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A NEW ERA IN MIGRAINE CARE: CLINICAL ADVANCES WITH RIMEGEPANT, UBROGEPANT, ATOGEPANT, AND ZAVEGEPANT – A NARRATIVE REVIEW

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ABSTRACT

Research objectives: To review and compare the mechanisms of action, clinical efficacy, safety, and unique clinical applications of four gepants - rimegepant, ubrogepant, atogepant, and zavegepant—in the management of migraine. To highlight the advantages of gepants over traditional migraine therapies, especially for patients with cardiovascular risks or medication overuse headache.
Methods: Narrative review synthesizing evidence from randomized controlled trials, observational studies, and meta-analyses. Literature search conducted via PubMed and Google Scholar, focusing on studies published between 2023 and 2025.
Key findings: Rimegepant is effective for both acute and preventive migraine treatment, with high patient satisfaction and a favorable safety profile. Ubrogepant is approved for acute treatment, showing efficacy particularly when administered early and in patients with cardiovascular contraindications. Atogepant is the first oral gepant approved specifically for migraine prevention, demonstrating significant reductions in monthly migraine days and acute medication use, even in patients unresponsive to other therapies. Zavegepant offers rapid relief via intranasal administration, making it suitable for patients with nausea or vomiting, though it has higher discontinuation rates compared to other gepants. All gepants exhibit generally mild and transient adverse events, with lower discontinuation rates than triptans.
Conclusions: Gepants represent a significant advancement in migraine management, providing effective and well-tolerated options for both acute and preventive treatment. Their distinct mechanisms and safety profiles allow for more personalized and safer migraine care, especially in populations unsuitable for older therapies. Future research should focus on direct comparative studies, long-term outcomes, and personalized treatment strategies to further optimize migraine management.

KEYWORDS

Migraine, Gepants, CGRP Antagonists, Acute Migraine Treatment, Migraine Prevention

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1. Introduction

1.1 Migraine and its impact on society

Migraine is a complex neurological disorder consisting of recurrent, mild to severe headaches often accompanied by a variety of different symptoms subject to individual variation.

Migraine can be classified into two main categories: migraine with aura and migraine without aura, as well as into episodic migraine (EM) and chronic migraine (CM). Chronic migraine is defined by the presence of headache on 15 or more days per month for a period longer than three months, of which at least eight days fulfill the diagnostic criteria for migraine with or without aura. Episodic migraine does not meet these criteria and it occurs with lower frequency. (Headache Classification Committee of the International Headache Society (IHS), 2018)

Migraine attack can include premonitory phase which can precede the pain up to 48 hours. In this time, the most commonly reported symptoms include fatigue, altered mood and hunger. Following this, some individuals may experience aura phase. Aura, which occurs in about 25–30% of migraineurs, is characterized by transient focal neurological symptoms, most commonly visual, but can also include sensory, motor, or language disturbances. The aura typically resolves within approximately 5 to 60 minutes. After aura the pain phase begins. The pain is often described as unilateral, pulsatile or throbbing, increased by physical activity. Headache is often accompanied by nausea, vomiting, photophobia, phonophobia, dizziness, cognitive dysfunction, sleep disorders, cutaneus allodynia and vertigo. In the aftermath, postdromal phase begins. It is reported by almost 80% of patients. Main symptoms include fatigue, neck stiffness, difficulties in concentrating, increased apetite, dull head pain and mood changes. (Puledda et al., 2023; Raggi et al., 2024)

An analysis from the 2016 Global Burden of Disease study, encompassing data from 132 countries, estimated that approximately 1.04 billion people worldwide experienced migraine. This corresponds to an overall global prevalence of 14.4%. Migraine is recognized as the second most disabling condition globally, surpassed only by low back pain. In 2016, migraine was responsible for an estimated 45.1 million years lived with disability worldwide (Burch et al., 2018). The median age for migraine onset is around 25 years, with most individuals experiencing it before age 35. The highest prevalence occurs in the fourth decade of life for both men and women. Migraine's high prevalence during the second, third, fourth, and fifth decades of life, which are peak periods for work and family responsibilities, contributes to its substantial global disability burden (Simmonds et al., 2023). Migraine is notably more common in women, a difference often attributed to female sex hormones. Women have a 3.25-fold higher risk of developing migraine than men. Globally, prevalence is 18.9% among women and 11.4% among men (Waliszewska-Prosół et al., 2025).

Yearly economic burden of migraine among patients with chronic migraine can range from £6,443 to £53,446 (Eltrafi et al., 2023).

Migraine is also associated with a range of comorbidities involving psychiatric comorbidities: anxiety, depression, PTSD, bipolar spectrum disorders. Cardiovascular and cerebrovascular comorbidities such as increased risk of cerebrovascular events, increased risk of deep white matter lesions (Raggi et al., 2024)

1.2 Pathophysiology

The pathophysiology of migraine is complex and multifaceted, shaped by both genetic factors and environmental triggers that contribute to episodic neurological disturbances. Consequently, the central mechanisms involving CGRP pathways will be examined to highlight the significance of therapies that target this system. Current research indicates that modulating CGRP activity can alter the trajectory of migraine through several identified mechanisms.

1.2.1 Calcitonin gene-related peptide (CGRP)

CGRP is a critical mediator in migraine. Elevated levels of CGRP are observed during migraine attacks in various bodily fluids, and its administration can induce migraine-like headaches in susceptible individuals. CGRP and its receptors are extensively distributed throughout the peripheral and central nervous systems, where they modulate inflammatory and nociceptive responses. The understanding of CGRP's role has led to the development of novel therapeutic strategies, including gepants, targeting either the peptide itself or its receptor (Durham, 2006, 2008; Durham & Vause, 2010; Raggi et al., 2024).

1.2.2 Trigeminovascular system (TVS) activation

The trigeminovascular system, which includes dural vessels, trigeminal endings, the trigeminal ganglion, and the trigeminal nucleus caudalis, plays a crucial role in processing pain signals (Biscetti et al., 2023). The activation of the TVS is a pivotal event in migraine pathophysiology. This results in the release of various vasoactive neuromodulators, prominently including Calcitonin Gene-Related Peptide, pituitary adenylate cyclase-activating polypeptide, and nitric oxide. When these molecules bind to their respective receptors, they initiate signaling cascades that lead to alterations in vascular tone, promoting vasodilatation and the transmission of pain signals. (Al-Hassany et al., 2023; Biscetti et al., 2023; Raggi et al., 2024).

1.2.3 Cortical Spreading Depression (CSD)

CSD is widely accepted as the neurophysiological basis for migraine aura and is thought to trigger migraine pain mechanisms. It manifests as a slowly propagating wave of neuronal and glial depolarization followed by a period of suppressed neuronal activity (Charles & Brennan, 2009; Takano & Nedergaard, 2008; Vitale et al., 2023). CSD involves significant alterations in brain ion homeostasis, neurotransmitter efflux (including glutamate), and changes in cerebral blood flow (Costa et al., 2013; Lauritzen et al., 2010). Furthermore, CSD can activate the trigeminal nervous system and upregulate CGRP expression, thereby contributing to the development of migraine pain (Kitamura & Imai, 2024).

1.2.4 Neuroinflammation

A growing body of preclinical evidence highlights the significant involvement of neuroinflammation in both episodic and chronic migraine (Erdener et al., 2021). This process involves the release of various inflammatory mediators, such as interleukins (e.g., IL-1β, IL-6, IL-8, IL-10), tumor necrosis factor-alpha, and chemokines, which contribute to glia-neuron crosstalk and the overall pathogenesis of migraine (Morgan & Nkadimeng, 2025; Song et al., 2024). CSD itself can also induce neuroinflammatory responses (Biscetti et al., 2023; Kurşun et al., 2021). CGRP also takes part in modulating inflammation (Durham, 2006, 2008; Durham & Vause, 2010; Raggi et al., 2024).

