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REVIEW

The pharmacotherapeutic management of episodic and chronic migraine with gepants

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ABSTRACT

Introduction: The small molecule non-peptide calcitonin gene-related peptide (CGRP) receptor antagonists named gepants offer a breakthrough novel approach in migraine acute and prophylactic drug treatment. This review aimed to determine the place of gepants in the treatment of episodic and chronic migraine.

Areas covered: The new generation gepants are ubrogepant, atogepant, rimegepant, and zavegepant. Ubrogepant is ratified for acute migraine treatment, atogepant is validated for preventive therapy, whereas rimegepant is ratified for both indications, all via oral administration and while zavegepant is administered intranasally for migraine attacks. Gepants are effective, safe, and well-tolerated in acute or prophylactic therapy. The PubMed literature search included randomized controlled trials, meta-analyses, real-world data, and review articles published in English until January 2023.

Expert opinion: Whether gepants will be real game changers in the acute treatment of migraine compared to triptans and ditans or in the prophylactic therapy compared to standard-of-care preventive drugs or CGRP-targeting monoclonal antibodies cannot be answered yet based on the available literature data.

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1. Introduction

Migraine is a primary headache disorder with well-characterized clinical features. Migraine has several subclasses, the main ones are migraine without (M0) and with aura (MA). Both forms can be episodic (EM) or chronic (CM). The term chronic means that the patient has 15 or more headache days per month for more than 3 consecutive months, which, on at least 8 days per month, has the features of migraine either M0 or MA [1]. Migraine is the leading cause of years of life lived with disability (YLD) in people under age of 50 years [2,3].

The pathomechanism of migraine is still unclear; however, crystallized hypotheses exist. These theories implicate the role of sensitization and overexcitation of the trigeminovascular system (TS) due to migraine-related neuropeptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide (PACAP) [4–9]. CGRP has been implicated in both EM and CM pathophysiology. This opens up a novel therapeutic pathway by targeting CGRP or its receptor with human or fully humanized monoclonal antibodies (mAb) or by using non-peptide small-molecule CGRP receptor antagonists, gepants. The therapeutic indication of CGRP-targeting mAbs is the prophylaxis of EM and CM. Gepants are capable of both providing relief from migraine attacks as well as preventing migraine attacks [4]. The possible sites of action of gepants in the TS are the cerebral arteries, the meninges, and the trigeminal nucleus caudalis (TNC). Gepants are capable of inhibiting cerebral vasodilation without causing vasoconstriction, inhibiting neurogenic inflammation in the meninges, and blocking pain signaling in the TNC [10]. The early concept was to block CGRP receptors by using C-terminally truncated (CGRP8–37) peptides that inhibit the binding of the endogenous full-length CGRP. Unfortunately, these substances had very short half-life; therefore, non-peptide CGRP receptor inhibitors were developed, which leads to the synthesis of gepants [10,11]. The first-generation CGRP receptor antagonists were olcegepant (intravenous, IV) and telcagepant (oral, PO). The second-generation gepants such as ubrogepant, rimegepant, and atogepant and the third-generation zavegepant have recently been validated as being effective and devoid of the hepatotoxic features of the first-generation gepants. For the acute treatment of migraine, ubrogepant (PO) and zavegepant (IN) are indicated, whereas for the prophylaxis of EM, atogepant PO is recommended. Rimegepant is effective for both the acute and preventive treatment of migraine [12–18].

This review was conducted to summarize the clinical efficacy and safety profile of gepants in the acute and prophylactic treatment of EM and CM.

The literature analysis included randomized controlled clinical trials (RCTs), meta-analyses, real-world data, and review articles published in English. The electronic literature search was conducted using the PubMed database until January 2023, by using multiple combinations of keywords such as 'acute,' 'antagonist,' 'CGRP,' 'chronic,' 'episodic,' 'gepant,'

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Article highlights

- CGRP is a well-characterized migraine-associated neuropeptide, which acts on the trigeminovascular system.
- Previous acute and prophylactic therapeutic options do not provide pain relief for all patients with migraine.
- Gepants as small-molecule non-peptide CGRP receptor inhibitors offer a novel approach in the acute treatment for migraine with and without aura and in the prophylactic drug treatment for episodic migraine. No published data are available regarding chronic migraine.
- Ubrogepant (oral) and zavegepant (intranasal) are consented for acute migraine treatment, atogepant (oral) is validated for preventive therapy, whereas rimegepant (standard and orally disintegrated tablets, oral) is validated for both indications.
- All available gepants are effective, safe, and well-tolerated in the acute and prophylactic treatment of migraine based on the results of randomized controlled trial.
- This review discusses the possibility whether gepants can become real game changers in migraine treatment.

'migraine,' 'preventive,' 'prophylactic,' 'randomized controlled trial,' 'real-world,' 'receptor,' 'therapy,' and/or 'treatment.'

2. Pharmacotherapy of migraine

Treating migraine involves pharmacological and non-pharmacological options. The pharmacological treatment is divided into acute and preventive therapeutic possibilities. The acute pharmacological treatment of migraine can be further divided into nonspecific treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and antiemetics, and into specific pharmacons, such as triptans. The triptans are 5-hydroxytriptamine (5-HT) 1B/1D receptor agonists, and they act on the peripheral and central branches of the trigeminovascular system [19,20]. The novel migraine-specific drugs are ditans (lasmiditan) and gepants (ubrogepant, rimegepant, and zavegepant) [8,21]. The ditans are 5-HT 1F receptor agonists, and they act on the trigeminal nucleus caudalis as a central part of the trigeminovascular system [22].

In the American Headache Society (AHS) consensus statement, the criteria for the application of gepants for the acute treatment of migraine are well described and include the following: gepants should be prescribed and recommended by neurologists, headache specialists for adult migraine patients who fulfilled the ICHD-3 diagnostic criteria. Gepants are recommended for those patients with migraine who have failure or contraindications to or do not tolerate triptans. The statement also suggested to assess the effects of gepants with validated patient-reported outcome questionnaires [23].

