

DOI: <https://dx.doi.org/10.18203/2319-2003.ijbcp20213373>

Review Article

Gepants, calcitonin gene-related peptide antagonists, for abortive treatment of migraine: current status

Soni Gaddam, Satyanarayana S. V. Padi*

Department of Pharmacy Practice, Care College of Pharmacy, Warangal, Telangana, India

Received: 11 July 2021

Revised: 11 August 2021

Accepted: 12 August 2021

***Correspondence:**

Dr. Satyanarayana S. V. Padi,

Email: ssvpadi@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Migraine is a neurovascular disorder characterized by unilateral, recurrent, pulsating, throbbing, and moderate to severe headache. Triptans use is often limited by their poor efficacy, reports of poor responders, and contraindicated in patients with cardiovascular disorders. Calcitonin gene-related peptide (CGRP), a neuropeptide, regulates vascular tonicity as well as potent pain mediator, and both the mechanisms involved in development of migraine headache. Gepants are non-peptide, small molecules, highly selective, and potent CGRP antagonists. These novel drugs have been approved for abortive treatment of acute migraine with or without aura. These are being evaluated for their effectiveness and showing promising results in the prevention of migraine. Gepants do not have vasoconstrictive properties, are safe to use in patients with cardiovascular risk, and best alternative to triptan therapy. These are available in tablet, orally disintegrating tablet, and nasal forms to improve patient compliance. Ubrogепant and rimegepant are the two oral CGRP antagonists approved whereas atogepant and zavegepant are at late stage of development for approval.

Keywords: Atogepant, Calcitonin gene-related peptide, Gepants, Migraine, Rimegepant, Ubrogепant, Zavegepant

INTRODUCTION

Migraine is a common, genetically influenced, complex neurological disorder, and classified as a primary headache disorder with extremely incapacitating neurological symptoms. It is characterized by recurrent episodes of headache that can cause severe throbbing pain or a pulsing sensation, usually on one side of the head. It is often accompanied by nausea and vomiting. In some cases migraine headache is associated with extreme sensitivity to light, sound, and smell, collectively known as an aura that arise most often before headache but that may occur during or afterward.^{1,2} Migraine attacks can last for hours to days, and the pain can be so severe that it interferes with migrainer's daily activities. Nevertheless, the Global burden of disease study 2019 revealed that headache disorders ranked 14th among global causes of disability-adjusted life years; however, migraine remains second

among the world's causes of disability, especially in under 50s, and first among young women.³ Recently, the Chronic Migraine Epidemiology and Outcomes (CaMEO) study highlighted that migrainers' have higher family burden in that migraine can negatively affect many important aspects of life including marital, parenting, and family relationships, and have decreased quality of life, lower employment rates as well.⁴ Further, both migraine with or without aura has been reported to be associated with increased risk of stroke, endothelial dysfunction, and cardiovascular disorders.⁵⁻⁷

CURRENT STATUS OF MANAGEMENT OF MIGRAINE

There are several evidence-based guidelines for the acute and chronic management of migraine headaches nationally and internationally. Apart from avoiding known triggers,

such as emotional stress, hormones in women, sleep disturbance and modifications in lifestyle, such as smoking cessation, exercise, pharmacotherapeutics remains the main stay in the management of acute and chronic migraine. Several guidelines focused on personalized medicine that follows stepwise strategy of combining oral over-the-counter medications with oral and parenteral prescription therapies customised to the migrainer. It is not advisable to use opioids or butalbital containing medications as first-line therapies for recurrent headache disorders owing to undesired effects.⁸⁻¹⁰ Analgesics, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAID), such as naproxen, ibuprofen or diclofenac, at onset of migraine symptoms are the most widely used first line therapies for mild to moderate migraine.^{9,10}