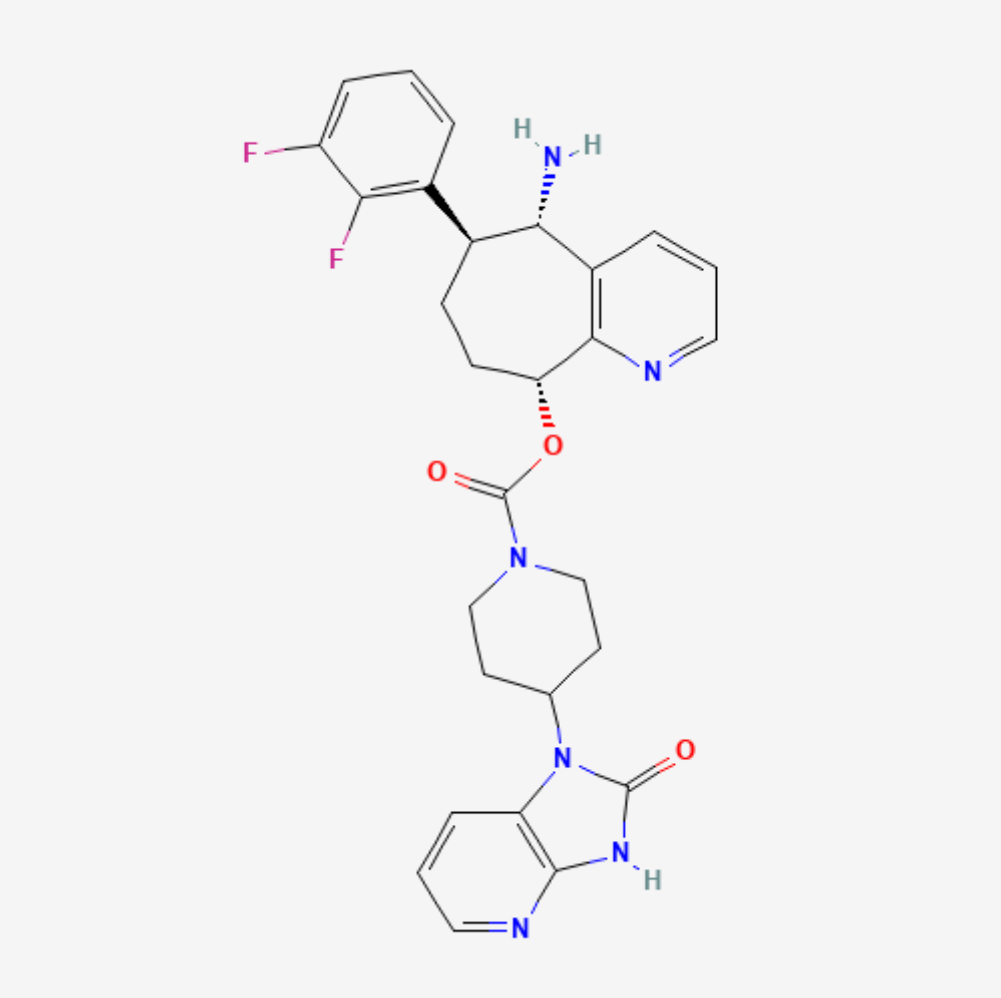
2. Methodology

The methodology for this article involved synthesizing evidence from randomized controlled trials, observational studies, and meta-analyses. A literature review was gathered using PubMed and Google Scholar. This article compiled data primarily from studies conducted between 2023 and 2025, representing the most recent research on this rapidly developing class of drugs.

3. Results

3.1 Rimegepant

3.1.1 General information



Rimegepant, a small-molecule calcitonin gene-related peptide receptor antagonist, is chemically identified as [(5*S*,6*S*,9*R*)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridin-9-yl] 4-(2-oxo-3*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate, with a molecular weight of 534.6. (National Center for Biotechnology Information, 2025, PubChem Compound Summary for CID 51049968, Rimegepant. Retrieved November 19, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Rimegepant.)

Rimegepant, was developed by Biohaven Pharmaceutical Holding Company Ltd., with initial Phase I trials commencing in November 2011. The orally disintegrating tablet formulation was specifically designed to enhance patient convenience and accelerate the response time (Scott, 2020).

Nurtec® ODT received its U.S. approval from the FDA in 2021 for the acute treatment of migraine and preventive treatment of episodic migraine in adults (NURTEC ODT- rimegepant sulfate tablet, orally disintegrating. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9ef08e09-1098-35cc-e053-2a95a90a3e1d&audience=professional; Kim et al., 2025). Rimegepant (Vydura®) was approved by the European Medicines Agency in 2022 for both the acute and preventive treatment of episodic migraine in adults (Vydura: EPAR - Product Information, 2025, Retrieved November 19, 2025 from https://www.ema.europa.eu/en/medicines/human/EPAR/vydura)

3.1.2 Mechanism of action

Rimegepant's primary mechanism of action involves its function as a calcitonin gene-related peptide receptor antagonist. It works by selectively binding with high affinity to the human CGRP receptor, thereby blocking or antagonizing the normal function of this receptor (Vydura: EPAR - Product Information, 2025, Retrieved November 19, 2025 from https://www.ema.europa.eu/en/medicines/human/EPAR/vydura)

3.1.3 Efficacy

Rimegepant has demonstrated significant efficacy in the acute treatment of migraine, based on recent real-world studies and meta-analyses.

A 2025 real-world study on Rimegepant's effectiveness and tolerability reported that 44.7% of participants achieved complete pain freedom two hours post-dose, and 82.7% experienced pain relief. Freedom from the most bothersome symptom two hours after administration was reported by 56.3% of participants. The study also found that 64.1% of participants were pain-free at 24 hours without rescue medication, and 39.8% showed no pain relapse within the 2-24 hour timeframe post-dose. In this same 2025 study, the rate of pain freedom two hours post-dose was 44.7%, with a higher rate observed when Rimegepant was taken within one hour of pain onset (Iannone et al., 2025).

The 2025 GAINER study highlighted that pain freedom rates at two hours post-dose were higher compared to older randomized trials. (Iannone et al., 2025). A 2024 systematic review and network meta-analysis supported Rimegepant's efficacy, showing that Rimegepant 75 mg had a relative risk of 1.75 (95% CI: 1.34, 2.28) for pain freedom at two hours compared to placebo. For freedom from main bothersome symptom at two hours, Rimegepant 75 mg demonstrated an RR of 1.61 (95% CI: 1.07, 2.43) against placebo (Laohapiboolrattana et al., 2024).

Rimegepant has demonstrated notable efficacy in the preventive treatment of migraine. In a randomized controlled clinical trial, leading to a mean reduction of monthly migraine headache days by –4.4 (0.2) across three months, with a reduction of –4.9 (0.2) specifically at month 3. Furthermore, 61.0% of participants receiving rimegepant achieved at least a 50% reduction in monthly migraine headache days over three months, with this figure rising to 69.0% at month 3. More significant reductions were also observed, with 33.0% of participants experiencing a 75% response rate and 15.0% achieving a 100% response rate. The use of acute migraine medication also decreased, with a reduction of –3.5 (0.1) monthly migraine headache days requiring such treatment in the rimegepant group (Schwedt et al., 2024).

In another double-blind, randomized controlled trial conducted in Japan, rimegepant 75 mg administered every other day showed a statistically significant reduction in monthly migraine days, with a mean difference of -1.1 days compared to placebo in the last four weeks of the treatment phase ($p = 0.002$) (Kitamura et al., 2025).

3.1.4 Quality of life and patient satisfaction

The 2025 GAINER study indicated that overall Rimegepant tolerability was rated as good or excellent by 85.4% of participants. Patient-reported outcomes supported high subjective satisfaction, largely driven by its excellent tolerability and effectiveness (Iannone et al., 2025).