Until now, the gold standard for acute migraine-specific treatment was the use of triptans. The latest Consensus Panel of the European Headache Federation (EHF) set up the definitions of effective treatment of a migraine attack and of triptan failure. Effective drug treatment refers to improvement of headache and accompanying symptoms, with no AEs. By definition, being a triptan responder means that in at least 3 out of 4 treated attacks, the triptan was effective. Being a triptan nonresponder means that one triptan was found to be ineffective, being triptan-resistant means that 2 triptans were found ineffective, whereas a triptan-refractory condition means ≥3 ineffective triptans (including≥1 subcutaneous (SC) triptan(s)). Triptan ineligibility refers to the presence of a contraindication to triptan use. In the case of triptan failure, gepants represent a possible option for treating migraine attacks and may reduce public and personal disadvantages for people with migraine [24,25].

The prophylactic treatment of EM can be separated into classical drugs, such as beta-adrenergic receptor blockers (propranolol and metoprolol), calcium ion channel antagonists (flunarizine), and neuromodulators (valproate and topiramate), and tricyclic antidepressant (amitriptyline), and into novel pharmacons such as CGRP-targeting mAbs (eptinezumab, erenumab, fremanezumab, and galcanezumab) and CGRP receptor antagonists, gepants (rimegepant and atogepant). The drugs acting on CGRP pathway might be a turning point in the migraine prevention, but they are expensive in most countries [26]. Botulinum toxin type A and CGRP targeting mAbs are ratified for CM, and there are also data for topiramate [8,21,27]. As per the AHS guideline, the goals of a migraine prophylactic treatment are to reduce attack frequency, severity, duration, and disability, to improve the patients' functioning and health-related quality of life (HR-QoL), and to reduce the intake of acute drugs and headache-related distress. The criteria for identifying patients for preventive migraine treatment address the degree of disability and the numbers of monthly headache days (MHD). The more severe the degree of the disability is, the less MHDs (2–3 or more days) are enough for the indication. Further indications include the contraindication or intolerance to, or a failure or overuse of acute migraine drugs [23].

2.1. Gepants in the acute treatment of migraine

2.1.1. Ubrogepant

The United States, Food and Drug Administration (US FDA) approved ubrogepant tablets as the first drug in the class of oral non-peptide CGRP receptor antagonists on 23 December 2019 for the acute treatment of migraine with or without aura in adults. The pharmacokinetic profile of ubrogepant includes a 1.5 hour (h) time to maximum concentration (Tmax), an 87% *in vitro* plasma protein binding, metabolization by CYP3A4 (hepatic), an elimination half-life of 5–7 h, and excretion through feces [28]. Ubrogepant is contraindicated for co-administration with strong CYP3A4 inhibitors.

2.1.1.1. Results from RCTs. Chronologically, the first published ubrogepant study was a phase 2b randomized, double-blind, placebo-controlled, single-attack trial with different doses (1 mg, 10 mg, 25 mg, 50 mg, and 100 mg) of ubrogepant for the acute treatment of migraine. The first primary endpoint was 2 h pain freedom, where the results showed that 25.5% of the 100 mg ubrogepant-treated patients reached this endpoint compared to the placebo group (8.9%), which was statistically significant. The other primary efficacy end point was the 2 h headache response, where 58.8% of the ubrogepant-treated patients with migraine reached this end point *versus* 44.6% of the placebo group participants. The secondary end points focused on the absence of the most bothersome migraine-associated symptoms (MBS) such as phonophobia,

photophobia, and nausea at 2 h after a single dose of ubrogepant 100 mg. The results showed that in the absence of phonophobia at 2 h post-dose, 60.8% of the ubrogepant 100 mg-treated patients reached this target *versus* 42.0% in the placebo group. Regarding the absence of photophobia at 2 h post-dose, the result was 54.9% (ubrogepant 100 mg) *versus* 30.4% (placebo group). The absence of nausea at 2 h post-dose was 70.6% (ubrogepant 100 mg) compared to 62.5% (placebo). The most common adverse events (AEs) were dry mouth (4.9% for ubrogepant 100 mg *versus* 3.9% for placebo), nausea (6.9% for ubrogepant 100 mg *versus* 3.5% for placebo), and fatigue (2.9% ubrogepant 100 mg *versus* 2.7% for placebo) (Table 1) [15]. The beneficial results of this early RCT with ubrogepant opened up a new perspective for the continuation of further clinical studies.

The ACHIEVE I multicenter, randomized controlled trial (RCT) addressing the efficacy and safety of oral ubrogepant as a single migraine attack treatment in adult patients with M0 and MA demonstrated that 19.2% of the ubrogepant-treated patients achieved headache freedom at 2 h after the initial dose of 50 mg and 21.2% of 100 mg *versus* 11.8% in the placebo group. Regarding the absence of MBS at 2 h post-dose, the results showed that the absence of photophobia was found in 58.6% of patients receiving ubrogepant 50 mg, in 54.9% of patients receiving ubrogepant 100 mg, *versus* in 55.7% in the placebo group. The absence of phonophobia was found in 19.4% of patients in the ubrogepant 50 mg group, 25.9% in the ubrogepant 100 mg group, *versus* 21.5% in the placebo group, whereas the absence of nausea was detected in 21.3% of patients in the ubrogepant 50 mg group, 19.2% in the ubrogepant 100 mg group, *versus* 22.4% in the placebo group. The incidence of AEs within 48 h after the initial dose was 9.4% for ubrogepant 50 mg, 16.3% for ubrogepant 100 mg, *versus* 12.8% in placebo group. The most frequent AEs were nausea, somnolence, and dry mouth. Serious AEs were not reported in any study groups, and there were no AEs that led to discontinuation of the trial regimen [16].

