

**EVIDENCE BRIEFING
AUGUST 2018**

Rimegepant for the treatment of acute migraine

NIHRIO ID	7157	NICE ID	9868
Developer/Company	Biohaven Pharmaceuticals	UKPS ID	N/A

Licencing and market availability plans	Currently in phase III clinical trials
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SUMMARY

Rimegepant is a medicinal product that is in clinical development as an oral tablet for acute treatment of migraine in adults. Rimegepant works by blocking a receptor called calcitonin gene-related peptide (CGRP). This receptor plays an important role in migraine pathophysiology. 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). Migraine is a common health condition, affecting around one in every five women and around one in every 15 men.

Rimegepant potentially offers an alternative to current agents, particularly for patients who have contraindications to the use of triptans. This includes patients with underlying cardiovascular diseases, or who either do not respond or have inadequate or inconsistent response to triptans or are intolerant to them.

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 unavailable to comment.

PROPOSED INDICATION

Acute treatment of migraine in adults

TECHNOLOGY

DESCRIPTION

Rimegepant (BHV-3000) is in clinical development for acute treatment of migraine in adults. Rimegepant is an orally-dosed calcitonin gene-related peptide (CGRP) receptor antagonist.¹ CGRP plays an important role in migraine pathophysiology, and may provide a novel mechanism for acute migraine treatment.²

Activation and sensitisation of the trigeminovascular system are known to be painful, and its stimulation has been shown to result in increased levels of CGRP. CGRP is most abundant in the cerebellum, with further expression observed in several migraine-relevant brainstem, hypothalamic, and thalamic nuclei.³

In the phase III clinical trials (BHV-3000-301 (NCT03235479) and BHV3000-302 (NCT03237845)), rimegepant is administered as an oral tablet at 75mg, taken at the onset of a migraine attack.^{4,5} Rimegepant is also in phase III clinical trial as an orally disintegrating tablet at 75mg (BHV3000-303 (NCT03461757)).⁶

INNOVATION AND/OR ADVANTAGES

CGRP receptor antagonists represent a novel class of drug candidates for the treatment of migraine and are the first new class specific to the acute treatment of migraine in over 25 years. This unique and specific mode of action potentially offers an alternative to current agents, particularly for patients who have contraindications to the use of triptans. This includes patients with underlying cardiovascular diseases, or who either do not respond or have inadequate or inconsistent response to triptans or are intolerant to them.¹

Rimegepant represents a novel mechanism that targets the underlying pathophysiology of migraine without causing vasoconstriction. Additionally, rimegepant has demonstrated a liver safety profile similar to placebo.¹

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

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).⁷

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.⁷

CGRP, a neuropeptide released from activated trigeminal sensory nerves, dilates intracranial blood vessels and transmits vascular nociception. Therefore, CGRP may have an important role in migraine pathophysiology, and inhibition of trigeminal CGRP release or CGRP-induced cranial vasodilatation may abort migraine.⁸

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.⁷

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.⁹

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Acute migraine can be diagnosed by a GP using a table of headache features.¹⁰ Patients may be offered acute treatment (to be taken at onset of a migraine) or prophylactic treatment (used to reduce the number of attacks in circumstances when acute therapy, used appropriately, gives inadequate symptom control). Non-drug interventions including physical therapy, dental treatment or psychological therapy may also be useful.¹¹

CURRENT TREATMENT OPTIONS

For adults with migraine (with or without aura) NICE recommends¹²:

- 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. When prescribing a triptan, start with the one with the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.
- 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. When prescribing a triptan, start with the one with the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.
- For people in whom oral preparations 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, rimegepant may offer an alternative to current agents, particularly for patients who have contraindications to the use of triptans. This includes patients with underlying cardiovascular diseases, or who either do not respond or have inadequate or inconsistent response to triptans or are intolerant to them.

