



## Antimigraine Agents, Other Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
<b>Calcitonin gene-related peptide (CGRP) antagonists</b>		
atogepant (Qulipta™) <sup>1</sup>	Abbvie	Preventive treatment of episodic migraine in adults
erenumab-aooe(Aimovig®) <sup>2</sup>	Amgen	Preventive treatment of migraine in adults
fremanezumab-vfrm (Ajovy®) <sup>3</sup>	Teva	Preventive treatment of migraine in adults
galcanezumab-gnlm (Emgality®) <sup>4</sup>	Eli Lilly	Preventive treatment of migraine in adults Treatment of episodic cluster headache in adults
rimegepant (Nurtec® ODT) <sup>5</sup>	Biohaven	Acute treatment of migraine with or without aura in adults Preventive treatment of episodic migraine in adults
ubrogepant (Ubrelvy®) <sup>6</sup>	Allergan	Acute treatment of migraine with or without aura in adults
<b>Serotonin (5-HT) 1F receptor agonist</b>		
lasmiditan* (Reyvow®) <sup>7</sup>	Eli Lilly	Acute treatment of migraine with or without aura in adults

\*Lasmiditan is a schedule V controlled substance.

The intravenous (IV) CGRP inhibitor eptinezumab-jjmr (Vyepti®), approved in February 2020, is not included in this review.

## OVERVIEW

### Migraine Headache

Headache is one of the most common complaints by patients when presenting to a physician. Migraine accounts for 10% to 20% of all headaches in adults and affects over 39 million men, women, and children in the United States (US).<sup>8,9</sup> It is estimated that 18% of women, 6% of men, and 10% of children experience migraine; migraine is the sixth most disabling illness in the world.<sup>10,11</sup> The American Migraine Study 2 found that migraine decreases productivity and causes absenteeism from work for many patients, which creates a large economic impact for the US.<sup>12</sup> Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month.<sup>13</sup> The median frequency of migraine attacks among migraine sufferers is 1.5 per month.<sup>14</sup>

Migraine is a complex neurological condition that can involve debilitating headache and sensory changes.<sup>15</sup> During a migraine attack neurologic changes occur in the cortex, brainstem, hypothalamus, thalamus, as well as peripheral and central portions of the trigeminovascular system. Migraine attacks are usually episodic, occurring < 15 days per month, but some migraine sufferers experience chronic daily headaches ≥ 15 days per month, often with migrainous features. Key features for the diagnosis of migraine headache includes an episodic headache lasting 4 to 72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity.<sup>16</sup> During the migraine at least 1 of the following are present: nausea and/or vomiting, or photophobia and/or phonophobia.

Several oral and non-oral treatments, including nonopioid analgesics, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), ergotamine derivatives, triptans, and combinations, are available for acute migraine pain, depending on severity and associated systems such as nausea.<sup>17</sup> Due to well-established efficacy, the triptans have become the drugs of choice for treating migraine attacks. Response rate to triptans is about 60%. Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy.<sup>18</sup> Indications for preventive therapy include  $\geq 4$  migraine attacks per month or  $\geq 8$  migraine days per month; acute medication overuse; and debilitating migraine.<sup>19,20</sup> The 2012 (reaffirmed in 2015) practice guidelines by the American Academy of Neurology (AAN) and the American Headache Society (AHS) advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention (Level A).<sup>21</sup> Frovatriptan is established for short-term menstrually associated migraine (MAM) prevention (Level A). Naratriptan, zolmitriptan (both for short-term MAM), antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention (Level B). However, no triptan is approved for the prevention of migraines. While there is a wide variety of agents to consider for episodic migraine prevention, side effects and failure to completely eliminate migraine attacks have resulted in an estimated adherence to therapy of only 20% after 1 year of treatment.<sup>22</sup> OnabotulinumtoxinA (Botox®) injection is indicated for prophylaxis of chronic migraine in adults.<sup>23</sup>

In 2018, the FDA approved the first calcitonin gene-related peptide (CGRP) inhibitors, erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality), for preventative treatment of migraines in adults. The 2021 American Headache Society (AHS) consensus statement on integrating new migraine treatments into clinical practice.<sup>24</sup> Unlike oral prophylaxis agents, these CGRP inhibitors do not require slow dose escalation, have a faster onset of therapeutic benefit, and have favorable tolerability profiles. The AHS recommends initiating CGRP inhibitors for migraine prophylaxis in patients  $\geq 18$  years of age with the following:

- Diagnosis of migraine (with or without aura) experiencing 4 to 7 monthly headache days with at least moderate disability and inability to tolerate or inadequate response to an 8-week trial of at least 2 oral prophylactic agents
- Diagnosis of migraine (with or without aura) experiencing 8 to 14 monthly headache days and inability to tolerate or inadequate response to a 8-week trial of at least 2 oral prophylactic agents
- Diagnosis of chronic migraine and either inability to tolerate or inadequate response to a 8-week trial of at least 2 oral prophylactic agents or at least 6 months (2 quarterly injections) of onabotulinumtoxinA treatment

According to the AHS, response to CGRP inhibitor therapy should be assessed after at least 3 months (for monthly injections) or 6 months (for quarterly injections). Therapy should only be continued if clinically meaningful treatment benefit can be documented. The statement also addresses non-pharmacologic therapy, including neuromodulation and biobehavioral therapies.

In December 2019, ubrogepant (Ubrovelvy) became the first FDA-approved oral CGRP inhibitor; rimegepant (Nurtec ODT) followed in February 2020. Both agents are approved for the acute treatment of migraines with or without aura in adults. The 2021 AHS consensus statement regarding integrating new migraine treatments into practice states these agents may be considered in patients who have contraindications to or have failed to respond to or tolerate at least 2 oral triptans, as assessed by a validated questionnaire.<sup>25</sup> Other therapeutic classes that are indicated for migraine prevention/treatment or with compelling data to support their use in this setting including, NSAIDs, anti-

epileptic agents, beta adrenergic blockers, select triptans, and onabotulinumtoxinA (Botox), are not addressed in this therapeutic class review. In May and September of 2021, rimegepant (Nurtec ODT) and atogepant (Qulipta), respectively, were approved for the preventive treatment of episodic migraine in adults. The AHS acknowledges that daily and near-daily long-term use of multiple drugs in the gepant class result in reductions in MMDs with no medication-overuse signals suggesting the possibility of using a single drug to achieve acute and preventive treatment, as seen with rimegepant, which is approved for both acute and preventive treatment of migraine. This Therapeutic Class Review will focus on the newest generation of antimigraine agents, composed largely of self-injectable (e.g., subcutaneous [SC]) and oral CGRP inhibitors for migraine prevention and acute treatment, respectively, as well as the oral serotonin 1F (5-HT<sub>1F</sub>) agonist lasmiditan (Reyvow). Eptinezumab-jjmr (Vyepti), an intravenous (IV) CGRP inhibitor indicated for migraine prevention, is not included in this review.

Ergotamine and dihydroergotamine target the 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> antimigraine receptors.<sup>26</sup> According to the AHS, ergotamine is probably effective and ergotamine derivatives have established efficacy for the acute treatment of migraine.<sup>27</sup> Non-oral formulations may provide benefit in patients who experience migraine associated with severe nausea or vomiting or who have difficulty swallowing oral medications. Ergotamine tartrate is available at a sublingual orally disintegrating tablet and as a fixed-dose oral tablet in combination with caffeine (Cafergot®, generics).<sup>28,29</sup> Dihydroergotamine mesylate injectable solution is administered via intravenous, intramuscular, or subcutaneous injection (D.H.E. 45®, generics) and as a metered-dose intranasal spray (Migranal® 0.5 mg/spray [and generics]; Trudhesa™ 0.75 mg/spray).<sup>30,31,32</sup> In addition, oral solution NSAID formulations of celecoxib (Elyxyb™) and diclofenac (Cambia®) are indicated for the acute treatment of migraine with or without aura in adults.<sup>33,34</sup> The ergotamine derivatives, dihydroergotamine mesylate, as well as the NSAID agents will not be reviewed in detail in this Therapeutic Class Review.

## Cluster Headache

Cluster headache (CH) is a severe, primary headache disorder characterized by extreme pain on one side of the head as well as autonomic symptoms (e.g., nasal congestion, lacrimation).<sup>35,36</sup> Periods of CH can persist for weeks to months with daily or more frequent attacks of 15 to 180 minutes in duration. The estimated lifetime prevalence of CH is more than one in 1,000. CH can be either episodic or chronic in nature with episodic CH being the predominant form. Individuals with episodic CH experience periods of attack followed by periods of remission, whereas individuals with chronic CH have minimal to no periods of remission between headache attacks.

