location(s): US Study completion date: March 2021
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled	Non-randomised, single group assignment, open-label
Population	N=910; adults aged 18 to 80 years; at least a 1 year history of migraine with or without aura;	N=695; participated in study NCT03777059; aged 18 to 80 years old
Intervention(s)	Atogepant (oral tablet) once daily	Atogepant 60mg (oral tablet) once daily
Comparator(s)	Matched placebo (oral tablet)	No comparator

Outcome(s)	Primary outcome: Change From Baseline in Mean Monthly Migraine Days Across the 12-Week Treatment Period [Time Frame: Baseline (Day -28 to Day -1) to Week 12] See trial record for full list of other outcomes	Primary outcome: Percentage of Participants with at Least 1 Treatment Emergent Adverse Event [Time Frame: 40 Weeks] See trial record for full list of other outcomes
Results (efficacy)	See trial record	-
Results (safety)	See trial record	-

Trial	PROGRESS, NCT03855137, 2018-004337-32 ; A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Atogepant for the Prevention of Chronic Migraine Phase III – Active, not recruiting Location(s): 8 EU countries, UK, USA, Canada and other countries Primary completion date: December 2021	NCT04686136 ; A Phase 3, Multicenter, Open-Label 52-Week Extension Study To Evaluate The Long-Term Safety And Tolerability Of Oral Atogepant For The Prevention Of Migraine In Participants With Chronic Or Episodic Migraine Phase III – Recruiting Location(s): 10 EU countries, UK, USA, Canada and other countries Primary completion date: July 2023
Trial Design	Randomised, parallel assignment, triple-masked, placebo-controlled	Single group assignment, open label
Population	N=750; at least a 1 year history of chronic migraine; aged 18 to 80 years old	N=670; Subjects participated in NCT03855137 or NCT04740827 without significant protocol deviations and who did not experience an adverse event that may indicate an unacceptable safety rise; aged 18 to 80 years old
Intervention(s)	Atogepant (oral tablet)	Atogepant 60mg (oral tablet) once daily
Comparator(s)	Matched placebo (oral tablet)	No comparator
Outcome(s)	Primary outcome: Change from baseline in mean monthly migraine days across the treatment period [Time Frame: 12 Weeks] See trial record for full list of other outcomes	Primary outcome: Percentage of Participants with at Least 1 Treatment Emergent Adverse Event [Time Frame: 52 weeks] See trial record for full list of other outcomes
Results (efficacy)	-	-

Results (safety)	-	-
Trial	<p>ELEVATE, NCT04740827, 2019-003448-58; A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants With Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments Phase III – Recruiting Location(s): 10 EU countries, UK, USA, Canada and other countries Primary completion date: May 2022</p>	
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled	
Population	N=300; at least a 1 year history of migraine with or without aura; previously failed oral migraine prophylaxis medications from 2 to 4 medication classes; aged 18 to 80 years old	
Intervention(s)	Atogepant 60mg (oral tablet) once daily	
Comparator(s)	Matched placebo (oral tablet)	
Outcome(s)	Primary outcome: Change from Baseline in mean monthly migraine days across the 12-week treatment period. [Time Frame: 12 weeks] See trial record for full list of other outcomes	
Results (efficacy)	-	
Results (safety)	-	

Estimated Cost
The cost of atogepant is not yet known.

Relevant Guidance
NICE Guidance
<ul style="list-style-type: none"> • NICE technology appraisal in development. Rimegepant for treating or preventing migraine (GID-TA10839). Expected date of issue to be confirmed. • NICE technology appraisal in development. Eptinezumab for preventing migraine (GID-TA10677). Expected date of issue to be confirmed. • NICE technology appraisal in development. Fremanezumab for preventing migraine (Rapid Review of TA631) (GID-TA10915). Expected February 2022. • NICE technology appraisal. Erenumab for preventing migraine (TA682). March 2021. • NICE technology appraisal. Galcanezumab for preventing migraine (TA659). November 2020. • NICE technology appraisal. Fremanezumab for preventing migraine (TA631). June 2020. • NICE technology appraisal. 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). December 2021.

- NICE interventional procedure guidance in development. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (GID-IPG10175). Expected date to issue to be confirmed.
- 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. Occipital nerve stimulation for intractable chronic migraine (IPG452). April 2013.
- 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 Migraines and Medically Refractory Chronic Cluster Headaches. D08/P/c. July 2015.

Other Guidance

- Scottish Intercollegiate Guidelines Network. Pharmacological management of migraine. 2018.²⁰
- Berkshire West Integrated Care System. Migraine: Adult Prophylactic Therapy Guidelines. 2015.²¹
- 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. 2010.¹⁵

Additional Information

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