With the understanding that migraine is a neurovascular disorder in which serotonin (5-HT) plays a key role in regulating tonicity of blood vessels, several triptans are approved in the 90s of the last century. Triptans are selective agonists of 5-HT 1B/1D receptors and first-line abortive agents used for treatment of migraine.¹⁰⁻¹² It is well reported that acute migraine headache is best managed by the administration of parenteral triptans, sumatriptan is the commonly used among others.^{9,13} As on today, pharmaceutical development focused on new administration methods and formulations, triptan combination therapies, and treatment in menstrually related migraines.^{9,10,13} Although triptans are highly effective for short term treatment of migraine attacks, these are not used for prophylaxis of migraine owing to their associated risk of vasoconstrictive effects, Accumulated data indicate that triptan therapy is contraindicated in migraine sufferers with cardiovascular diseases, such as ischemic heart disease, uncontrolled hypertension, coronary spasms, coronary artery diseases, peripheral artery diseases as these are associated with arrhythmia and stroke and making treatment challenging in this subset of patients.^{14,15} It is also reported that triptans showed insufficient efficacy and/or tolerability and poor responders exist that allow switching or optimizing acute treatment of migraine highlighting the need for more effective acute treatment options.^{16,17}

ROLE OF CGRP IN MIGRAINE

Calcitonin gene-related peptide (CGRP) is a 37-aminoacid neuropeptide, an autacoid, exist in two forms CGRP alpha and CGRP beta. It is a highly potent vasodilator released from peripheral and central nerve terminals.¹⁸ Importantly, CGRP is abundant in trigeminal ganglion that plays a key role in primary headache pathophysiology. It is released from sensory neurons located in the ganglion and nucleus of the trigeminal nerve. Indeed, CGRP receptors are expressed in trigeminal neurons that form C-fibers and A-fibers and mediate nociception in both the CNS and the periphery. Besides, it is a potent regulator of cerebrovascular blood flow which is dysregulated in migraine.^{11,19} It has been reported that CGRP, particularly alpha-isoform, primarily involved in migraine

pathogenesis.^{20,21} During a migraine attack the CGRP levels are increased, it causes intense inflammation of meninges, there is vasodilation of middle meningeal arteries and middle cerebral arteries.^{22,23} This vasodilation leads to increased blood flow and pooling of blood occurs that causes headache. Indeed, in acute migraine and cluster headache attacks, there is release of CGRP into the cranial venous outflow in humans. In addition, intravenous CGRP can induce migraine-like symptoms in migraine patients.^{24,25} These findings led to the development of anti-migraine therapies that inhibit CGRP action.

One of the early discoveries of CGRP modulators are CGRP inhibiting antibodies that can prevent migraine headache by blocking CGRP-induced vasodilation. These CGRP inhibitors are safe and effective for migraine patients with hypertension and cardiovascular disorders.^{9,10} As of today, anti-CGRP antibodies therapy includes erenumab that targets CGRP receptor, and eptinezumab, fremanezumab, and galcanezumab that targets CGRP alpha and beta forms have been approved by the food and drug administration (FDA) for prevention of migraine.^{20,21,26} In addition to this, several novel, small molecules targeting CGRP receptors, which are called 'GEPANTS' have recently been approved and few are undergoing clinical investigation.^{12,20,21,27}

GEPANTS, THE CGRP RECEPTOR ANTAGONISTS

Gepants are non-peptide small molecules approved for treatment of acute migraine with or without aura and are not indicated for migraine prophylaxis. Depending on the development time, gepants are chronologically classified into three generations. The first generation gepants include BI-44370 TA, MK-3207, olcegepant, and telcagepant, the second generation includes ubrogepant, rimegepant, and atogepant and the third generation includes zavegepant (Table 1). Ubrogepant followed by rimegepant are the first and second gepants approved by the FDA for the treatment of acute migraine with or without aura in adults.^{12,27} Atogepant and zavegepant have been developed for prevention of episodic migraine and are currently under clinical trial.^{27,28}

These molecules have attracted enough attention because of being developed and approved as abortive agents in the management of migraine.^{20,21,27} The goal of abortive treatment is to stop a migraine once it starts. Abortive medications stop a migraine when migrainer feel headache is coming or once it has begun. Importantly, abortive medications have patient preferences as these agents can be taken by self-injection, mouth, skin patch, or nasal spray which improve patients compliance and medication adherence.⁹⁻¹¹ It has been reported that gepants are as effective as triptans without cardiovascular effects and clinically tested as an alternative to triptans in patients who have cardiovascular risk factors.^{9,12,26} Indeed, gepants are different from the injectable anti-CGRP monoclonal antibodies in that gepants are oral pills, dissolvable tablets

or nasal sprays that allow ease of administration and improve patient compliance. Moreover, gepants are approved to take readily on need basis whereas these four approved anti-CGRP antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) are administered under the skin or infused intravenously once

monthly or every three months, depending on the particular antibody and are given to prevent episodic and chronic migraines. Furthermore, the anti-CGRP monoclonal antibodies take few months to be eliminated from body whereas gepants will be completely eliminated over the course of a few days.^{10,21,28}

Table 1: Current status of gepants for abortive treatment and prevention of migraine.