In one analysis, rimegepant 75 mg showed a mean change of 3.50 in the Migraine-Specific Quality of Life questionnaire version 2.1 (MSQ v2.1) Role Function–Restrictive domain score when compared to placebo. The minimally important difference for the MSQ-RFR between groups is 3.2, suggesting a clinically meaningful improvement (Tassorelli et al., 2024). Across various scenario analyses, rimegepant was associated with MSQ v2.1 RFR scores ranging from 5.36 to 9.20 (Tassorelli et al., 2024). It also performed significantly better than erenumab across all MSQ v2.1 domains (Tassorelli et al., 2024).

Another study observed that rimegepant 75 mg resulted in a mean change from baseline at week 12 of 3.5 (with a standard error of 1.0) in the EQ VAS score, an indicator of health-related quality of life. This compared to 0.8 (standard error 1.1) for placebo, with the difference between rimegepant and placebo being 2.7 (95% CI: -0.19 to 5.54; $p = 0.067$) (Kitamura et al., 2025). Improvements from baseline in MSQoL, MIDAS, and EQ VAS scores at week 12 indicated benefits of rimegepant over placebo regarding quality of life and headache-related disability (Kitamura et al., 2025).

3.1.5 Adverse events

A 2025 double-blind, randomized controlled trial on Rimegepant for preventive migraine treatment in Japan reported that 54.7% of participants on Rimegepant experienced any adverse event, compared to 41.0% on placebo. Adverse events considered related to the study drug occurred in 9.7% of the Rimegepant group versus 4.4% in the placebo group. Serious adverse events were infrequent, affecting 0.8% (2 participants) of the Rimegepant group and 0.4% (1 participant) of the placebo group, with none deemed related to the study drug. The most common adverse events (occurring in ≥2% of any treatment group) in this study included

nasopharyngitis (Rimegepant 8.5%, Placebo 10.0%), oropharyngeal pain (Rimegepant 3.6%, Placebo 3.2%), coronavirus infection (Rimegepant 3.2%, Placebo 1.6%), upper abdominal pain (Rimegepant 3.2%, Placebo 0.8%), COVID-19 (Rimegepant 2.8%, Placebo 2.8%), constipation (Rimegepant 2.8%, Placebo 0.4%), pyrexia (Rimegepant 2.4%, Placebo 2.0%), influenza (Rimegepant 2.0%, Placebo 2.0%), and back pain (Rimegepant 1.2%, Placebo 2.4%) (Kitamura et al., 2025).

In a 2025 real-world study evaluating Rimegepant for acute migraine treatment, at least one adverse event was reported in 15.5% of cases (16 out of 103 participants). All reported adverse events were mild and self-limiting. The most common adverse events identified in over 2% of participants were fatigue (5.8%), gastrointestinal symptoms (5.8%), somnolence (3.9%), and transient cognitive difficulties (2.9%) (Iannone et al., 2025).

A 2024 analysis focusing on Rimegepant safety in patients with migraine and co-existing anxiety or depression, or those using antidepressants, showed varying rates of adverse events across subgroups. For instance, 67.1% of participants with anxiety experienced adverse events, compared to 58.4% without anxiety. Among those with depression, 62.0% reported adverse events, while 60.0% without depression did. When considering antidepressant use, 64.1% of those using SSRIs reported adverse events versus 60.0% not using SSRIs, and 66.2% using other antidepressants reported adverse events versus 59.8% not using them. Serious adverse events in these subgroups ranged from 2.3% to 5.1% (Kudrow et al., 2024).

Furthermore, a 2024 subgroup analysis examined Rimegepant safety in patients using preventive migraine medications. The proportion of participants experiencing at least one on-treatment adverse event was 68.7% among those using preventive medication and 59.2% among those not using preventives. Serious adverse events occurred in 4.5% of the group using preventive medication and 2.3% of the group not using preventives. Common adverse events (occurring in ≥5% of either cohort) included upper respiratory tract infection (7.4% with preventives vs 9.0% without), nasopharyngitis (7.8% with preventives vs 6.6% without), sinusitis (7.0% with preventives vs 4.8% without), urinary tract infection (5.3% with preventives vs 3.6% without), and back pain (5.3% with preventives vs 2.8% without) (Berman et al., 2024)

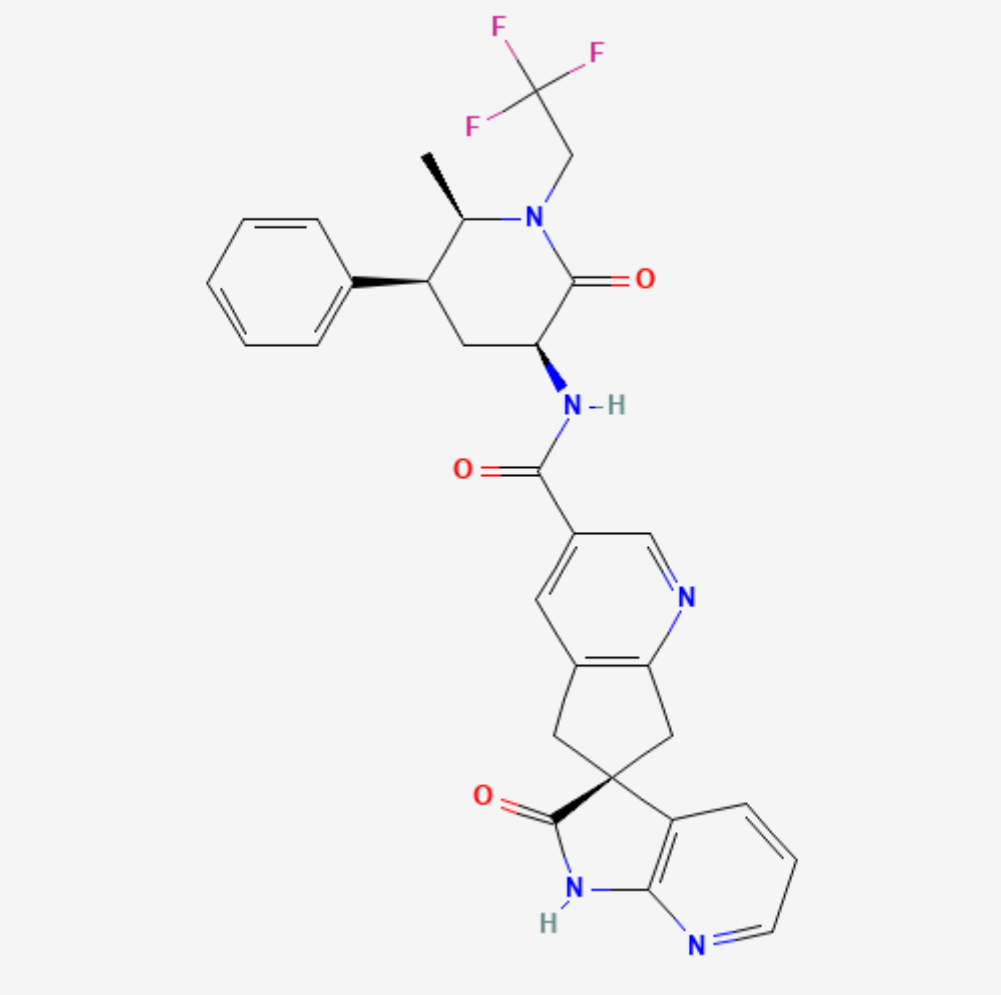
Another 2024 study noted that across subgroups based on cardiovascular risk factors, proportions of participants reporting adverse events and serious adverse events were consistent, and adverse events leading to study drug discontinuation were low (True et al., 2024).

3.1.6 Discontinuation

Discontinuation rates for rimegepant vary depending on the study population and the specific reasons for cessation.

