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New Drug Update

## Rimegepant: first novel oral calcitonin gene-related peptide inhibitor for migraine

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### ABSTRACT

Migraine is a neurological condition characterized by intense, debilitating headaches. Symptoms may include nausea, vomiting, numbness or tingling, sensitivity to light and sound. There are multitude of drugs available to treat migraine like triptans, non-steroidal anti-inflammatory drugs, ergots and opioids. But these drugs are associated with adverse effects especially triptans causing cardiovascular effects limiting its use. During last decade, calcitonin gene-related peptide (CGRP) has emerged as a possible mechanism for management of migraine. CGRP has been shown to release during episode of migraine attack and it may play a causative role in induction of migraine. Rimegepant is a novel CGRP antagonist has been approved by FDA for treatment of acute migraine. Rimegepant is a first oral CGRP antagonist compared to other gepants. The oral bioavailability of Rimegepant is 64% and high fat meal can decrease the C<sub>max</sub>, T<sub>max</sub> and area under the curve. This drug is mainly metabolized by CYP3A4 and to lesser extent by CYP2C9. Most common adverse reactions associated with this drug were nausea and urinary tract infection. Clinical trials for Rimegepant have been positive, and results suggest that the drug may be a new safe and effective option for treatment of acute migraine.

**Keywords:** Calcitonin gene-related peptide, Migraine, Rimegepant, Triptans

### INTRODUCTION

Migraine is the most common neurological disorder presenting with the transient nature of primary headaches.<sup>1</sup> Currently, many drugs are available in the market to treat migraine, such as triptans, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ergots, and opioids. The main disadvantages of these drugs were either they have more contraindications or adverse effects. Previously, serotonin 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptor agonists (triptans) were most commonly used for acute treatment of migraine. However, only 34%

patients using triptans shows a good response while 30-40% patients have recurrent episodes.<sup>2,3</sup> In addition, more than 50% patients who received triptans developed mild and severe adverse effects including cardiovascular effects, due to the vasoconstriction effect leading to fatal consequences and limit the use of triptans in patients with cardiovascular disease comorbidity.<sup>4</sup> Most of the patients discontinued these drugs due to the lack of efficacy or troubling adverse effects.<sup>5</sup> Thus, there is still an urgent need for the development of new therapeutic methods for acute management of migraine headache.

## CALCITONIN GENE RELATED PEPTIDE AND MIGRAINE

Calcitonin gene related peptide (CGRP) is a 37 amino acid long peptide produced by the neurons in central and peripheral nervous system. CGRP was found to be involved in various activities like neuroimmune activity, vasodilatation, bone metabolism and fracture healing.<sup>6</sup> CGRP has been discovered to be associated with pathogenesis of migraine. During migraine attacks, it has been observed that there is an elevated levels of CGRP.<sup>7</sup> there are possible mechanisms including central neurogenic vasodilation, inhibiting both vascular nociceptive transmission, and thalamic trigeminal nociceptive activation.<sup>8</sup> There are several CGRP receptor antagonists (called gepants), including Olcegepant (BIBN4096BS), Telcagepant (MK-0974), (MK-3207), (BI-44370 TA), Rimegepant (BMS-927711), and Ubrogepant (MK-1602).<sup>9</sup> According to previous studies, Olcegepant and BI-44370 have good efficacy against migraine but come with relatively high toxicity. These two types of gepants thus have limited clinical usefulness.<sup>10</sup>

Rimegepant is an oral CGRP antagonist approved by FDA on February 27,2020 for the acute treatment of migraine. While several parenteral antagonists of CGRP and its receptor have been approved for migraine therapy (e.g. erenumab, fremanezumab, galcanezumab), rimegepant and ubrogepant are the only members of the "gepant" family of medications remaining in development, and the only CGRP antagonists that possess good oral bioavailability. Antagonism of the CGRP pathway has become an attractive target for migraine therapy as, unlike the triptans, oral CGRP antagonists have no observed vasoconstrictive properties and are therefore safer for use in patients with contraindications to standard therapy.<sup>9</sup>