Generations	Dosage	Indications	Side effects	Status
First				
BI-44370 TA MK-3207 Olcegepant Telcagepant	-	-	Paresthesia, increase in hepatic transaminase	Discontinued
Second				
Ubrogepant (MK-1602)	50 mg, 100 mg, maximum 200 mg tablets	Acute migraine with or without aura	Nausea, somnolence, dry mouth, pericardial effusion, appendicitis	Approved in December 2019
Rimegepant (BHV-3000, BMS-92771)	75 mg, 150 mg, maximum 300 mg oral disintegration tablet	Acute migraine with or without aura ^a , prevention ^b	Difficulty in breathing or swallowing, fever, hives, nausea, reddening of the skin route	Approved in February 2020 ^a , June 2021 ^b
Atogepant (AGN-241689, MK-8031)	10 mg, 30 mg, maximum 60 mg tablets	Acute migraine with or without aura, targeted specifically for prevention	Fatigue, headache, and dizziness, nausea, constipation	Undergoing phase 3 trial, NDA submitted
Third				
Zavegepant (BHV-3500)	5 mg, 10 mg, maximum 20 mg nasal spray	Acute migraine with or without aura, prevention	Dysgeusia, nasal discomfort	Undergoing phase 3 trial, NDA submitted

Note: NDA: New drug application. ^{a,b}denote approved indications and corresponding time of FDA approval.

Olcegepant (BIBN-4096)

Boehringer Ingelheim Pharmaceuticals' olcegepant is the first non-peptide antagonist of CGRP receptor studied as a potential treatment for migraine.²⁷⁻²⁹ Owing to low oral bioavailability, only the parenteral route was used, available only in the intravenous form limiting its use in clinical practice. It was more effective, but discontinued due to its high molecular weight, limited ability to penetrate the brain, and its associated risk of paresthesia.^{27,28}

Telcagepant (MK-0974)

Merck's telcagepant is another gepants and was evaluated for acute treatment of migraine. In clinical trials, frequently reported adverse reactions included dry mouth, lethargy, dizziness, weakness, nausea, vomiting, paresthesia, however later its use was stopped due to increase in serum alanine transaminases suggestive of hepatotoxicity.²⁷⁻²⁹

Boehringer Ingelheim's (BI-44370) and (Merck's MK-3207)

Both are gepants, tested for the treatment of acute migraine. Development of these drug candidates also

terminated due to poor bioavailability and adverse reactions.^{27,30}

Ubrogepant (MK-1602)

Merck's ubrogepant is a competitive antagonist with high affinity, potency, and selectivity for the human CGRP receptor developed by Allergan under license to Merck and Co.²⁸⁻³¹ It was developed in order to avoid the hepatotoxicity risks associated with Merck's own failed discoveries telcagepant and MK-320.^{27,29,32} Several clinical trials (ACHIEVE I, ACHIEVE II, UBR-MD-04 and 3110-105-002) demonstrated its efficacy, safety, and tolerability in the acute treatment of migraine in patients (a) who had an insufficient response to a triptan, (b) in whom triptans were contraindicated, and (c) who had moderate to severe cardiovascular risk profile.^{27,31,33} It is the first drug in the class of oral CGRP antagonists approved on the 23 December 2019 by US FDA for the acute treatment of migraine. It is not recommended for preventive treatment of migraine. In clinical trials, most of patients had shown relieved pain freedom two hours after treatment and most troublesome migraine symptoms, such as nausea, light sensitivity or sound sensitivity stopped two hours after treatment. The usual recommended dose is 50 mg or 100 mg, to be taken orally and the maximum daily dose should not exceed 200 mg. It is rapidly absorbed after