One study specifically on healthy Chinese adults reported no AEs leading to discontinuation (Li et al., 2023).In another study, the rate of discontinuation due to adverse events was reported as 2.8% (Lipton et al., 2023). Another study found a 1.6% discontinuation rate from the study drug due to AEs (Kitamura et al., 2025). In a comparative clinical trial, 1.4% of participants in the rimegepant group discontinued the study due to an adverse event (Schwedt et al., 2024). When examining specific subgroups, AEs leading to discontinuation occurred in 4.5% of individuals also using preventive migraine medications, compared to 2.4% in those not using preventive medications (Berman et al., 2024). Furthermore, in participants with co-occurring anxiety or depression, discontinuation rates due to AEs ranged from 2.2% to 5.0%, depending on the specific subgroup and antidepressant use (Kudrow et al., 2024). Beyond adverse events, early discontinuation of rimegepant treatment has also been observed, with one real-world study in Denmark indicating that 45% of initiators filled only a single prescription (Pellesi et al., 2025). For comparison, triptans exhibit notably higher discontinuation rates. Studies report that discontinuation rates for triptans can be as high as 55.2% to 81.5% (Yang et al., 2021). The primary reasons for discontinuing triptan treatment often include a lack of efficacy or issues with tolerability (Laohapiboolrattana et al., 2024).

3.2 Ubrogepant
3.2.1 General information



Ubrogepant, a small-molecule calcitonin gene-related peptide receptor antagonist, is chemically identified as (3*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-yl]-2-oxospiro[1*H*-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxamide, with a molecular weight of 549.5. (National Center for Biotechnology Information, 2025, PubChem Compound Summary for CID 68748835, Ubrogepant. Retrieved November 19, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Ubrogepant.)

Ubrogepant (Ubrelvy™) was developed by Allergan under license from Merck & Co. The licensing agreement between Merck & Co. and Allergan for the worldwide rights of small molecule CGRP receptor antagonists, including ubrogepant, was established in July 2015. Allergan assumed full responsibility for the development, manufacturing, and commercialization of the products upon approval (Scott, 2020). As of 2025, Ubrelvy is manufactured for AbbVie Inc., with UBRELVY and its design being trademarks of Allergan Pharmaceuticals International Limited, an AbbVie company (UBRELVY- ubrogepant tablet. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fd9f9458-fd96-4688-be3f-f77b3d1af6ab)

Ubrogepant received its first global approval in the USA in 2019 (UBRELVY- ubrogepant tablet. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fd9f9458-fd96-4688-be3f-f77b3d1af6ab). This marked the first approval of an oral calcitonin gene-related peptide antagonist for the acute treatment of migraine (Scott, 2020).

Ubrogepant is indicated for the acute treatment of migraine attacks, with or without aura, in adults. It is important to note that Ubrogepant is not indicated for the preventive treatment of migraine (UBRELVY- ubrogepant tablet. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fd9f9458-fd96-4688-be3f-f77b3d1af6ab).

3.2.2 Mechanism of action

Ubrogepant is an orally administered, small molecule, highly-selective, calcitonin gene-related peptide receptor antagonist (UBRELVY- ubrogepant tablet. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fd9f9458-fd96-4688-be3f-f77b3d1af6ab).

3.2.3 Efficacy

In multicenter, randomized, placebo-controlled Phase III trials and their subsequent 52-week extension, as well as real-world studies, ubrogepant has demonstrated notable efficacy in the acute treatment of migraine.

Regarding pain freedom at two hours, the ACHIEVE I trial reported 19.2% for the 50 mg ubrogepant group and 21.2% for the 100 mg group, compared to 11.8% for placebo. Similarly, ACHIEVE II showed 21.8% pain freedom for 50 mg ubrogepant and 20.7% for 25 mg ubrogepant, versus 14.3% for placebo. Efficacy was particularly pronounced when treating attacks of mild intensity, with 57.1% achieving two-hour pain freedom with 50 mg ubrogepant and 51.1% with 100 mg, compared to 30.9% with 50 mg and 27.2% with 100 mg for moderate to severe attacks. Long-term data from the extension trial indicated sustained two-hour pain freedom at one year for approximately 23% of attacks treated with 50 mg and 25% with 100 mg ubrogepant.

For pain relief at two hours, long-term studies showed rates of 65% for the 50 mg dose and 68% for the 100 mg dose. In a real-world study, 74.7% of patients experienced a reduction of at least 3 points in pain intensity, and 21.8% experienced a reduction of 6 points or more on an 11-point visual analog scale. The two-hour pain relief rates were consistent between perimenstrual migraine attacks (64.8% and 67.1% for 50 mg and 100 mg doses) and non-perimenstrual attacks (64.9% and 67.8%) (Begasse de Dhaem et al., 2023).

A secondary analysis of randomized clinical trials was conducted to assess ubrogepant's efficacy in acute migraine treatment.

For pain freedom at two hours ubrogepant 50 mg demonstrated an odds ratio of 2.10 (1.40, 3.15) for female participants in the UBR-MD-01 trial compared to placebo. In the UBR-MD-02 trial female participants treated with ubrogepant 50 mg achieved an odds ratio of 1.63 (1.13, 2.34) for pain freedom at two hours versus placebo. For male participants in the UBR-MD-01 trial ubrogepant 50 mg had an odds ratio of 0.66 (0.22, 2.01) for pain freedom at two hours.

Regarding the absence of most bothersome symptom at two hours ubrogepant 50 mg in the UBR-MD-01 trial showed an odds ratio of 1.86 (1.36, 2.53) for female participants compared to placebo In the UBR-MD-02 trial female participants receiving ubrogepant 50 mg achieved an odds ratio of 1.71 (1.27, 2.31) for MBS freedom at two hours. For male participants in the UBR-MD-01 trial ubrogepant 50 mg had an odds ratio of 0.92 (0.39, 2.18) for MBS freedom at two hours (Goadsby et al., 2025)

A systematic review and network meta-analysis evaluated ubrogepant's efficacy in acute migraine treatment for triptan-insufficient responders.

Ubrogepant 50 mg demonstrated superior efficacy over placebo for two-hour pain freedom with a relative risk of 2.01 (95% CI: 1.18, 3.42). This was comparable to rimegepant 75 mg (RR 1.75, 95% CI: 1.34, 2.28) and lasmiditan 100 mg (RR 2.11, 95% CI: 1.55, 2.88). Across all novel abortive therapies including ubrogepant the pooled RR for pain freedom at two hours was 1.93 (95% CI: 1.52, 2.46). For two-hour pain relief ubrogepant 50 mg yielded an RR of 1.27 (95% CI: 1.05, 1.54) versus placebo. This was lower than lasmiditan 200 mg (RR 1.56, 95% CI: 1.34, 1.81), rimegepant 75 mg (RR 1.49, 95% CI: 1.33, 1.67), and lasmiditan 100 mg (RR 1.49, 95% CI: 1.28, 1.73)

For two-hour most bothersome symptom freedom ubrogepant 50 mg was not significantly superior to placebo with an RR of 1.54 (95% CI: 0.96, 2.47). This was similar to lasmiditan 50 mg (RR 1.49, 95% CI: 0.93, 2.40) which also showed no significant superiority. However, rimegepant 75 mg (RR 1.61, 95% CI: 1.07, 2.43), lasmiditan 200 mg (RR 1.52, 95% CI: 1.07, 2.16), and lasmiditan 100 mg (RR 1.50, 95% CI: 1.05, 2.13) did demonstrate superiority to placebo for MBS freedom. The pooled estimate for novel oral therapies for MBS freedom at two hours was 1.55 (95% CI: 1.37, 1.75) (Laohapiboolrattana et al., 2024)

3.2.4 Quality of life and patient satisfaction

In a prospective, multiple-attack, observational real-world effectiveness study employing an app-based design, ubrogepant's impact on patient satisfaction and quality of life for acute migraine treatment was evaluated. The study found that after 30 days, 69.8% (81/116) of participants reported satisfaction with ubrogepant, and 58.6% (68/116) were satisfied with ubrogepant in combination with their current preventive treatment. Furthermore, acute treatment optimization, defined as a mTOQ-4 score of 4 or greater, was achieved by 77.6% (90/116) of participants, with a mean mTOQ-4 score of 5.5 (SD 2.6) and a median of 6.0 (IQR 4.0; 8.0). Related to functional improvement, a return to normal function was observed in 25.4% of participants two hours post-dose and in 45.9% at four hours post-dose following the first treated attack. These findings collectively highlight a positive influence of ubrogepant on patient satisfaction and the ability to return to normal functioning (Manack Adams et al., 2023).