The ACHIEVE II, a multicenter, randomized, double-blind, placebo-controlled, single migraine attack, phase 3 trial was conducted with 25 mg and 50 mg doses of ubrogepant. Both regimen doses resulted in a higher rate of pain freedom at 2 h (21.8% in the ubrogepant 50 mg group and 20.7% in the ubrogepant-25 mg group) compared to placebo (14.3%). The superiority in terms of the absence of MBS (i.e. photophobia, phonophobia, or nausea) at 2 h was statistically significant only regarding the ubrogepant 50 mg group (38.9% *versus* 11.5% in the placebo group). The most common treatment-emergent AEs (TEAEs) occurring within 48 h after the initial dose in any group were nausea (2.0% at 50 mg dose; 2.5% at 25 mg dose *versus* 2.0% placebo) and dizziness (1.4% at 50 mg dose, 2.1% at 25 mg dose *versus* 1.6% placebo). No serious AEs or AEs leading to discontinuation were reported [17].

An early phase 1, multicenter, double-blind, parallel-group trial focused on the safety and tolerability of ubrogepant 100 mg, which was administered intermittently with high-frequency dosing to healthy adults. The dosing regimen was ubrogepant 100 mg (50 mg tablets bid) on two consecutive days followed by two consecutive days of placebo, alternating for 8 weeks. TEAEs were observed in 44% and 45% of the ubrogepant and placebo study subjects, respectively. In this special study design, ubrogepant was well tolerated and hepatotoxicity was not detected [30].

A *post hoc* pooled analysis of the ACHIEVE I and II randomized, double-blind single attack phase 3 trials focused on the time course (1 h, 1.5 h, and 2 h) of efficacy of ubrogepant 50 mg. The earliest (at 1 h post dose) observed clinical effect (i.e. statistically significant separation from placebo) was pain relief (43% in the ubrogepant 50 mg group), followed by (at 1.5 h post dose) the absence of MBS (28% in the ubrogepant 50 mg group) and subsequently (at 2 h post dose) pain freedom (20% in the ubrogepant 50 mg group). This efficacy was sustained until 24 h and remained separated from placebo at 48 h. A single dose of ubrogepant 50 mg reached the maximum plasma concentrations at 1 h [31]. Another *post hoc* analysis of pooled data from the ACHIEVE I and II studies aimed to determine the impact of the previous gold-standard acute migraine-specific treatment, triptans, on the efficacy of ubrogepant, in three categories of M0 or MA patients (i.e. triptan responder, triptan insufficient responders, and triptan naïve). The analysis revealed that the efficacy (in terms of pain freedom and absence of MBS 2 h post dose) and tolerability of ubrogepant 50 mg did not differ in these three subgroups of patients with migraine [32]. In triptan insufficient responder patients with migraine, a post hoc analysis of the phase 3 ACHIEVE I and II trials treated with ubrogepant improvement in Functional Disability Scale, satisfaction with medication, and Patient Global Impression of Change were demonstrated compared with placebo [33].

The objective of a long-term (52-week) phase 3, multicenter, randomized, open-label extension trial was to evaluate the safety and tolerability of intermittent use of ubrogepant (50 mg or 100 mg) given as 1 or 2 doses per attack (21,454 treated migraine attacks) for the acute treatment of M0 or MA. The study results demonstrated that the reported treatment-related AEs were 10% for a 50 mg dose of ubrogepant and 11% for a 100 mg dose of ubrogepant. On the other hand, TEAEs were detected 66% of the patients in the ubrogepant 50 mg group and 73% in the ubrogepant 100 mg group. The most frequent TEAE was upper respiratory tract infection. Serious AEs occurred in 2% and 3% of patients in the ubrogepant 50 mg and 100 mg groups, respectively. The liver enzyme parameters were also analyzed during this 1-y study, which showed that three times higher of normal value of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) was detected in 20 participants of the total of 1203 participants eligible (including 4 in the usual care arm), with only a total of 3 ubrogepant-treated cases being deemed as possibly or probably related to study medication [34].

A phase 1, single-center, open-label, randomized, 3-way cross-over (ubrogepant 100 mg alone, sumatriptan 100 mg alone, and ubrogepant 100 mg plus sumatriptan 100 mg), single-dose, pharmacokinetic interaction study in healthy participants showed only slight alteration in ubrogepant pharmacokinetic parameters when coadministered with sumatriptan. There were no TEAEs reported after co-administration of ubrogepant (100 mg) and sumatriptan (100 mg). The pooled safety data from ACHIEVE I and II trials M0 and MA

Table 1. Summary of characteristics of gepants indicated for acute migraine therapy.

Drug	RCT (Phase)	Number of participants (completed)	Route of administration	Dose (mg)	Efficacy at 2 hour pain freedom	Adverse events (drug%/placebo%)	Authors (year)	Ref.
Ubrogepant	Phase 2b	107 (1 mg) 108 (10 mg) 103 (25 mg) 107 (50 mg) 102 (100 mg) 113 (placebo)	PO tablet	1, 10, 25, 50, 100	25.5% (100 mg)	100 mg/placebo: nausea (6.9%/3.5%) dizziness (5.9%/0.9%) dry mouth (4.9%/3.5%) somnolence (3.9%/5.3%) fatigue (2.9%/2.7%)	*Voss et al (2016)*	[15]
Ubrogepant	ACHIEVE I (Phase 3)	466 (50 mg) 485 (100 mg) 485 (placebo)	PO tablet	50, 100	19.2% (50 mg) 21.2% (100 mg)	100 mg/placebo: nausea (4.1%/1.6%) somnolence (2.5%/0.8%) dry mouth (2.1%/0.4%)	*Dodick et al (2019)*	[16]
Ubrogepant	ACHIEVE II (Phase 3)	478 (25 mg) 488 (50 mg) 499 (placebo)	PO tablet	25, 50	20.7% (25 mg) 21.8% (50 mg)	50 mg/placebo: nausea (2%/2%) dizziness (1.6%/1.6%)	*Lipton et al, 2019*	[17]
iRmegepant	Phase 3	537 (75 mg) 535 (placebo)	PO tablet	75	19.6% (75 mg) 12% (placebo)	75 mg/placebo: nausea (1.8%/1.1%) urinary tract inection (1.5%/1.1%)	Lipton *et al, 2019*	[29]
Rimegepant	Phase 3	669 (75 mg) 682 (placebo)	PO (ODT)	75	21% (75 mg) 11% (placebo)	75 mg/placebo: nausea (2%/1%) urinary tract infection (1%/1%) dizziness (1%/1%)	*Croop et al, 2019*	[13]
Zavegepant	Phase 2/3	387 (5 mg) 391 (10 mg) 402 (20 mg) 401 (placebo)	IN (spray)	5, 10, 20	NA (5 mg) 22.5% (10 mg) 23.1% (20 mg) 15.5% (placebo)	10 mg/placebo: dysgeusia (13.5%/3.5%) nausea (4.1%/0.5%) nasal discomfort (1.3%/0.2%)	*Croop et al, 2022*	[12]