oral administration with peak plasma concentration in 1.5 hrs and has 87% plasma protein binding. It is primarily metabolized by CYP3A4, however, a weak inhibitor of CYP2C8, 2C9, 2D6, 2C19, monoamino oxidase A. Owing to its metabolism, concomitant administration of strong CYP3A4 inhibitors, such as rifampin, phenytoin, barbiturates, St. John's wort should be avoided.³²⁻³⁴ Elimination half life is 5-7 hrs, excretion is by faecal route, and rarely through renal route. Besides, concomitant use of ubrogepant with breast cancer resistance protein (BCRP) inhibitors, such as fumitremorgin C (FTC), the FTC analogue Ko143, the acridone carboxamide derivative GF120918, anti-HIV protease inhibitors nelfinavir and ritonavir, the dietary flavonoids chrysin and biochanin A, the tyrosine kinase inhibitors gefitinib and imatinib and P-gp efflux transporter inhibitors should be avoided.³⁴

The most common side effects of ubrogepant are nausea, somnolence, tiredness, dry mouth, and its long-term administration is associated with pericardial effusion, appendicitis, spontaneous abortion, and seizures.³¹⁻³⁴ Data are not available regarding the risks associated with its use in pregnant and lactating women. Its safety and effectiveness in pediatric patients have not been established.^{34,35} In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger patients. Dosage adjustment is recommended for patients with severe hepatic impairment but not in patients with mild to moderate hepatic impairment. On the other hand, dose adjustment is recommended for patients with severe renal impairment as well.³⁴⁻³⁶ It can be administered with or without food; however, second tablet should not be taken within 24 hrs if migrainer consumed grapefruit juice or taking any medications such as verapamil, ciprofloxacin, fluconazole, cyclosporine.³⁶ Recent studies on mechanistic investigations in both *in vitro* and *in vivo* models support liver safety of ubrogepant and reported that it has lower potential to cause hepatotoxicity than has been observed with telcagepant and MK-3207.^{35,37,38} It has also been reported that ubrogepant use is not associated medication overuse headache.^{31,33}

Rimegepant (BHV-3000; formerly BMS-927711)

Bristol-Myers Squibb's rimegepant is a competitive antagonist with high affinity, potency, and selectivity for the human CGRP receptor developed by Biohaven Pharmaceuticals.³⁹ Several clinical trials (NCT03235479, NCT03237845, NCT03461757, NCT03732638) demonstrated its efficacy, safety, and tolerability in the acute treatment of migraine in patients (a) who had an insufficient response to a triptan or other therapies, (b) in whom triptans were contraindicated, (c) who are unable to tolerate adverse effects of triptans, and (d) who had moderate to severe cardiovascular risk profile as well.^{27,29,40} It is approved for treating acute migraine with or without aura in adults in February 2020 and its approval has been extended to preventing episodic migraine in June

2021. It is a prescription medicine available as 75 mg oral disintegration tablet and has rapid onset of action.^{40,41} The maximum dose is 75 mg in a day, with no repeated dosing, that means one dose is recommended to be taken in a 24 hrs time period. It is 96% plasma protein bound, and has 64% oral bioavailability with maximum plasma concentration in 1.5 hrs. It is metabolized by CYP3A4 and less likely by CYP2C9. It is primarily eliminated unchanged, and also by fecal route and urine, elimination half life was found to be 11 hrs. It is recommended that simultaneous administration with strong and moderate CYP3A4 inhibitors and inducers, and also with inhibitors of P-gp or BCRP inhibitors should be avoided.