3.2.5 Adverse events

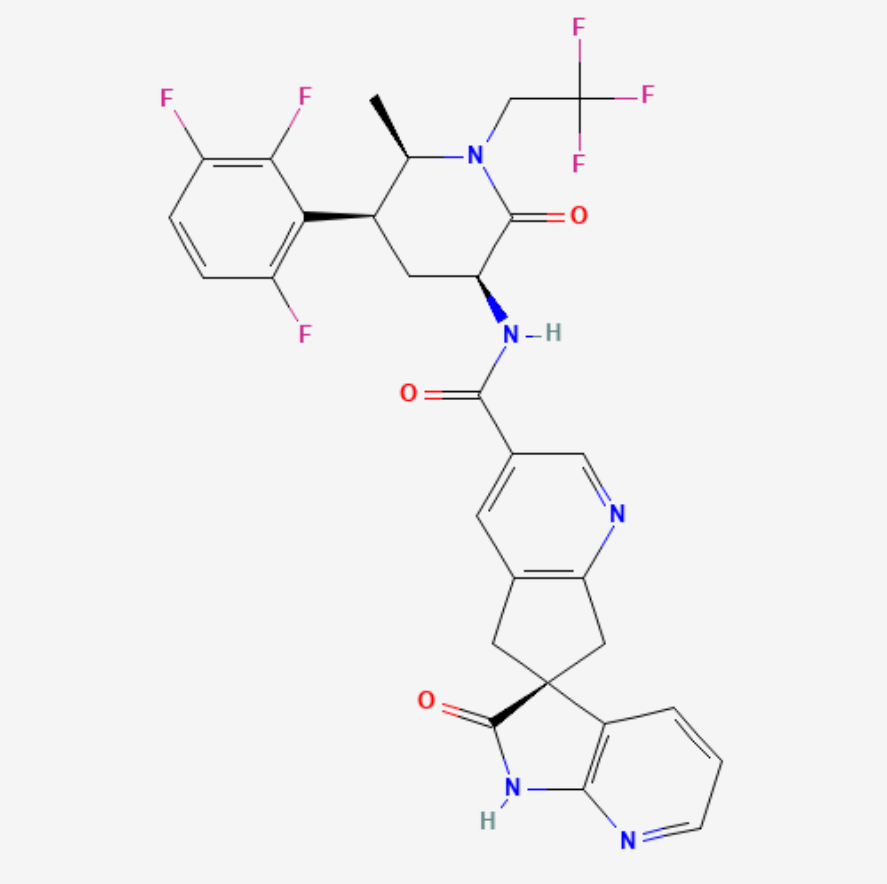
Based on a pharmacovigilance analysis of the U.S. Food and Drug Administration Adverse Event Reporting System database, ubrogepant exhibits a distinct safety profile among gepants. The most prevalent adverse event reported for ubrogepant was fatigue, affecting 7.19% of cases (n = 60). This contrasts with rimegepant, where "feeling abnormal" was most common (6.81%), and atogepant, frequently presenting with "constipation" (16.09%). Further analysis reveals other significant adverse events for ubrogepant across various System Organ Classes using ROR025 - the lower limit of the 95% two-sided reporting odds ratio of the information component. This includes nervous system disorders (314 cases, ROR025=1.92), gastrointestinal disorders (211 cases, ROR025=1.13), and psychiatric disorders (128 cases, ROR025=1.15). Specifically, a post-marketing investigation highlighted ubrogepant-induced constipation in 4.7% of patients. Additional reported adverse events include general disorders and administration site conditions (242 cases, ROR025=0.80), skin and subcutaneous tissue disorders (106 cases, ROR025=0.93), musculoskeletal and connective tissue disorders (102 cases, ROR025=0.96), and eye disorders (70 cases, ROR0%25=1.41). Of the 1958 ubrogepant reports identified in the study period from January 2020 to December 2024, the majority (n = 604, 30.85%) were recorded in 2022, with most cases classified as non-serious (1627 cases, 83.09%). However, death was also reported as an outcome in 30 cases (1.53%) associated with ubrogepant. (Song et al., 2025).

3.2.6 Discontinuation

In a long-term open-label study, the discontinuation rate attributed to adverse events was 2.2% for participants receiving 50 mg of ubrogepant and 2.7% for those receiving 100 mg (Begasse de Dhaem et al., 2023). In the TANDEM study, which investigated ubrogepant alongside atogepant, specific reasons for ubrogepant discontinuation during Treatment Period 2 included withdrawal by the participant (2.3%), being lost to follow-up (0.8%), other reasons (0.8%), and adverse events (0.4%). The mean ubrogepant use days for participants in Treatment Period 2 of the TANDEM study who took at least one dose was 6.6 (SD 5.0) days (Ailani et al., 2025).

3.3 Atogepant

3.3.1 General information



Atogepant, a small-molecule calcitonin gene-related peptide receptor antagonist, is chemically identified as (3*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl]-2-oxospiro[1*H*-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxamide, with a molecular weight of

603.5. (National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 72163100, Atogepant. Retrieved November 19, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Atogepant.)

Preclinical studies for atogepant were initiated in April 2008.Atogepant was developed by AbbVie. Initially, in July 2015, Merck entered into a licensing agreement with Allergan (which was later acquired by AbbVie) to divest the worldwide rights for atogepant and ubrogepant (Deeks, 2022).

Atogepant (marketed as Qulipta™) received its initial U.S. approval in September 2021. (QULIPTA- atogepant tablet. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8c8ab8f4-32bd-497a-befa-70c8a51d8d52)

In Europe, marketing authorization was granted in 2023. (Aquipta: EPAR - Product Information, 2025, Retrieved November 19, 2025 from https://www.ema.europa.eu/en/medicines/human/EPAR/aquipta).

It has been evaluated for the prophylaxis of episodic migraine (4 to 14 migraine days per month) and chronic migraine (15 or more headache days per month with at least 8 migraine days) (Aquipta: EPAR - Product Information, 2025, Retrieved November 19, 2025 from https://www.ema.europa.eu/en/medicines/human/EPAR/aquipta).

3.3.2 Mechanism of action

Atogepant is a calcitonin gene-related peptide receptor antagonist. Its mechanism involves inhibiting CGRP-induced vasodilatory responses in cultured human coronary, cerebral, and middle meningeal arteries. It shows affinity to several receptors of the calcitonin/CGRP-receptor family. The inhibitory effects on CGRP and amylin-1 receptors, which are considered involved in migraine pathophysiology, could be clinically relevant. (Aquipta: EPAR - Product Information, 2025, Retrieved November 19, 2025 from https://www.ema.europa.eu/en/medicines/human/EPAR/aquipta, 2025; QULIPTA- atogepant tablet. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8c8ab8f4-32bd-497a-befa-70c8a51d8d52; Deeks, 2022).