Abbreviations: IN (intranasal); NA: not available/not reported; ODT: orally disintegrating tablet; PO: per os; RCT: randomized controlled trial.

patients taking ubrogepant alone or ubrogepant and a triptan as a rescue medication together reported that the prevalence of treatment-related TEAEs was 14.9% in the ubrogepant 100 mg group, whereas it was 12.8% in the ubrogepant 100 mg plus triptan group. The co-administration of ubrogepant with triptans was well-tolerated in both study design regimens [35].

A randomized, phase 1b, drug–drug interaction, two-arm (ubrogepant 100 mg ± erenumab 140 mg SC or ubrogepant 100 mg ± galcanezumab 240 mg SC), multicenter, open-label study conducted in patients with migraine revealed that the pharmacokinetic and safety profile of ubrogepant 100 mg co-administered with CGRP-targeting monoclonal antibodies (4 days after erenumab or galcanezumab SC injection once daily for 4 days) did not change [36].

A long-term, phase 3, open-label, dose-blinded, 52-week extension trial evaluating the efficacy of ubrogepant (50 mg or 100 mg) in the acute treatment of migraine with mild pain *versus* moderate/severe pain revealed that the 2 h pain freedom rates were higher for attacks with mild pain (47.1% for ubrogepant 50 mg; 55.2% for ubrogepant 100 mg) *versus* those with moderate/severe pain (23.6% for ubrogepant 50 mg; 26.1% for ubrogepant 100 mg). The rates of freedom from the MBS at 2 h post-dose are as follows: the absence of photophobia in 63.5% in mild pain *versus* 36.2% in moderate/severe pain in the ubrogepant 50 mg group and 62.6% *versus* 38.1% in the ubrogepant 100 mg group; the absence of phonophobia in 68.9% in mild pain *versus* 43.0% in moderate/severe pain in the ubrogepant 50 mg group and 69.8% *versus* 47.1% in the ubrogepant 100 mg group; the absence of nausea in 87.9% in mild pain *versus* 68.3% in moderate/severe pain in the ubrogepant 50 mg group and 85.0% *versus* 69.7% in the ubrogepant 100 mg group. In conclusion, ubrogepant treatment of migraine attacks with mild pain resulted in significantly higher rates of both freedom from pain and associated symptoms compared to attacks with moderate/severe pain [37].

2.1.1.2. Results from meta-analyses. The first meta-analysis of three RCTs with 3326 participants including ACHIEVE I and II evaluating the efficacy and safety of short-term use of ubrogepant for the acute treatment of EM revealed that the effect of ubrogepant on pain freedom at 2 h post-dose was significantly higher compared to the placebo (20.8% for ubrogepant *versus* 12.6% for placebo). The absence of the MBS at 2 h post-dose in the ubrogepant-treated group was significantly higher (37.3%) compared to placebo (27.6%). The evaluation of treatment-related AEs within 48 h or 30 days for ubrogepant *versus* placebo revealed that the risk ratio (RR) was 1.07 at 48 h and 1.03 at 30 days [38].

A further meta-analysis of five RCTs (including 4903 patients) of ubrogepant as a treatment for acute migraine demonstrated that the 2 h post-dose pain relief was significantly higher in the verum group than in the placebo group (odds ratio (OR) = 1.71). As a secondary outcome point, the absence of MBS at 2 h post-dose was analyzed. The associated ORs were 1.33 for photophobia, 1.07 for nausea, and 1.21 for phonophobia. The safety profiles of ubrogepant and placebo were similar. The incidence of common AEs is as follows: headache in 7.89% *versus* 8.68%, oropharyngeal pain in 9.18% *versus* 3.47%, whereas nasopharyngitis in 4.58% *versus*

6.25% for the ubrogepant and placebo groups, respectively [39].

A recent meta-analysis of three RCTs focusing on the comparison of the efficacy and safety of ubrogepant 50 mg and 100 mg for the acute treatment of migraine revealed that the OR of pain freedom at 2 h post-dose was 0.86, whereas the respective ORs for the absence of photophobia, phonophobia, and nausea at 2 h post-dose were 0.80, 1.07, and 1.02. Ubrogepant 100 mg is associated with higher likelihood of AEs compared to ubrogepant 50 mg (OR = 0.81). Based on the above data, both doses of ubrogepant showed similar effectiveness, with an increased incidence of AEs observed at 100 mg compared to 50 mg [40].

A network meta-analysis was conducted to examine the benefit-risk profile using the number needed to treat (NNT) and to harm (NNH) for ubrogepant in the acute treatment of migraine. The results showed that regarding pain freedom at 2 h post-dose, the NNTs for ubrogepant 25 mg, 50 mg, and 100 mg were 15, 12, and 9, respectively. Regarding freedom from MBS at 2 h post-dose, the NNTs were 15, 9, and 10 for ubrogepant 25 mg, 50 mg, and 100 mg, respectively. The NNHs to observe dizziness were 54 and −84 for ubrogepant 25 mg and 50 mg, respectively, whereas for nausea, the respective NNHs were 99, 83, and 47 for ubrogepant 25 mg, 50 mg, and 100 mg [41].

2.1.1.3. Results from real-world studies. A real-world, single-center, questionnaire-based, cohort study evaluating the efficacy, tolerability, and safety of ubrogepant predominantly in CM patients (86.8% of the study population) revealed that headache freedom at 2 h post-dose was achieved in 19% of the patients, whereas headache relief (≥75% of all treated attacks) at 2 h after taking ubrogepant was observed in 47.6% of patients with migraine. The most common reported AEs were fatigue (27.4%), dry mouth (7.5%), and nausea/vomiting (6.6%). These real-world results demonstrated higher AE rates associated with ubrogepant compared to data reported in clinical trials [42].