### MECHANISM OF ACTION

The currently accepted theory of migraine pathophysiology considers dysfunction of the central nervous system, in particular the trigeminal ganglion, to be the root cause behind the condition.<sup>9</sup> Stimulation of the trigeminal ganglion triggers the activation of trigeminal afferents that project to the spinal cord and synapse on various pain-sensing intra- and extracranial structures, such as the dura mater. Pain signals are then further transmitted via second-order ascending neurons to the brainstem, hypothalamus, and thalamic nuclei, and from there to several cortical regions (e.g. auditory, visual, motor cortices).<sup>9</sup>

The trigeminal ganglion appears to amplify and perpetuate the migraine headache pain through the activation of perivascular fibres and the release of molecules involved in pain generation, such as CGRP.<sup>9</sup>

The  $\alpha$ -isoform of CGRP, expressed in primary sensory neurons, is a potent vasodilator and has been implicated in migraine pathogenesis - CGRP levels are acutely elevated during migraine attacks, return to normal following treatment with triptan medications, and intravenous infusions of CGRP have been shown to trigger migraine-like headaches in migraine patients. In addition to its vasodilatory properties, CGRP appears to be a pronociceptive factor that modulates neuronal excitability to facilitate pain responses.<sup>11</sup>

Rimegepant is an antagonist of the calcitonin gene-related peptide receptor- it competes with CGRP for occupancy at these receptors, preventing the actions of CGRP and its ability to amplify and perpetuate migraine headache pain, ultimately terminating the headache.<sup>11</sup>

### CLINICAL PHARMACOLOGY

#### *Pharmacodynamics*

Pharmacodynamics and clinical effects of Rimegepant are quite different and mechanism of action of the drug is still unknown. Even at a dose four times higher than recommended, it had no effect on QT interval.

#### *Pharmacokinetics*

Following oral administration, maximum concentration of the drug occurred at 1.5 hours. The absolute oral bioavailability is observed as approximately 64%.<sup>12</sup>

Experiments with high fat meal showed that T<sub>max</sub> is delayed by one hour, reduction in C<sub>max</sub> by 42 to 53% and a reduction of 32 to 38% in AUC. However, interaction of Rimegepant with various foods is yet to be studied. With plasma protein binding of 96%, steady state volume distribution of the drug is estimated as 120L.

Mostly, the drug is metabolised by CYP3A4 and to a lesser extent by CYP2C9. The drug is mostly eliminated in unchanged form (77%) with elimination half-life of 11 hours. The drug is seen to be eliminated mostly in faeces (78%) and to a lesser extent in urine (24%). Pharmacokinetics of the drug was independent of age, sex, race/ethnicity, body weight, or CYP2C9 genotype.

In patients with moderate renal impairment, C<sub>max</sub> and AUC were seen to be 40% higher than that of normal subjects. In patients of severe hepatic impairment, C<sub>max</sub> and AUC were twice than that of normal subjects.

#### *Drug interaction*

The drug is a substrate of CYP3A4 and CYP2C9 and not an inhibitor of CYP1A2, 2B6, 2C9, 2C19, 2D6 and UGT1A1 at clinically relevant concentrations. However, weak inhibition was seen with CYP3A4. Concomitant administration of strong inhibitors of CYP3A4 with Rimegepant should be avoided as they would result in

increased exposure of the drug. However, with moderate inhibitors of CYP3A4, dose repetition should be avoided for 48 hours. On the contrary, simultaneous administration with moderate and severe inducers of CYP3A4, would result in decreased exposure of the drug affecting its efficacy. On co-administering with oral contraceptives (norelgestromin, ethinyl estradiol), midazolam or sumatriptan, no significant pharmacokinetic interactions were observed. As the drug is a substrate of P-gp and BCRP, effects of concomitant administration with these substrate inhibitors needs to be evaluated.

### Pharmacogenomics

CYP2C9 activity is reduced in individuals with the CYP2C9\*2 and CYP2C9\*3 genetic variants. C<sub>max</sub> and AUC<sub>0-inf</sub> were similar in CYP2C9 metabolizers (normal and intermediate). However, no data is available regarding interaction with poor metabolizers.