3.3.3 Efficacy

Meta-analyses of randomized controlled trials consistently demonstrate the efficacy of atogepant, an oral calcitonin gene-related peptide receptor antagonist, for the preventive treatment of both episodic and chronic migraine. A comprehensive meta-analysis of four randomized controlled trials, involving 2732 subjects, reported that atogepant significantly reduced monthly migraine days compared to placebo, with a standardized mean difference of −0.40 (95% CI -0.46 to -0.34, P<0.00001). This reduction in MMDs was observed across all dosage groups, and significant improvements were seen at different time points, including week 4 (SMD −0.47, 95% CI -0.53 to -0.41), week 8 (SMD −0.28, 95% CI -0.35 to -0.22), and week 12 (SMD −0.27, 95% CI -0.33 to -0.21) (Hou et al., 2024). Another meta-analysis, incorporating six randomized controlled trials with 4325 patients, similarly found a significant reduction in MMDs favoring atogepant over placebo (SMD −0.39, 95% CI: -0.45 to -0.33; $p < 0.00001$) (Shaukat et al., 2025). Furthermore, atogepant treatment also led to a significant decrease in monthly acute medication use days, with an SMD of −0.45 (95% CI -0.51 to -0.39, P<0.00001) (Hou et al., 2024). The 50% responder rate, defined as a 50% or greater reduction in MMDs over 12 weeks, was significantly higher with atogepant compared to placebo, with a combined relative risk of 11,63 (95% CI: 1,45–1,83; $p < 0,004$). Emerging evidence suggests that approximately 80% of long-term users achieve a ≥ 50% reduction in migraine frequency (Shaukat et al., 2025). In real-world settings, such as the prospective, multicentric STAR study, atogepant demonstrated effectiveness in reducing migraine frequency and improving patient-reported outcomes over a 12-week treatment period. Notably, 43.3% of patients who achieved a 50% MMD responder rate in this study had previously experienced an unsatisfactory response to anti-CGRP monoclonal antibodies (Vernieri et al., 2025). Comparative analyses further highlight atogepant's efficacy; a matching-adjusted indirect comparison analysis revealed that atogepant 60 mg once daily demonstrated a significantly greater reduction in mean MMDs across weeks 1–12 (mean difference −1.65, 95% CI −2.49 to −0.81; p< 0.001) and acute medication use days (MD −2.08, 95% CI −3.00 to −1.16; $p < 0.0001$) compared to rimegepant 75 mg once every other day (Tassorelli et al., 2024).

3.3.4 Quality of life and patient satisfaction

In a 2025 real-world, prospective, multicentric observational cohort study (the STAR study), Atogepant treatment demonstrated substantial improvements in patient-reported outcomes and satisfaction. Patients experienced a significant increase of 3 points in the mTOQ-6 score, signifying an optimized response to acute migraine treatment and restoration of function for daily activities. The study also reported a notable reduction in disability, with the Migraine Disability Assessment Scale score decreasing by over 40 points, from an average of 69 at baseline to approximately 28 after 12 weeks of therapy. The Allodynia Symptom Checklist score also decreased consistently from 6.2 at baseline to 3.8, suggesting an improvement in central sensitization. Patient satisfaction was further evidenced by a significant increase in the Migraine Specific Quality of Life Questionnaire scale score, both globally and in the role-function restrictive domain (Vernieri et al., 2025).

3.3.5 Adverse events

A systematic review and meta-analysis of randomized controlled trials indicate that Atogepant generally has a favorable safety profile, with some adverse events showing a higher incidence compared to placebo.

Across six randomized controlled trials involving 4256 participants, Atogepant treatment was associated with a statistically significant increase in the overall incidence of treatment-emergent adverse events compared to placebo, with a relative risk of 1.11 (95% CI: 1.02–1.21; $p = 0.02$). For Atogepant 60 mg once daily, the RR for TEAEs was 1.09 (95% CI: 0.93, 1.26) (Hou et al., 2024).

The most frequently reported adverse events include gastrointestinal issues such as constipation and nausea. Constipation demonstrated a combined relative risk of 2.55 (95% CI: 1.91, 3.41; $p < 0.00001$) across all Atogepant doses compared to placebo. Specifically, for Atogepant 60 mg once daily, the relative risk for constipation was 2.74 (95% CI: 1.74, 4.32; $p < 0.0001$). Nausea had a combined relative risk of 2.19 (95% CI: 1.67, 2.87; $p < 0.00001$). Other notable adverse events and their relative risks were urinary tract infection (RR 1.49 [1.05, 2.11]), upper respiratory tract infection (RR 0.86 [0.65, 1.13]), nasopharyngitis (RR 1.12 [0.82, 1.52]), and fatigue (RR 1.06 [0.75, 1.51]). For Atogepant 60 mg BID, the risk of fatigue was significantly higher (RR 3.07, 95% CI 1.13–8.35; $P = 0.03$) (Hou et al., 2024).

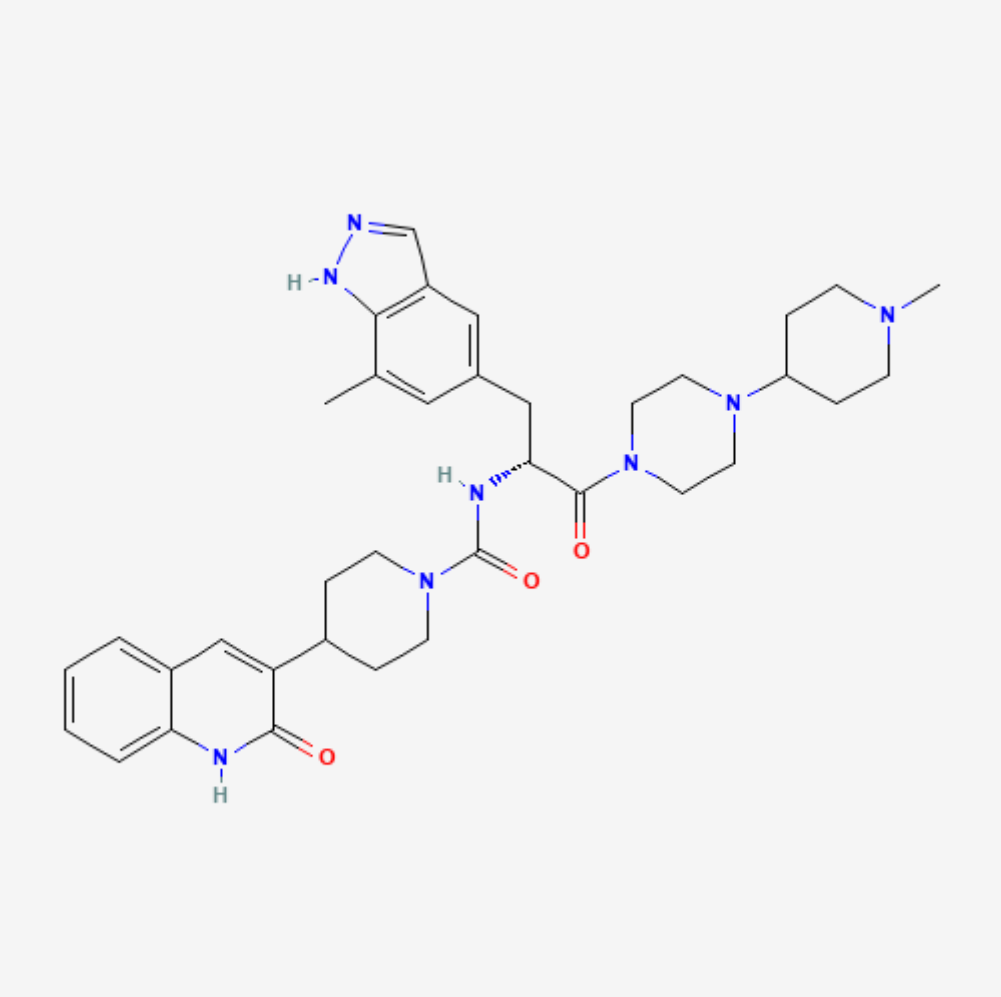
A real-life, prospective, multicentric study focusing on Atogepant 60 mg once daily reported that 10% (26 participants) experienced constipation and 10% (25 participants) experienced nausea. In comparison, the placebo group had 3% (8 participants) with constipation and 4% (9 participants) with nausea. In the ADVANCE trial, constipation rates ranged from 6.9% to 7.7% and nausea from 4.4% to 6.1% across various Atogepant doses. Serious treatment-emergent adverse events were reported in 4.4% (24 out of 543 participants) in a phase 3 open-label randomized trial (Vernieri et al., 2025). Transient, mild elevations of liver enzymes (ALT/AST) were observed in approximately 1–2% of patients in clinical trials, with most resolving upon drug discontinuation and no evidence of progressive liver injury over 52 weeks. Commonly reported adverse events also included tiredness, arthralgia, and dizziness in ≥5% of patients (Shaukat et al., 2025).