The UNIVERSE study, an observational, cross-sectional trial of Migraine Buddy mobile application users taking at least four doses of ubrogepant, reported that the patients had high satisfaction with pain relief and improvement in QoL [43,44].

2.1.2. Rimegepant

Rimegepant is a potent, selective, and competitive human CGRP receptor antagonist. On 27 February 2020, the US FDA approved rimegepant for the acute treatment of migraine in adults. This is the first CGRP receptor antagonist, which is available also as a fast-acting orally disintegrating tablet (ODT). Regarding the pharmacokinetics of rimegepant ODT, the Tmax is 1.5 h, the plasma protein binding is 96%, it metabolized by CYP3A4 (hepatic), the elimination half-life is 11 h, and it is excreted through feces [28].

2.1.2.1. Results from RCTs. A single-dose, dose-ranging (10, 25, 75, 150, 300, or 600 mg), randomized, multicenter, double-blind, placebo-controlled, outpatient study of BMS-927711 (later called rimegepant) for the acute treatment of migraine reported the rates of achieving pain freedom at 2 h post-dose to be 31.4% for rimegepant 75 mg, 32.9% for 150 mg, 29.7% for 300 mg, and 24.4% for 600 mg *versus* 15.3% for placebo. The most frequent AEs were nausea (3% for 75 mg, 3% for 150 mg, 4% for 300 mg, and 8% for 600 mg), dizziness (1% for 75 mg, 2% for 150 mg, 0% for 300 mg, and 4% for 600 mg), and vomiting (2% for 75 mg, 0% for 150 mg, 0% for 300 mg, and 2% for 600 mg). No serious AEs and no discontinuation were reported. Based on the study results, doses of 75 mg, 150 mg, and 300 mg of the investigational drug were superior to placebo in aspect of efficacy [45].

A multicenter, double-blind, randomized, placebo-controlled, phase 3 trial investigating the efficacy and safety of a single dose of rimegepant (75 mg oral standard tablet) in the acute treatment of low-frequency EM revealed that, in a modified intention-to-treat analysis of patients at 2 h post-dose, pain freedom was achieved in 19.6% (rimegepant) *versus* 12.0% (placebo). Another primary end point was the freedom of MBS at 2 h post-dose, which was achieved in 37.6% of patients in the rimegepant group and 25.2% in the placebo group. The most common AEs were nausea (1.8% for rimegepant *versus* 1.1% for placebo) and urinary tract infection (1.5% for rimegepant *versus* 1.1% for placebo). The liver function test showed that serum AST or ALT level above three times the upper limit of the normal range was zero in both study groups (Table 1) [29].

Another multicenter, double-blind, randomized, placebo-controlled, phase 3 trial was conducted to compare the efficacy and safety of an ODT formulation of rimegepant (75 mg single dose) in the acute treatment of low-frequency and moderate/severe intensity migraine. The results demonstrated that rimegepant ODT was superior to that of placebo in terms of 2 h post-dose pain freedom (21% *versus* 11%). Regarding the co-primary end point, the freedom of MDS at 2 h post-dose was achieved in 35% in the rimegepant group compared to 27% in the placebo group. The most common AEs were nausea (2% in the rimegepant group *versus* < 1% in the placebo group) and urinary tract infection (1% in rimegepant group *versus* 1% in placebo group), and no serious AEs were reported. Only one out of the 1466 participants in each treatment group had an elevated liver enzyme (transaminase) concentration more than three times the upper limit of normal [13].

A matching-adjusted indirect comparison study of rimegepant 75 mg every other day as a migraine prophylaxis and of erenumab and galcanezumab revealed that the change in monthly migraine days (MMDs) from baseline achieved by rimegepant was not statistically significantly different from that achieved by galcanezumab or erenumab. Regarding disability, rimegepant showed no statistically significant differences from galcanezumab and erenumab in terms of changes in the MIDAS score. Regarding the HR-QoL, rimegepant was favorable *versus* erenumab and generally similar to galcanezumab across all migraine-specific quality-of-life version 2 (MSQv2) domains [46].

A *post hoc* analysis of a long-term safety study of rimegepant 75 mg in patients with EM is performed, and the MSQv2

survey was collected and mapped to EuroQol five-dimension (EQ-5D) utilities. Descriptive associations were noted between lower MMDs and better HR-QoL. Rimegepant is therefore capable of reducing the frequency of MMDs and in parallel increasing the quality of life [47].

A *post hoc* analysis of a multicenter, long-term, open-label, phase 2/3 safety study of rimegepant 75 mg for the acute treatment of migraine (BHV3000–201) conducted by *Lipton et al* [48] evaluated the changes in MMDs, tablet utilization, and HR-QoL. The patients treated as needed (PRN) with oral rimegepant 75 mg had reduced MMD frequency and improved HR-QoL. During this 52-week-long period, tablet utilization remained stable [49].

Addressing the benefit-risk profile of rimegepant 75 mg ODT in the acute treatment of migraine by using NNT and NNH, a recent meta-study demonstrated an NNT of 8 to achieve pain freedom at 2 h post-dose, an NNT of 12 to achieve freedom from MBS at 2 h post dose, and NNHs of −81 and 24 for dizziness and nausea, respectively [41]. A phase 1, open-label, single-center study enrolled healthy lactating women assessing the pharmacokinetic profile of a single 75 mg oral dose of rimegepant revealed that the estimated infant exposure to maternal rimegepant from human milk is very low. The mean relative infant dose of rimegepant was less than 1% of the maternal dose [50].

2.1.2.2. Results from meta-analyses.

At present, no published data are available regarding this topic.

2.1.2.3. Results from real-world studies.

At present, no published data are available regarding this topic.