Some of the rare side effects associated with rimegepant are difficulty in breathing or swallowing, fever, hives, nausea, reddening of the skin route and contraindicated in patients with hypersensitivity reactions. It is not safe in breastfeeding, liver diseases and kidney diseases.⁴¹ In randomized controlled clinical trials, it was demonstrated that rimegepant when taken as oral acute treatment in patients receiving anti-CGRP mAbs was well tolerated, without any safety issues.⁴² Of note, concomitant use of rimegepant with erenumab can effectively treat refractory migraine.⁴³ There is enough evidence that preclude its use in women. It has been documented that there is no need of dosage adjustment in patients with mild to moderate hepatic and renal impairment; however, should be avoided in severe liver and renal dysfunction cases.⁴⁴

Atogepant (AGN-241689, MK-8031)

AbbVie's atogepant is an oral CGRP receptor antagonist with a high affinity at CGRP receptors as that of other gepants, and currently it just completed phase 2b/3 clinical trials indicated for the prophylaxis and specifically being developed for prevention of migraine. Its chemical structure is different from telcagepant and other gepants whereas its inhibitory activity on vasodilatory response has been well demonstrated *in vitro*.^{9,40} This agent is currently undergoing phase 2b/3, multicentered, randomized, double blind clinical trials, daily doses ranging from 10-60 mg taken once or twice a day. In this trial, it was shown that all doses of oral atogepant were associated with significant decrease in monthly migraine days over 12 weeks compared with placebo.^{12,40,45}

Earlier, it was studied for migraine prophylaxis and considered safe and well tolerated over 12 weeks, supporting its phase 3 development in migraine prevention. In clinical trials, the common side effects reported were fatigue, nausea, and constipation. It is recently reported that oral atogepant was rapidly absorbed with median T max of about 2 hours and an apparent t1/2 of about 11 hrs.^{45,46} Moreover, it had not shown accumulation and elevated serum alanine transaminase level following once-daily dosing for 28 days in healthy human volunteers. Recently, the FDA has accepted new drug application of atogepant and demonstrates longstanding commitment to providing multiple migraine

treatment options, including BOTOX® (onabotulinumtoxin A), a preventive treatment for those with chronic migraine.⁴⁶

Zavegepant (BHV-3500; formerly BMS-742413)

Biohaven's zavegepant is a third generation, high affinity, selective, small molecule CGRP receptor antagonist, and structurally distinct from rimegepant. The chemical properties of zavegepant make the product candidate potentially suitable for multiple routes of delivery, including nasal, subcutaneous, inhalation or oral administration.^{47,48} This is the only CGRP antagonist undergoing clinical trials with both intranasal and oral formulations being developed for both acute treatment as well as prevention of migraine. In clinical trials, commonly reported adverse events are dysgeusia, nasal discomfort, but hepatotoxicity is not noticed.^{40,47}

CONCLUSION

CGRP plays an important role in the pathogenesis of migraine and its modulators alleviate migraine headache. Gepants are small molecules that antagonize the CGRP receptors and do not have direct vasoconstrictive effects. There are two gepants already approved and another two are in the late stages of development and regulatory approval in the USA. Ubrogepant tablet is approved for acute treatment of migraine. Rimegepant oral disintegrating tablet approved for acute treatment as well as prevention of migraine. Atogepant tablet is specifically being developed for prevention of migraine. Zavegepant nasal spray is being evaluated for both acute treatment and prevention of migraine.