3.3.6 Discontinuation

In a 2025 real-world, prospective, multicentric observational cohort study (the STAR study) tolerability was favorable, with only 6.6% (7 out of 106 subjects) discontinuing treatment; 4 due to lack of effectiveness and 3 due to adverse events or poor tolerability. Although 44.3% of patients reported adverse events, only 3 discontinued due to tolerability issues. Notably, 43% of patients who were previously resistant to anti-CGRP monoclonal antibodies still benefited from Atogepant after 12 weeks (Vernieri et al., 2025).

3.4 Zavegepant

3.4.1 General information



Zavegepant, a small-molecule calcitonin gene-related peptide receptor antagonist, is chemically identified as *N*-[(2*R*)-3-(7-methyl-1*H*-indazol-5-yl)-1-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-1-oxopropan-2-yl]-4-(2-oxo-1*H*-quinolin-3-yl)piperidine-1-carboxamide, with a molecular weight of 638.8. (National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 53472683, Zavegepant. Retrieved November 19, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Zavegepant.)

Zavegepant was initially part of an exclusive, worldwide license agreement between Biohaven Pharmaceutical Holding Company and Bristol-Myers Squibb in July 2016 for its development and commercialization. Later, in October 2022, Pfizer acquired Biohaven Pharmaceutical Holding Company, thereby integrating zavegepant into its portfolio. It is currently developed by Pfizer under this license from Bristol-Myers Squibb (Dhillon, 2023).

Zavegepant, in its nasal spray formulation (ZAVZPRET™), received its first approval on March 9, 2023, in the USA. It is indicated for the acute treatment of migraine with or without aura in adults. However, it is not indicated for the preventive treatment of migraine (ZAVZPRET- zavegepant spray. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9c4a7aec-daef-4961-ba77-92f4b58be780.)

3.4.2 Mechanism of action

Zavegepant functions as a calcitonin gene-related peptide receptor antagonist (ZAVZPRET- zavegepant spray. Retrieved November 19, 2025 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9c4a7aec-daef-4961-ba77-92f4b58be780.). It is described as a highly potent, selective, and competitive third-generation, small-molecule CGRP receptor antagonist. Its action involves inhibiting the binding of CGRP to its receptor and effectively reversing CGRP-induced dilation in ex vivo human intracranial arteries (Dhillon, 2023).

3.4.3 Efficacy

Analysis from a meta-analysis showed that Zavegepant in total (95%Cl) showed Odds Ratio in Pain Freedom at 2 hours: 1.60 (Cl: 1.35, 1.90) and in most bothersome symptom freedom in 2 hours: 1.40 (Cl: 1.40, 1.61) (Waqas et al., 2023). A systematic review also quantified efficacy, reporting a relative risk of 1.54 (95% CI: 1.28–1.82, P < 0.001) for pain freedom and 1.26 (95% CI: 1.13–1.42, P < 0.001) for MBS freedom at 2 hours for Zavegepant 10 mg compared to placebo (Zhu et al., 2025). Rapid onset of action was observed, with pain relief starting as early as 15 minutes post-dose and a return to normal function at 30 minutes. Specifically, 21.9% of Zavegepant patients with moderate baseline pain achieved mild or no pain at 15 minutes, versus 12.0 % in the placebo group. Zavegepant also provided sustained effects; Patients spent over 2.5 hours more in pain freedom and approximately 3 hours longer with normal functioning over a 48-hour period compared to placebo. The proportion of time spent in a none/mild pain state was higher in the Zavegepant group, showing a 6% difference over placebo in MNAR imputation analysis (Powell et al., 2025). Additionally, treated patients were significantly more likely to achieve sustained pain freedom between 2 and 48 hours, indicated by an odds ratio of 1.74 (95% CI = 1.4–2.16, P <.00001) (Waqas et al., 2023). While it offers rapid and safe acute efficacy, a network meta-analysis indicated no significant superiority in long-term symptom relief or overall primary efficacy outcomes when directly compared to oral CGRP receptor antagonists (Zhu et al., 2025).

3.4.4 Quality of life and patient satisfaction

From a pharmacoeconomic perspective, zavegepant has been found to be cost-effective compared to rimegepant, with an incremental cost-effectiveness ratio of $67,941 per quality-adjusted life year gained, resulting in 0.016 higher QALY and an incremental cost of $1,115 (Qin & Barthold, 2025).

3.4.5 Adverse events

Zavegepant has demonstrated a generally favorable safety profile and is well-tolerated across various safety endpoints. In long-term open-label treatment over one year, 76.1% of participants experienced at least one treatment-emergent adverse event. The most frequently reported adverse events (occurring in ≥5% of participants) associated with zavegepant 10 mg nasal spray include dysgeusia (39.1%), nasal discomfort (10.3%), COVID-19 (7.5%), nausea (6.1%), nasal congestion (5.5%), throat irritation (5.5%), and back pain (5.3%). Serious adverse events were uncommon, reported in 1.2% (7 out of 603) of participants, with none considered treatment-related. Importantly, no cardiovascular adverse events were reported, even in participants with pre-existing cardiovascular contraindications to triptans (Mullin et al., 2024). While elevations in aminotransferases to >3 times the upper limit of normal occurred in 2.6% of participants, no concurrent elevations in bilirubin >2 times the upper limit of normal were observed, suggesting no indication of hepatotoxicity (Mullin et al., 2024).

3.4.6 Discontinuation

A Phase 2/3 open-label safety study evaluating zavegepant nasal spray for the acute treatment of migraine over one year observed significant discontinuation rates among participants. Out of 603 treated participants, 260 individuals (43.1%) did not complete the study. A total of 41 participants, representing 6.8% of those treated, discontinued the study due to adverse events. The most frequently reported AE leading to discontinuation was dysgeusia, affecting 1.5% (9/603) of participants. Other notable reasons for discontinuation included lack of efficacy (10.1%), participant withdrawal (9.5%), infrequent study drug usage (7.1%), and being lost to follow-up (5.5%). Local irritation AEs led to discontinuation in 2.3% (14 participants), with dysgeusia (1.5%, 9 participants) and nasal discomfort (0.8%, 5 participants) being the most frequent local irritation causes. Hepatic-related AEs resulted in discontinuation for 0.8% (5 participants) (Mullin et al., 2024)

4. Discussion

4.1 A summary of current approval status by FDA and EMA and administration routes is presented below:

Table 1. Approval status and administration pathways of gepants: FDA

Drug	Acute migraine treatment	Preventive treatment of episodic migraine	Preventive treatment of chronic migraine	Route of administration
Rimegepant	Yes	Yes	No	Oral (orally disintegrating tablet)
Ubrogepant	Yes	No	No	Oral (tablet)
Atogepant	No	Yes	Yes	Oral (tablet)
Zavegepant	Yes	No	No	Intranasal (nasal spray)

Table 2. Approval status and administration pathways of gepants: EMA

Drug	Acute migraine treatment	Preventive treatment of episodic migraine	Preventive treatment of chronic migraine	Route of administration
Rimegepant	Yes	Yes	No	Oral (orally disintegrating tablet)
Ubrogepant	Not approved	Not approved	Not approved	Not approved
Atogepant	No	Yes	Yes	Oral (tablet)
Zavegepant	Not approved	Not approved	Not approved	Not approved

4.2 What distinguishes rimegepant?

Rimegepant stands out among other gepants like ubrogepant and atogepant primarily because of its approval for both acute migraine treatment and migraine prevention. While ubrogepant is approved for acute treatment only, atogepant is primarily indicated for prevention (Laohapiboolrattana et al., 2024).