In 2016, the AHS published an update to the American Academy of Neurology (AAN) 2010 guidelines for the treatment of cluster headache.<sup>37</sup> The guidance recommends sumatriptan administered subcutaneously (SC) at a dose of 6 mg, zolmitriptan nasal spray at a dose of 5 mg or 10 mg, and 100% oxygen at 6 to 12 L/minute for the acute treatment of episodic or chronic CH (Level A recommendation [established as effective]). Pharmacological therapies considered to be probably effective (Level B) for episodic and chronic CH include sumatriptan nasal spray 20 mg as well as zolmitriptan oral at a 5 mg or 10 mg dose. Sphenopalatine ganglion stimulation is a potential nonpharmacological treatment option for patients with chronic CH who are not satisfied with current therapy (Level B); however, it is not routinely available in the US. Octreotide 100 mcg SC as well as lidocaine 10% nasal spray are considered to be possibly effective (Level C) for both episodic and chronic CH. As of the date of guideline publication, insufficient evidence (Level U) existed to support the use of dihydroergotamine nasal spray, somatostatin, or prednisone. In general, the strength of the recommendation for the treatment modality

should be considered in conjunction with the potential safety profile, prescriber experience, patient-specific factors, and cost. Galcanezumab-gnlm (Emgality) is the first FDA-approved treatment for episodic CH that decreases the frequency of acute attacks.<sup>38</sup> It was not available at the time of the AHS guideline development.

## PHARMACOLOGY<sup>39,40,41,42,43,44,45</sup>

Migraine onset is believed to involve stimulation of the trigeminovascular system leading to the release of inflammatory mediators during neurogenic inflammation and/or cortical spreading depression (CSD).<sup>46</sup> The neuropeptide, calcitonin gene-related peptide (CGRP) is expressed in the trigeminal ganglia and acts in both the periphery to enhance nociceptor sensitization and the central nervous system (CNS) to enhance sensory input, thereby intensifying pain perception. In the periphery, CGRP may cause endothelium- and nitric oxide-independent dilation of vascular beds, including intracranial arteries. Conflicting evidence suggests that elevated levels of CGRP may occur in external jugular blood flow during migraine attack. Moreover, administration of sumatriptan have been shown to normalize elevated CGRP levels in patients with migraine.

Erenumab-aooe (Aimovig) is a human immunoglobulin G2 (IgG2) monoclonal antibody that inhibits CGRP expression by binding directly to the CGRP receptor. Fremanezumab-vfrm (Ajovy) and galcanezumab-gnlm (Emgality) are humanized IgG2 and IgG4 monoclonal antibodies, respectively, that bind to the CGRP ligand and prevent its reaching the CGRP receptor.

Atogepant (Qulipta), rimegepant (Nurtec ODT), and ubrogepant (Ubrelvy) are small molecule inhibitors of the CGRP receptor.

Lasmiditan (Reyvow) is a highly selective serotonin 1F (5-HT<sub>1F</sub>) receptor agonist. It's mechanism for treating migraines is not fully understood. Unlike triptans, which are selective 5-HT<sub>1B/D</sub> agonists, lasmiditan has not been associated with vasoconstriction.

## PHARMACOKINETICS<sup>47,48,49,50,51,52,53</sup>

Drug	T <sub>max</sub> (day)	Half-life (days)	Metabolism	Excretion
<b>Calcitonin gene-related peptide receptor antagonists</b>				
atogepant (Qulipta)	1–2 hours	11 hours	primarily by CYP3A4	Feces: 42% Urine: 5%
erenumab-aooe (Aimovig)	6	28	at low concentrations, predominantly through saturable binding to target (CGRP receptor); at higher concentrations, through a proteolytic pathway	--
fremanezumab-vfrm (Ajovy)	5-7	31	enzymatic proteolysis into small peptides and amino acids	--
galcanezumab-gnlm (Emgality)	5	27	enzymatic proteolysis into small peptides and amino acids	--
rimegepant (Nurtec ODT)	1.5 hours	11 hours	primarily by cytochrome P450 3A4 (CYP3A4); no major metabolites	Feces: 42% Urine: 51%
ubrogepant (Ubrelvy)	1.5 hours	5-7 hours	primarily by CYP3A4 metabolism	Feces: 42% Urine: 6%
<b>Serotonin (5-HT) 1F receptor agonist</b>				
lasmiditan (Reyvow)	1.8 hours	5.7 hours	primarily by non-CYP enzymes (hepatic and extrahepatic); also metabolized to M7 and M18; no active metabolites	Urine: 3% unchanged 66% as S-M8 metabolite