All the gepants had shown similar clinical effectiveness, minimal side effects, and without liver toxicity. Importantly, gepants can be used safely in patients with cardiovascular events and in whom triptans are contraindicated. Chronic use of gepants is not associated with increase in number of episodes and severity of headache, and rebound headache.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol.* 2018;17(2):174-82.
2. Peters GL. Migraine overview and summary of current and emerging treatment options. *Am J Manag Care.* 2019;25(2):23-34.
3. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z. Lifting the burden: the global campaign against headache. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain.* 2020;21(1):137.
4. Buse DC, Fanning KM, Reed ML, Murray S, Dumas PK, Adams AM, et al. Life with migraine: effects on relationships, career, and finances from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache.* 2019;59(8):1286-99.
5. Chen D, Parker M, Lundberg GP. Migraine headache: Is it only a neurological disorder? Links between migraine and cardiovascular disorders. *Trends Cardiovasc Med.* 2020;30(7):424-30.
6. Quintanilla V, Toriello M, Palacio E, Gay MA, Castillo J, Montes S, et al. Systemic and cerebral endothelial dysfunction in chronic migraine. A case-control study with an active comparator. *Cephalalgia.* 2016;36(6):552-60.
7. Sumelahti ML, Sumanen MS, Mattila KJ, Sillanmäki L, Sumanen M. Stroke and cardiovascular risk factors among working-aged Finnish migraineurs. *BMC Public Health.* 2021;21(1):1088.
8. Takahashi TT, Ornello R, Quatrosi G, Torrente A, Albanese M, Vigneri S, et al. European Headache Federation School of Advanced Studies (EHF-SAS). Medication overuse and drug addiction: a narrative review from addiction perspective. *J Headache Pain.* 2021;22(1):32.
9. Ong JJY, De Felice M. Migraine treatment: current acute medications and their potential mechanisms of action. *Neurotherapeutics.* 2018;15(2):274-90.
10. Mayans L, Walling A. Acute migraine headache: treatment strategies. *Am Fam Physician.* 2018;97(4):243-51.
11. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev.* 2017;97(2):553-622.
12. Negro A, Martelletti P. Gepants for the treatment of migraine. *Expert Opin Investig Drugs.* 2019;28(6):555-67.
13. Maccone AE, Perloff MD. Triptans and migraine: advances in use, administration, formulation, and development. *Expert Opin Pharmacother.* 2017;18(4):387-97.
14. Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, Alessandro R, et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. *Cephalalgia.* 2015;35(2):118-31.
15. Li H, Vincent M, Zhang X, Dennehy EB, Goodloe R, Aurora SK, Smith TR. Acute migraine prescription patterns vary by baseline cardiovascular risk and clinical characteristics: a real-world evidence study. *Pain Ther.* 2020;9(2):499-509.
16. Leroux E, Buchanan A, Lombard L, Loo LS, Bridge D, Rousseau B, et al. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: a systematic literature review. *Adv Ther.* 2020;37(12):4765-96.
17. Hirata K, Ueda K, Komori M, Ye W, Kim Y, Cotton S, et al. Unmet needs in Japanese patients who report