CLINICAL TRIAL INFORMATION

Trial	NCT03235479 , BHV-3000-301; rimegepant vs placebo; phase III	NCT03266588 , BHV3000-201; rimegepant; phase III extension study
Sponsor	Biohaven Pharmaceuticals, Inc.	Biohaven Pharmaceuticals, Inc.
Status	Published in abstract	Ongoing
Source of Information	Trial registry, ⁴ poster ¹³	Trial registry ¹⁴
Location	USA	USA
Design	Randomised, placebo-controlled, double-blind	Non-randomised, open label
Participants	n=1,162; aged 18 yrs and older; at least 1-yr history of migraine, with or without aura according to the International Classification of Headache Disorder, 3rd Edition (ICHD-3) beta, 2-8 moderate or severe migraines attacks per mth, fewer than 15 monthly headache days over 3 months prior to enrolment	n=2,000 (planned); aged 18 yrs and older; 4-14 moderate or severe migraine attacks per month, age of onset of migraines <50 yrs, migraine attacks lasting 4-72 hrs on average if untreated

Schedule	Randomised to rimegepant 75mg oral tablet, or placebo 75mg oral tablet. One tablet dispensed to pt at baseline visit, for pt to take when having migraine attack	Rimegepant 75mg oral tablet. Schedule not reported.
Follow-up	Follow-up within 7 days of treatment	Follow-up 52 wks
Primary Outcomes	- Pain freedom at 2 hrs post-dose - Freedom from most bothersome symptom (MBS) at 2 hrs post-dose	Frequency and severity of treatment-emergent adverse events and discontinuations due to adverse events
Secondary Outcomes	- Photophobia-free at 2 hrs - Pain relief at 2 hrs - Nausea-free at 2hrs - Rescue medication within 24 hrs - Sustained pain-free, 2-24 hrs and 2-48 hrs - Sustained pain relief, 2-24 hrs and 2-48 hrs - Pain relapse from 2-48 hrs - Ability to function normally at 2 hrs	- Elevated liver function tests - Adverse events related to liver
Key Results	Significant and durable clinical effects were seen with a single dose or rimegepant across multiple outcome measures, including pain freedom, freedom from MBS, pain relief and recovery of normal function	-
Adverse effects (AEs)	Rimegepant 75mg oral tablet demonstrated favourable tolerability and safety, and it was comparable to placebo on tests of liver function	-
Expected reporting date	-	Study completion date reported as October 2019

Trial	NCT03237845 , BHV3000-302; rimegepant vs placebo; phase III
Sponsor	Biohaven Pharmaceuticals, Inc.
Status	Presentation
Source of Information	Trial registry, ⁵ presentation ¹⁵
Location	USA
Design	Randomised, placebo-controlled, double-blind
Participants	n=1,072; aged 18 yrs and older; at least 1-year history of ICHD-3 beta migraine, with or without aura, 2-8 moderate or severe migraines attacks per month, fewer than 15 monthly headache days over 3 months prior to enrolment
Schedule	Randomised to rimegepant 75mg oral tablet, or placebo 75mg oral tablet. One tablet dispensed to pt at baseline visit, for pt to take when having migraine attack
Follow-up	Follow-up within 7 days of treatment
Primary Outcomes	- Pain freedom at 2 hrs post-dose - Freedom from MBS at 2 hrs post-dose
Secondary Outcomes	- Photophobia-free at 2 hrs - Pain relief at 2 hrs

	<ul style="list-style-type: none"> - Nausea-free at 2hrs - Rescue medication within 24 hrs - Sustained pain-free, 2-24 hrs and 2-48 hrs - Sustained pain relief, 2-24 hrs and 2-48 hrs - Pain relapse from 2-48 hrs - Ability to function normally at 2 hrs <p>Exploratory endpoints</p> <ul style="list-style-type: none"> - Nausea-free at 3hrs - Sustained ability to function normally at 2-48 hrs - Sustained freedom from the MBS at 2-28 hrs
Key Results	Primary endpoints met, majority of patients achieve pain relief, durability of benefit (24 and 48 hours), lower use of rescue meds, greater proportion of patients achieving normal function
Adverse effects (AEs)	AEs reported: nausea (1.8%), urinary tract infection (1.5%). Safety profile similar to placebo including liver function tests, tolerability profile similar to placebo and favourable compared to historical triptan experience