### Special conditions

Animal studies suggested decreased foetal body weight and an increased incidence of foetal variations on administering Rimegepant. Few studies suggested the increased occurrence of gestational hypertension and pre-eclampsia in pregnant females with migraine. No data is available assessing the effects of Rimegepant on birth

defects in humans. Hence care should be taken while administering the drug in this group of patients. Efficacy of the drug is not established in paediatric population. In geriatric age group, pharmacokinetics of the drug was similar to that of younger age group. In patients with severe hepatic and renal impairment, the drug should not be administered.

### CLINICAL TRIALS

#### Clinical trials conducted to assess the efficacy of Rimegepant

The efficacy and safety of Rimegepant in migraine is derived from phase 2 and phase 3 trials, which is summarized in Table 1.<sup>5,12,13</sup>

#### Safety and adverse effects

The safety of Rimegepant was evaluated in two phase 3 clinical trials. In one of the phase 3 trial (NCT03461757), the most common on-study adverse events were nausea (11 [2%] of 682 participants vs three [<1%] of 693 participants) and urinary tract infection (ten [1%] of 682 participants vs four [1%] of 693 participants).

**Table 1: Summary of clinical trials conducted to assess the efficacy of Rimegepant.**<sup>5,12,13</sup>

Study	Study design	n <sup>a</sup>	Drugs compared	Outcome <sup>b</sup> (2 h pain freedom)
Phase 2 <sup>c</sup>	Double blind placebo controlled dose ranging study	885	Placebo	15.3%
			Rimegepant75mg	31.4%
			Rimegepant150mg	32.9%
			Rimegepant300mg	29.7%
			Rimegepant600mg	24.4%
			Sumatriptan	35%
Phase 3 <sup>d</sup>	Double blind Placebo controlled Multicentric	1466	Placebo	11%
			Rimegepant75mg	21%
Phase 3 <sup>e</sup>	Double blind Placebo controlled Multicentric	1186	Placebo	12%
			Rimegepant75mg	19.6%

a – number of patients, b - % of patients achieving this outcome, c- NCT01430442

d- NCT03461757, e- NCT03237845

**Table 2: Adverse events with Rimegepant 75 mg and placebo.**<sup>5</sup>

Adverse events	Rimegepant 75 mg (n=543)	Placebo (n=543)
	N (%)	N (%)
Any adverse event	93 (17.1)	77 (14.2)
Nausea	10 (1.8)	6 (1.1)
Urinary tract infection	8 (1.5)	6 (1.1)
Serious adverse event <sup>b</sup>	1 (0.2)	2 (0.4)
Serum AST/ALT above ULN	13 (2.4)	12 (2.2)
Serum AST/ALT >3 X ULN	0	0
Total bilirubin >2 x ULN	0	0

a = reported from NCT03237845, b - The serious adverse event reported in the Rimegepant group was back pain, and the serious adverse events reported in the placebo group were chest pain (1 patient) and urinary tract infection (1 patient).

No serious adverse events were reported in treated participants. In other phase trial (NCT03237845), The most common adverse events were nausea (1.8% in the Rimegepant group and 1.1% in the placebo group) and urinary tract infection (1.5% and 1.1%, respectively). Serious adverse events were reported in one patient in the Rimegepant group (back pain) and in two patients in the placebo group (Table 2).<sup>5</sup>

## CONCLUSION

CGRP antagonists are greatest advances in the field of migraine. Rimegepant, one such drug can be used in treating acute migraine when triptans are not effective or contraindicated due to cardiovascular disorders. The monoclonal antibodies against CGRP and its receptor have high responder rates with favourable adverse event profiles. Given that approximately 40–50% of migraine patients do not respond to monoclonal antibodies, future studies should focus on identification of biomarkers that can predict treatment response. Collectively, novel migraine therapies represent a major progress in migraine treatment and will undoubtedly transform headache medicine.

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