2.1.3. Zavegepant

Zavegepant (BHV3500–201, formerly named vazegepant) is a third-generation intranasally administered, high-affinity, selective, structurally unique, small-molecule CGRP receptor antagonist in development for the acute treatment of migraine. The indications for non-oral, i.e. intranasal therapy for patients with migraine, are concomitant gastrointestinal distress (nausea or vomiting), inadequate response to or inability to take oral acute treatments, and/or rapidly progressing head pain [12]. Regarding pharmacokinetics, the Tmax of zavegepant 5–40 mg nasal spray was 30 min [12]. The risk of drug–drug interaction was according to *in vitro* studies [12]. A comprehensive *in vitro* hepatotoxicity study, using DILIsym (a quantitative system toxicology model of drug-induced liver injury (DILI)) to predict and compare the hepatotoxicity of telcagepant, rimegepant, ubrogepant, atogepant, and zavegepant demonstrated significantly lower likelihood for zevagepant to cause DILI compared to telcagepant [51].

2.1.3.1. Results from RCTs.

A phase 2/3, randomized, double-blind, dose-ranging, placebo-controlled trial with a single dose of zavegepant (5 mg, 10 mg, or 20 mg) reported that pain freedom at 2 h post-dose was achieved in 22.5% and 23.1% of patients receiving zevagepant 10 mg or 20 mg, respectively, compared to 15.5% in the placebo group. Freedom from MBS at 2 h post-dose was achieved in 41.9% and 42.5% of patients receiving 10 mg and 20 mg, respectively, *versus* 33.7% in the placebo group. The dose of 5 mg did not statistically differ from placebo. The most frequent AEs were dysgeusia (13.5% at 10 mg dose and 16.1% at 20 mg *versus* 3.5% for the placebo), nausea (2.7% at 10 mg dose and 4.1% at 20 mg *versus* 0.5% for the placebo) and nasal discomfort (1.3% at 10 mg dose and 5.2% at 20 mg *versus* 0.2% for the placebo). Hepatotoxicity was not detected (Table 1) [12].

2.1.3.2. Results from meta-analyses.

At present, no published data are available regarding this topic.

2.1.3.3. Results from real-world studies.

At present, no published data are available regarding this topic.

2.1.4. Meta-analyses of new generation CGRP receptor antagonists (rimegepant, ubrogepant) in acute treatment of migraine

Meta-analyses containing non-FDA-approved gepants (BI44370TA, BMS927711, MK3207, and telcagepant) were out of scope of this review [52–55]. A meta-analysis focusing on the comparison of lasmiditan, ubrogepant, and rimegepant *versus* triptans (i.e. sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan) for acute migraine treatment revealed that as regards achieving pain freedom at 2 h post-dose, lasmiditan, rimegepant, and ubrogepant were associated with higher ORs compared to placebo, whereas lower ORs compared to most triptans. Ditans and gepants showed less efficacy compared to triptans, while gepants were associated with fewer AEs than triptans [56]. A network meta-analysis aimed to indirect comparison of lasmiditan (50, 100, and 200 mg) versus rimegepant (75 mg) and ubrogepant (25, 50, and 100 mg) in acute treatment for migraine resulted no statistically significant differences were demonstrated in 50 mg lasmiditan and ubrogepant and rimegepant for pain freedom at 2 hours and pain relief at 1 and 2 hours post-dose. Gepants showed less AEs compared to lasmiditan [57].

2.2. Gepants in the prophylactic treatment of migraine

2.2.1. Rimegepant

2.2.1.1. Results from RCTs.

A multicenter, randomized, double-blind, placebo-controlled phase 2/3 trial investigating oral rimegepant 75 mg standard tablet every other day for the preventive treatment of M0 and MA patients (with at least 4 and not more than 18 migraine attacks per month over the 3-month period before the screening visit) revealed that rimegepant had superior efficacy to placebo. The change of mean number of MMDs during weeks 9–12 was −4.3 days for rimegepant and −3.5 days for placebo. The most common AEs were nasopharyngitis (4% in the rimegepant group versus 2% in the placebo group) and nausea (3% in the rimegepant group versus 1% in the placebo group) (Table 2) [14].

As a health state utility mapping of rimegepant for the preventive treatment of migraine, a secondary evaluation of trial BHV3000–305 conducted by Croop et al. [14] was designed to analyze the outcomes of long-term health-related

quality of life of the rimegepant group with 4–18 MMDs in an open-label extension period and to map MSQv2 to EQ-5D-4 L utility values over the 12-week-long double-blind treatment and open-label extension (13–64 weeks) periods. The results showed that rimegepant was superior to placebo in the double-blind treatment phase, revealed a similar improvement in MSQv2, and mapped health state utility values in both trial arms (originally taking either verum or placebo) over the 52-week open-label extension phase, where all patients were on rimegepant 75 mg every other day [59].

2.2.1.2. Results from meta-analyses. At present, no published data are available regarding this topic.

2.2.1.3. Results from real-world studies. At present, no published data are available regarding this topic.

2.2.2. Atogepant

On 28 September 2021, the FDA approved atogepant, a once-daily preventive treatment for EM in adults. Atogepant is an oral CGRP receptor antagonist developed for the preventive treatment of migraine. Atogepant tablets are available in different doses (10 mg, 30 mg, and 60 mg), all recommended to be taken once daily. Lower doses are specifically recommended for patients also taking other medications that are cytochrome P3A4 (CYP3A4) inducers.

The median Tmax of atogepant is 1–2 h, the plasma protein binding is 98.2%, it metabolized by CYP3A4, the elimination half-life is 11 h, and its excretion is predominantly through feces [28].

2.2.2.1. Results from RCTs. Atogepant PO was investigated in a double-blind, randomized, phase 2b/3 trial examining a range of oral doses (10 mg, 30 mg, and 60 mg once daily or 30 mg and 60 mg twice daily). Across the 12-week treatment period, the least square mean change from baseline in mean MMDs compared to the placebo was as follows: atogepant 10 mg once daily −4.0, 30 mg once daily −3.8, 60 mg once daily −3.6, 30 mg twice daily −4.2, and 60 mg twice daily −4.1 *versus* placebo −2.9. The most common TEAEs were nausea (ranging from 5% for atogepant 10 mg once daily to 12% for atogepant 60 mg once daily *versus* 5% for placebo) and fatigue (ranging from 1% for atogepant 10 mg once daily to 10% for atogepant 60 mg twice a day *versus* 3% for placebo). Significant decreases in MMDs were detected in all five atogepant dose groups. Atogepant was safe and well-tolerated in this study regimen (Table 2) [58].