- insufficient efficacy with triptans for acute treatment of migraine: retrospective analysis of real-world data. *Pain Ther*. 2021;10(1):415-32.
18. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev*. 2014;94(4):1099-142.
 19. Edvinsson L. The Trigeminovascular Pathway: Role of CGRP and CGRP Receptors in Migraine. *Headache*. 2017;57(2):47-55.
 20. Tepper SJ. History and review of anti-calcitonin gene-related peptide (CGRP) therapies: from translational research to treatment. *Headache*. 2018;58(3):238-75.
 21. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. *Cephalalgia*. 2019;39(3):366-73.
 22. Lassen LH, Jacobsen VB, Haderslev PA, Sperling B, Iversen HK, Olesen J, Hansen P. Involvement of calcitonin gene-related peptide in migraine: regional cerebral blood flow and blood flow velocity in migraine patients. *J Headache Pain*. 2008;9(3):151-7.
 23. Ashina H, Schytz HW, Ashina M. CGRP in human models of migraine. *Handb Exp Pharmacol*. 2019;255:109-20.
 24. Asghar MS, Hansen AE, Kapijimpanga T, Geest RJ, Koning P, Larsson HB, et al. Dilation by CGRP of middle meningeal artery and reversal by sumatriptan in normal volunteers. *Neurology*. 2010;75(17):1520-6.
 25. Christensen CE, Amin FM, Younis S, Lindberg U, Koning P, Petersen ET, et al. Sildenafil and calcitonin gene-related peptide dilate intradural arteries: A 3T MR angiography study in healthy volunteers. *Cephalalgia*. 2019;39(2):264-73.
 26. Haanes KA, Edvinsson L. Pathophysiological mechanisms in migraine and the identification of new therapeutic targets. *CNS Drugs*. 2019;33(6):525-37.
 27. Hong P, Tan T, Liu Y, Xiao J. Gepants for abortive treatment of migraine: A network meta-analysis. *Brain Behav*. 2020;10(8):1701.
 28. Chiang CC, Schwedt TJ. Calcitonin gene-related peptide (CGRP)-targeted therapies as preventive and acute treatments for migraine-The monoclonal antibodies and gepants. *Prog Brain Res*. 2020;255:143-70.
 29. Holland PR, Goadsby PJ. Targeted CGRP small molecule antagonists for acute migraine therapy. *Neurotherapeutics*. 2018;15(2):304-12.
 30. Diener HC, Barbanti P, Dahlöf C, Reuter U, Habeck J, Podhorna J. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. *Cephalalgia*. 2011;31(5):573-84.
 31. Moore E, Fraley ME, Bell IM, Burgey CS, White RB, Li CC, et al. Characterization of Ubrogepant: a potent and selective antagonist of the human calcitonin gene-related peptide receptor. *J Pharmacol Exp Ther*. 2020;373(1):160-66.
 32. Scott LJ. Ubrogepant: first approval. *Drugs*. 2020;80(3):323-28.
 33. Yang Y, Chen M, Sun Y, Gao B, Chen Z, Wang Z. Safety and efficacy of ubrogepant for the acute treatment of episodic migraine: a meta-analysis of randomized clinical trials. *CNS Drugs*. 2020;34(5):463-71.
 34. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM, et al. Ubrogepant for the treatment of migraine. *N Engl J Med*. 2019;381(23):2230-41.
 35. Edinoff AN, Casey CA, Colon MA, Zaheri AR, Gregoire CM, Bourg MM, et al. Ubrogepant to treat acute migraine in adults. *Neurol Int*. 2021;13(1):32-45.
 36. Allerga. Highlights of prescribing information, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211765s0001bl.pdf. Accessed on 01 July 2021.
 37. Ankrom W, Bondiskey P, Li CC, Palcza J, Liu W, Dockendorf MF, et al. Ubrogepant is not associated with clinically meaningful elevations of alanine aminotransferase in healthy adult males. *Clin Transl Sci*. 2020;13(3):462-72.
 38. Smith B, Rowe J, Watkins PB, Ashina M, Woodhead JL, Sistare FD, et al. Mechanistic investigations support liver safety of ubrogepant. *Toxicol Sci*. 2020;177(1):84-93.
 39. Luo G, Chen L, Conway CM, Denton R, Keavy D, Signor L, et al. Discovery of (5S,6S,9R)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (BMS-927711): an oral calcitonin gene-related peptide (CGRP) antagonist in clinical trials for treating migraine. *J Med Chem*. 2012;55(23):10644-51.
 40. Ajona D, Rodríguez A, Goadsby PJ. A new approach to the acute and preventive treatment of migraine. *Med Drug Discov*. 2020;(7):100053.
 41. Falco AP, Lazim R, Cope NE. Rimegepant Orally Disintegrating Tablet for acute migraine treatment: a review. *Ann Pharmacother*. 2021;55(5):650-7.
 42. Berman G, Croop R, Kudrow D, Halverson P, Lovegren M, Thiry AC, et al. Safety of rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. *Headache*. 2020;60(8):1734-42.
 43. Mullin K, Kudrow D, Croop R, Lovegren M, Conway CM, Coric V, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. *Neurology*. 2020;94(20):2121-5.
 44. Pan KS, Siow A, Hay DL, Walker CS. Antagonism of CGRP signaling by rimegepant at two receptors. *Front Pharmacol*. 2020;11:1240.
 45. Min KC, Kraft WK, Bondiskey P, González F, Liu W, Xu J, et al. Atogepant Is not associated with clinically meaningful alanine aminotransferase elevations in healthy adults. *Clin Transl Sci*. 2021;14(2):599-605.
 46. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-

blind, randomised phase 2b/3 trial. *Lancet Neurol.* 2020;19(9):727-37.

47. Mercer SE, Chaturvedula PV, Conway CM, Cook DA, Davis CD, Pin SS, et al. Azepino-indazoles as calcitonin gene-related peptide (CGRP) receptor antagonists. *Bioorg Med Chem Lett.* 2021;31:127624.
48. Chaturvedula PV, Mercer SE, Pin SS, Thalody G, Xu C, Conway CM, et al. Discovery of (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BMS-742413): a

potent human CGRP antagonist with superior safety profile for the treatment of migraine through intranasal delivery. *Bioorg Med Chem Lett.* 2013;23(11):3157-61.

Cite this article as: Gaddam S, Padi SSV. Gepants, calcitonin gene-related peptide antagonists, for abortive treatment of migraine: current status. *Int J Basic Clin Pharmacol* 2021;10:1156-62.