It offers versatility with demonstrated efficacy in pain freedom and reduction of monthly migraine days. Patients report high satisfaction due to its effectiveness and tolerability, leading to low discontinuation rates.

Rimegepant generally presents a milder side effect profile, especially when compared to older migraine treatments. Analyses indicate that gepants, including rimegepant, are associated with fewer adverse events when compared to triptans (Yang et al., 2021). This is largely due to rimegepant's mechanism of action, which avoids the cardiovascular risks associated with the vasoconstrictive effects of triptans (Puledda et al., 2023). Unlike older acute treatments (triptans), Rimigepant has not been associated with medication overuse headache (Alsaadi et al., 2025; Iannone et al., 2025; Johnston et al., 2022). This is a crucial benefit for patients who frequently require acute medication.

4.3 What distinguishes ubrogepant?

Ubrogepant is an acute migraine treatment option, particularly effective for mild attacks or when administered during the prodromal phase.

While ubrogepant can reduce the need for other acute treatments such as opioids (by approximately 28%), barbiturates (by 25%), ergots (by 15%), triptans (by 55%), and nonsteroidal anti-inflammatory drugs (by 38%), it is important to note that nearly all participants (99.5%) in an extension trial still required another acute treatment within two hours, including ibuprofen (54.5%), combination aspirin-acetaminophen-caffeine (36.4%), sumatriptan (27.6%), and acetaminophen (25.6%) (Begasse de Dhaem et al., 2023).

A key differentiation for Ubrogepant lies in its research supported for treating migraine during the prodromal phase. The PRODROME study, a phase 3 multicenter, randomized, double-blind, placebo-controlled, crossover trial, showed that Ubrogepant 100 mg administered during the prodrome significantly improved the ability to function normally, reduced activity limitations over 24 hours, and increased patient

satisfaction compared to placebo (Dodick et al., 2023; Lipton et al., 2024). In terms of direct efficacy, while a 2024 network meta-analysis noted no statistically significant differences in overall efficacy outcomes among Ubrogepant, rimegepant, and lasmiditan for triptan-insufficient responders, rimegepant did lead in relieving most bothersome symptoms (Laohapiboolrattana et al., 2024). However, initial phase III trials reported 2-hour pain freedom rates of only 19.2% for Ubrogepant 50 mg and 21.2% for Ubrogepant 100 mg, compared to 11.8% for placebo (Begasse de Dhaem et al., 2023). Furthermore, real-world data from 2023 indicates Ubrogepant's effective use for breakthrough migraines in patients concurrently receiving anti-CGRP monoclonal antibody preventive treatments, leading to meaningful pain relief and treatment satisfaction (Lipton et al., 2023). This highlights its utility within broader migraine management strategies, including its safety when co-administered with other CGRP receptor antagonists like atogepant (Brand-Schieber et al., 2024).

4.4 What distinguishes atogepant?

Atogepant stands out as the first oral CGRP receptor antagonist specifically approved for the preventive treatment of both episodic and chronic migraine. It reduces monthly migraine days and acute medication use, showing high efficacy, despite some gastrointestinal adverse events like constipation and nausea.

Atogepant significantly distinguishes itself from older-generation migraine drugs through its highly targeted mechanism of action, which involves specific calcitonin gene-related peptide receptor antagonism, unlike traditional preventive treatments such as antiseizure medications, beta-blockers, and antidepressants that have broader systemic effects (Hou et al., 2024; Shaukat et al., 2025; Song et al., 2025; Tassorelli et al., 2024). This selective CGRP pathway blockade directly interrupts the migraine cascade, leading to a more targeted and generally better-tolerated therapeutic approach compared to the less specific mechanisms of older treatments (Hou et al., 2024; Shaukat et al., 2025). While previous gepant generations faced challenges like hepatotoxicity, which led to their discontinuation, newer gepants like atogepant have demonstrated a safety profile in some studies that is comparable to placebo (Hou et al., 2024; Shaukat et al., 2025; Song et al., 2025). Atogepant has also proven effective in patients who had insufficient responses to conventional oral preventive treatments or other anti-CGRP monoclonal antibodies, thereby offering a valuable option for individuals unresponsive to prior therapies (Vernieri et al., 2025).

Atogepant distinguishes itself from other gepants primarily by being the first and only oral calcitonin gene-related peptide receptor antagonist specifically approved for the *preventive* treatment of both episodic and chronic migraine in adults. Atogepant possesses an extended half-life of approximately 11 hours, supporting its daily administration for prevention (Moore et al., 2024).

4.5 What distinguishes zavegepant?

Zavegepant introduces an intranasal route of administration for acute treatment, providing a rapid onset of action crucial for patients experiencing severe nausea or vomiting and has been shown to be cost-effective. However, it exhibits the highest discontinuation rate among all above, which raises concerns regarding its superiority over triptans.

Zavegepant, a calcitonin gene-related peptide receptor antagonist, represents a newer generation of acute migraine treatment that differs significantly from older-generation drugs, particularly triptans and some non-steroidal anti-inflammatory drugs, by offering a distinct mechanism of action and an improved safety profile for certain patient populations. Unlike triptans, which are serotonin 5-HT1B/1D receptor agonists that cause vasoconstriction and can be contraindicated in patients with cardiovascular disease, Zavegepant works by blocking CGRP receptor activity without inducing vasoconstriction (Zhu et al., 2025). This difference allows Zavegepant to be a viable option for patients for whom triptans are not suitable due to cardiovascular risks or intolerance (Zhu et al., 2025).

While the exact figures for older drugs can vary across studies, Zavegepant's profile demonstrates comparable efficacy to triptans in terms of acute pain relief, but with a potentially faster onset for some endpoints and a milder side effect profile. (Powell et al., 2025). The intranasal route of administration for Zavegepant also provides a non-oral option, which can be beneficial for migraineurs experiencing nausea or vomiting that might hinder the absorption of oral medications.

Zavegepant distinguishes itself from other gepant medications primarily through its unique intranasal administration, positioning it as the first calcitonin gene-related peptide receptor antagonist available as a nasal spray for acute migraine treatment (Mullin et al., 2024). This route of administration facilitates a rapid onset of action, with a time to maximum plasma concentration of approximately 30 minutes, which is notably faster than the typical 1.5 hours observed for oral gepants such as ubrogepant and rimegepant (Zhu et al., 2025).

Future perspectives

In the future, gepants may well become the treatment of choice for many individuals, alleviating the immense lifelong burden imposed by migraine, reducing disability, and enabling people to improve their overall quality of life and socioeconomic well-being. As research advances and access to modern therapies expands, these medications could mark a turning point in migraine care—shifting the focus from merely managing attacks to empowering patients with long-term stability, greater autonomy, and the possibility of living lives no longer defined by constant pain.

5. Conclusions

In this study, we underlined, that gepants, including rimegepant, ubrogepant, atogepant, and zavegepant, mark a significant advancement in migraine management by targeting the calcitonin gene-related peptide pathway. These CGRP receptor antagonists offer a novel approach distinct from older therapies, largely due to their lack of vasoconstrictive effects, making them a safer option for patients with cardiovascular concerns and posing no associated risk of medication overuse headache.

Collectively, gepants demonstrate significant efficacy in both acute and preventive migraine treatment, improving pain freedom, relief from other symptoms and reducing migraine frequency across various clinical settings. Each gepant offers unique advantages. Their safety profiles are generally favorable and well-tolerated, with common adverse events typically mild and transient, low discontinuation rates and high patient satisfaction. This can be compared to triptans, which are associated with poorly tolerated adverse events that frequently result in treatment discontinuation.

Future research should focus on comparative studies between gepants and other novel drugs to prioritise usage of most effective medications, further refine treatment algorithms, investigate long-term outcomes in diverse patient populations, and explore optimized treatment strategies, including combination therapies and personalized medicine approaches.

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