T<sub>max</sub> = time to maximum serum concentration; nr = not reported

Administration of rimegepant after a high-fat or low-fat meal has led to a delay in the T<sub>max</sub> by 1 to 1.5 hours, and a high-fat meal reduced the maximum concentration (C<sub>max</sub>) reached by 42% to 53%, and the overall exposure (area-under-the-curve [AUC]) by 32% to 38%; a low-fat meal decreased C<sub>max</sub> by 36% and AUC by 28%. For ubrogepant, the effect a high-fat meal is less pronounced on C<sub>max</sub> at 22% with no change in AUC; however, a high-fat meal delays T<sub>max</sub> by 2 hours.

## CONTRAINDICATIONS/WARNINGS<sup>54,55,56,57,58,59,60</sup>

Erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), galcanezumab-gnlm (Emgality), and rimegepant (Nurtec ODT) are contraindicated in patients with hypersensitivity to any component of the product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported in clinical trials with fremanezumab-vfrm; most events were mild to moderate in severity, but some led to therapy discontinuation or required corticosteroids therapy. Most occurred within hours of administration; however, some occurred days or weeks after administration. Anaphylaxis and angioedema have been reported in the postmarketing experience for erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm.

Constipation with complications as well as risk of hypertension or exacerbation of pre-existing hypertension have been observed with erenumab-aooe use.

Ubrogapant (Ubrelyv) is contraindicated with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)

Central nervous system (CNS) depression, including sedation and dizziness, may occur with use of lasmiditan. Use with alcohol or other CNS depressants may potentiate this affect. Lasmiditan may cause significant impairment in the ability to drive or operate machinery following a single dose. Patients should be advised not take lasmiditan unless they are able to avoid driving or operating machinery for at least 8 hours after each lasmiditan dose. In clinical trials, lasmiditan was associated with symptoms consistent with serotonin syndrome, which may occur with or without coadministration of other serotonergic drugs. If symptoms associated with serotonin syndrome occur, lasmiditan should be discontinued.

Lasmiditan labeling contains a warning about the overuse of acute migraine agents, which may lead to medication overuse headache. Medication overuse headache may present as migraine-like daily headaches or as a significant increase in frequency of attacks. Withdrawal of the offending agent(s) and treatment of symptoms may be necessary.

## **DRUG INTERACTIONS**<sup>61,62,63,64,65,66,67</sup>

No drug-drug interactions are reported for erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), or galcanezumab-gnlm (Emgality).

Use of atogepant (Qulipta) with strong cytochrome CYP3A4 inhibitors or organic-anion-transporting polypeptide (OATP) inhibitors may result in increased atogepant exposure; therefore, dose adjustment of atogepant is required with concomitant administration of any of these agents. In addition, concomitant administration with moderate and strong CYP3A4 inducers may result in decreased atogepant exposure and dose limitations of atogepant are recommended.

Avoid concomitant administration of rimegepant (Nurtec ODT) with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) due to a significant increase in rimegepant exposure. Increased exposure can also occur with concurrent administration with a moderate CYP3A4 inhibitor; another dose of rimegepant should not be taken within 48 hours when used concomitantly with a moderate CYP3A4 inhibitor. Coadministration of rimegepant and a strong or moderate CYP3A4 inducer may result in loss of effectiveness of rimegepant and should be avoided. Rimegepant is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters. Concurrent use may lead to a significant increase in rimegepant exposure and should be avoided with an inhibitor of any of these transporters.

Ubrogapant (Ubrelyv) has the potential for interactions with CYP3A4 inhibitors and inducers. Concurrent use with a strong, moderate, or weak CYP3A4 inhibitors increases plasma levels of ubrogapant; do not co-administer ubrogapant with strong CYP3A4 inhibitors. Dose adjustments are recommended if ubrogapant is used concurrently with moderate CYP3A4 inhibitors (e.g., cyclosporine, ciprofloxacin, fluconazole, fluvoxamine, grapefruit juice) or weak CYP3A4 inhibitors. Concurrent use of ubrogapant with a strong, moderate, or weak CYP3A4 inducer decreases plasma levels of ubrogapant which can result in loss of efficacy; avoid concurrent use with strong CYP3A4 inducers (e.g., phenytoin, barbiturates, rifampin, St. John's wort). Dose adjustments are recommended if ubrogapant is used concurrently with moderate or weak CYP3A4 inducers. Ubrogapant is a substrate for P-gp and BCRP and efflux transporters. Concurrent use with BCRP and P-gp inhibitors (e.g., quinidine, carvedilol, eltrombopag, curcumin) may

increase ubrogepant levels. Dose adjustments are recommended if ubrogepant is coadministered with BCRP and/or P-gp inhibitors.