Trial	NCT03461757 , BHV3000-303; rimegepant vs placebo; phase III
Sponsor	Biohaven Pharmaceuticals, Inc.
Status	Ongoing, not published
Source of Information	Trial registry ⁶
Location	USA
Design	Randomised, placebo-controlled, double-blind
Participants	n=1,812 ; aged 18 yrs and older; at least 1-year history of ICHD-3 beta migraine, with or without aura, age of onset of migraines <50 yrs, migraine attacks lasting 4-72 hrs on average if untreated, 2-8 moderate or severe migraines attacks per month, fewer than 15 monthly headache days over 3 months prior to enrolment
Schedule	Randomised to rimegepant 75mg oral disintegrating tablet (ODT), or placebo 75mg ODT
Follow-up	Not stated
Primary Outcomes	Pain freedom at 2 hrs post-dose Freedom from MBS at 2 hrs post-dose
Secondary Outcomes	Photophobia-free at 2 hrs Phonophobia-free at 2 hrs Pain relief at 2 hrs Nausea-free at 2hrs Rescue medication within 24 hrs Sustained pain-free, 2-24 hrs and 2-48 hrs Sustained pain relief, 2-24 hrs and 2-48 hrs Pain relapse from 2-48 hrs Ability to function normally at 2 hrs
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as October 2018

Trial	NCT01430442 , CN170-003; rimegepant vs placebo; phase II
Sponsor	Biohaven Pharmaceuticals, Inc.
Status	Published
Source of Information	Trial registry, ¹⁶ publication ²
Location	USA
Design	Randomised, placebo-controlled, double-blind
Participants	n=1,026; aged 18-65 yrs; at least 1-year history of ICHD-3 beta migraine, with or without aura, age of onset of migraines <50 yrs, migraine attacks lasting 4-72 hrs on average if untreated, <8 moderate or severe migraines attacks per month, fewer than 15 monthly headache days over 3 months prior to enrolment
Schedule	Randomised to receive one of six doses of rimegepant (10mg, 25mg, 75mg, 150mg, 300mg, or 600mg) or placebo or sumatriptan (100mg)
Follow-up	11 wks
Primary Outcomes	Pain freedom at 2 hrs post-dose
Secondary Outcomes	Sustained pain-free, 2-24 hrs and 2-48 hrs Pain relief at 2 hrs Sustained pain relief, 2-24 hrs Frequency and severity of adverse events (approx. 11 wks)
Key Results	Of patients who took the study drug, 799 had one post-randomization efficacy evaluation. Significantly more patients in the rimegepant 75mg (31.4%, p = 0.002), 150mg (32.9%, p < 0.001), and 300mg (29.7%, p = 0.002) groups and the sumatriptan group (35%, p < 0.001) had pain freedom at two hours post-dose versus placebo (15.3%). For the secondary endpoint of sustained pain freedom from two to 24 hours post-dose, rimegepant doses (25–600mg) were also statistically significant compared with placebo.
Adverse effects (AEs)	The most commonly seen adverse event in the rimegepant dosing groups was nausea, which was dose dependent: 1.4% in the 10mg; 0 in the 25mg; 3% in each of the 75mg and 150mg dose groups; 4% in the 300mg; and 8% in the 600mg group.

ESTIMATED COST

The cost of rimegepant 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. 2013/14 NHS Standard Contract for Pain Management (Adult). D08/S/a

OTHER GUIDANCE

- British Association for the Study of Headache (BASH). Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine. 2013.¹¹
- Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults: A national clinical guideline. 2008.¹⁷

REFERENCES

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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