A phase 3 multicenter, double-blind, parallel-group, randomized, placebo-controlled trial (the ADVANCE study) evaluated the efficacy of oral atogepant (in a once daily dose of 10 mg, 30 mg, or 60 mg) for prophylaxis in EM patients for 12 weeks. Regarding the primary efficacy end point, the changes of the mean number of MMDs from baseline across 12 weeks were −3.7 days for atogepant 10 mg, −3.9 days for atogepant 30 mg, and −4.2 days for atogepant 60 mg compared to −2.5 days for placebo. The most common AEs were constipation (6.9 to 7.7% across the doses) and nausea (4.4 to 6.1% across the doses). Regarding elevated ALT or AST serum levels being at least 3 times the upper limit of the normal range, two participants in the atogepant 10 mg group, two participants in the atogepant 30 mg group, one participant in the atogepant 60 mg group, and four participants in the placebo group were affected. The incidence of AEs leading to the discontinuation of atogepant was 4.1% for the 10 mg dose, 1.8% for the 30 mg dose, 2.6% for the 60 mg dose, and 2.7% for the placebo [18].

Another aspect of the ADVANCE trial addressed the time course of efficacy of atogepant for the preventive treatment of migraine. The mean change from baseline in weekly migraine days in week 1 ranged from −0.77 to −1.03 for atogepant *versus* −0.29 with placebo. Migraine headache reported by study subjects on post-dose day 1 ranged from 10.8% to 14.1% for atogepant *versus* 25.2% with placebo. This effect was sustained during the whole study period (12 weeks) [60].

A phase 1, open-label, randomized, five-way, cross-over, single-center, pharmacokinetic, drug-drug interaction trial investigated the safety of single-dose 60 mg atogepant, 1000 mg acetaminophen, 500 mg naproxen, or co-administered atogepant with acetaminophen or naproxen in healthy persons. It was revealed that in the case of co-administration, the mean pharmacokinetic values of atogepant (i.e. area under the plasma drug concentration-time curve, peak plasma concentration, time to peak plasma concentration, and half-life) were similar to any drugs administered alone. The above combinations were safe and well-tolerated, and no clinically significant drug–drug interactions were reported [61].

A phase 1b, multi-center, open-label, fixed-sequence study aimed to analyze the pharmacokinetic profile of the co-administration of atogepant (60 mg once daily) and ubrogepant (100 mg) on a fixed-dose schedule every 3 days. A single dose of ubrogepant had no statistically significant effect on atogepant pharmacokinetics. Co-administration of ubrogepant with atogepant resulted in no clinically meaningful changes in pharmacokinetic parameters [62].

A phase 1, open-label, single-center, 2-period, fixed-sequence study examined the effect of multiple-dose atogepant 60 mg once daily on the single-dose pharmacokinetics of a combined hormonal contraceptive (ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg) in healthy postmenopausal or oophorectomized women. Atogepant did not influence the pharmacokinetics of the widely used oral contraceptive [63].

2.2.2.2. Results from meta-analyses. A recent meta-analysis pooled 2,466 patients from three RCTs evaluated the efficacy and safety of atogepant (10, 30, and 60 mg once a day) for the prophylactic treatment of migraine revealed a significant reduction in MMDs with a beneficial safety profile [64].

2.2.2.3. Results from real-world studies. At present, no published data are available regarding this topic.

2.2.3. Meta-analyses of new generation CGRP receptor antagonists together (rimegepant, atogepant) in prophylactic treatment of migraine

At present, no published data are available regarding this topic.

Table 2. Summary of characteristics of gepants indicated for preventative migraine therapy.

Drug	RCT (phase)	Number of participants (completed)	Route of administration	Dose (mg)	Change from baseline in mean number of MMDs	Adverse events (drug%/placebo%)	Authors (year)	Ref.
Rimegepant	Phase 2/3	348 (75 mg) 347 (placebo)	PO (standard tablet) every other day	75 once daily	−4.3 (75 mg) −3.5 (placebo)	nasopharyngitis (4%/2%) nausea (3%/1%) urinary tract infection (2%/2%) upper respiratory tract infection (2%/3%)	*Croop, Lipton, Kudrow, Stock et al., Lancet 2021*	[14]
Atogepant	Phase 2b/3	92 (10 mg) 182 (30 mg) 177 (60 mg) 79 (30 mg BID) 87 (60 mg BID) 178 (placebo)	PO tablet	10 once daily 30 once daily 60 once daily 30 twice daily (BID) 60 twice daily (BID)	−4.0 (10 mg) −3.8 (30 mg) −3.6 (60 mg) −4.2 (30 mg BID) −4.1 (60 mg BID) −2.9 (placebo)	60 mg once daily/placebo: nausea (12%/5%) upper respiratory tract infection (5%/8%) nasopharyngitis (8%/2%) constipation (5%/2%) urinary tract infection (3%/2%) fatigue (3%/3%)	*Goadsby et al, Lancet Neurol 2020*	[58]
Atogepant	ADVANCE (Phase 3)	214 (10 mg) 223 (30 mg) 222 (60 mg) 214 (placebo)	PO tablet	10 once daily 30 once daily 60 once daily	−3.7 (10 mg) −3.9 (30 mg) −4.2 (60 mg) −2.5 (placebo)	60 mg once daily/placebo: constipation (6.9%/0.5%) nausea (6.1%/1.8%) upper respiratory tract infection (3.9%/4.5%) urinary tract infection (3.9%/3.6%) fatigue (3.9%/1.8%) nasopharyngitis (3.5%/3.6%) somnolence (1,7%/0.9%)	*Ailani, Lipton et al NEJM 2021*	[18]

Abbreviations: BID: twice daily; MMD: monthly migraine days; RCT: randomized controlled trial.

3. Conclusion

Small-molecule non-peptide CGRP receptor antagonists (i.e. ubrogepant, rimegepant, atogepant, and zavegepant) have a unique effect in different indications through the same mechanism of action, namely, by inhibiting the CGRP receptor. New-generation gepants represent the first drug group that was proved to be effective, safe, and well-tolerated in boththe acute and prophylactic pharmacological treatment of migraine, until now only for EM.

4. Expert opinion

Migraine as a frequent primary headache and a neurovascular disease is known for a long time, but neither its exact pathomechanism nor its effective acute or preventive treatment have so far been clarified. For patients with migraine who suffer from moderate or severe intensity of head pain and/or from serious non-painful accompanying symptoms, acute medication is needed. The current acute drug therapeutic options do not cover all migraine patients. Until now, triptans were the gold-standard specific acute drug treatment for migraine, but the rate of triptan failure due to its ineffectivity and/or intolerability is high; indeed, the ratio of triptan non-responders can reach some 30–40% among patients with migraine. Therefore, there was a strong need for pharmaceutical innovations, which resulted in the development of gepants. This road met several difficulties, such as the route of administration, which was first IV and subsequently a repeated PO formulation, both having been associated with substantially increased serum liver enzyme levels. The second- and third-generation gepants have been proved to be effective in the acute and/or preventive of migraine. The detailed data regarding their safety profile of gepants especially the risk of hepatotoxicity (drug-induced liver injury) for the long-term use are not available[51].

But there are still numerous questions rising up.

- One of them is that whether the new generation of gepants can fully substitute triptans in the acute treatment of migraine, not just in patients who had triptan failure but even in triptan-naïve patients. To answer this crucial question, head-to-head comparison of all gepants to all triptans and ditans is needed, because to date only oral rimegepant (75 mg) and oral sumatriptan (100 mg) have so far been compared.
- Following the principles of evidence-based medicine, it is fundamental to establish the level of the quality of evidence and the strength of the recommendation of gepants based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system.
- The next issue is whether the frequent use of gepants can cause medication overuse headache (MOH). Overuse of classic acute migraine medications leads to the development of MOH. Based on the diagnostic criteria of MOH, taking non-steroidal anti-inflammatory drugs (NSAIDs) more than 15 days per month or taking triptans more than 10 days per month is the upper limit. At present, based on the long-term study results, repeated acute rimegepant treatment is not likely to cause MOH; however, there are no available data about other gepants.
- Concerning the benefit-risk profile, being aware of the NNT and NNH values of an acute migraine drug is a landmark of clinical therapeutic decision-making. Regarding NNT, the pain freedom at 2 h post-dose and sustained pain freedom between 2 and24 h, pain relief at 2 h, and freedom from MBS are the main domains, whereas regarding NNH, dizziness and nausea are the most relevant factors. Until now, data on NNT and NNH are available only for ubrogepant (25 mg, 50 mg, and 100 mg) and rimegepant 75 mg ODT.
- Being familiar with drug–drug interactions, as a basic pharmacokinetic parameter, is crucial for clinicians. Orally administered gepants are metabolized by the CYP3A4 enzyme, and several other drugs use the same metabolizing enzyme system. The precise interactions of gepants with other pharmacons have not yet been comprehensively mapped.
- The peak prevalence of female patients with migraine is between 35 and 40 years of age, which is within the reproductive life period of women, which is relevant from the point of view of family planning and lactation. It is still questionable the safety profile of gepants during pregnancy and lactation. The only available data regarding this issue is due to rimegepant (75 mg single oral dose), which was considered safe and well-tolerated in healthy lactating women[50].
- In the therapeutic palette of prophylactic migraine medications (classic drugs, CGRP-targeting mAbs, and gepants), the exact place of gepants has not yet been clarified.
- At present, the strongly recommended migraine prophylactic treatment is CGRP-targeting mAbs. It is a question whether erenumab as a CGRP receptor targeting mAb can be co-administered with gepants, which also acts on the CGRP receptor.
- The efficacy and safety of gepants have not yet been proven in patients with CM. Based on the potential mechanism of action of CGRP in the chronification of migraine, it can be predicted that gepants can have beneficial effect in CM patients as prophylactic treatment.
- The aspects regarding cost-effectiveness of new generation of gepants strongly influence the recommendation of the health-care authorities.

Correct scientific answers for the above questions and comments will make it possible to decide whether gepants can be considered as real game changers in this field.

4.1. Five-year future perspectives

Further development of gepant-based therapy in acute and prophylactic migraine treatment needs continuous research and development.

(A) Real-world, long-term, well-designed, and large-subject-number studies are needed to delineate the efficacy and safety of gepants. Pharmacovigilance studies are also required.
(B) Meta-analyses are required for new-generation and FDA-approved gepants.
(C) The co-administration of atogepant as a prophylactic and ubrogepant as an acute migraine treatment resulted in no clinically meaningful changes in the pharmacokinetic parameters. In the near future, co-administration of all the other gepants for both acute and prophylactic treatment should be performed to address potential safety concerns.
(D) The economic aspects of the use of gepants should be mapped by making comparisons with the standard-of-care treatment.
(E) Expanding the spectrum of the possible routes of administration of gepants, such as with SC or rectal formulations, is required to provide relief for migraine patients with severe nausea and/or vomiting.
(F) It would be useful to determine the NNT and NNH of all the available gepants to aid the clinical decision-making.
(G) Biomarkers would be needed in order to follow the principles of personalized medicine to guide the choice between the two acute (i.e. ubrogepant and rimegepant) and two prophylactic (i.e. rimegepant and atogepant) gepants.
(H) There is a need for a biomarker to determine the rank of gepants in the ranking order of migraine prophylactic drugs.
(I) In specific populations of patients with migraine, such as in women who were not aware of their pregnancy, a registry is needed to evaluate the safety, tolerability, and side effects of gepants.
(J) The maximal monthly dose of gepants for acute indication should be defined.
(K) The maximal daily and monthly doses of each gepant should be clarified in order to define development of MOH regarding gepant use.
(L) The maximal duration of the prophylactic treatment period should be specified for each gepants. The possible restart time point after cessation of the preventive gepant therapy should be established.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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