Due to the propensity to cause CNS-related adverse effects, including sedation, lasmiditan (Reyvow) should be used cautiously in combination with alcohol or other CNS depressants. Use of lasmiditan with medications that increase serotonin may increase the risk of serotonin syndrome; therefore, caution is advised with use of lasmiditan in patients taking other serotonergic agents. Lasmiditan has been associated with a heart rate decrease. Use of heart rate lowering drugs with lasmiditan may result in further heart rate lowering. Avoid concomitant use of lasmiditan with P-gp or BCRP substrates.

## ADVERSE EFFECTS<sup>68,69,70,71,72,73,74</sup>

Injection site reaction, including pain, erythema, and pruritus, have been reported with the injectable CGRP agents: erenumab-aooe (Aimovig) 5% to 6% (3% placebo); fremanezumab-vfrm (Ajovy) 43% to 45% (38% placebo); and galcanezumab-gnlm (Emgality) 18% (13% placebo). Muscle spasms/cramps and constipation were reported in  $\leq$  3% in patients treated with erenumab-aooe. Adverse effects were found to be comparable with galcanezumab-gnlm when utilized for the treatment episodic cluster headache.

While anti-drug antibodies were detected for erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm, the available data were limited to determine their impact on safety and efficacy.

The most common adverse reactions in clinical trials with atogepant (Qulipta) (atogepant versus placebo, respectively) were nausea (5% to 9% versus 3%), constipation (6% versus 1%), and fatigue/somnolence (4% to 6% versus 3%). Also reported were transient, asymptomatic transaminase elevations  $>$  3 times the upper limit of normal (ULN) (1% versus 1.8%) and weight loss of  $\geq$  7% (3.2% to 4.9% versus 2.8%).

In clinical trials with oral rimegepant (Nurtec ODT) for the acute treatment of migraine, the most common adverse reaction was nausea (2% versus 0.4% with placebo). In clinical trials for the preventive treatment of episodic migraine with oral rimegepant, nausea (2.7% versus 0.8% with placebo) and abdominal pain/dyspepsia (2.4% versus 0.8% with placebo) were the most commonly reported adverse effects.

In clinical trials, the most common adverse effects ( $\geq$  2%) reported with ubrogepant (Ubrelvy) relative to placebo (reported as incidence with 50 mg, 100 mg versus placebo, respectively), were nausea (2%, 4% versus 2%) and somnolence (2%, 3% versus 1%). Dry mouth was also reported in 2% of ubrogepant patients receiving the 100 mg dose and  $<$ 1% of receiving ubrogepant 50 mg compared to 1% of placebo patients.

The most common adverse reactions reported in clinical trials (incidence  $\geq$  5% and greater than placebo) with lasmiditan (Reyvow) (reported as incidence with 50 mg, 100 mg, and 200 mg versus placebo, respectively) were dizziness (9%, 15%, and 17% versus 3%), fatigue (4%, 5%, and 6% versus 1%), paresthesia (3%, 7%, and 9% versus 2%), and sedation (6%, 6%, and 7% versus 2%).

## SPECIAL POPULATIONS<sup>75,76,77,78,79,80,81</sup>

### Pregnancy

There are no adequate data to inform of developmental risks associated with the use of atogepant (Qulipta), erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), galcanezumab-gnlm (Emgality), lasmiditan (Reyvow), rimegepant (Nurtec ODT), or ubrogepant (Ubrelvy) in pregnant women.

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Fremanezumab-vfrm has a long half-life that should be considered for women who are pregnant or plan to become pregnant.

## Pediatrics

Safety and effectiveness of the products in this review have not been established in pediatric patients.

## Geriatrics

Clinical studies of any of the CGRP inhibitors did not include an adequate number of patients aged  $\geq 65$  years to determine whether elderly patients respond differently from younger patients.

Clinical trials with lasmiditan reported a higher incidence of dizziness and larger increases in systolic blood pressure in patients aged  $\geq 65$  years compared to younger patients; however, the trials did not include an adequate number of patients aged  $\geq 65$  years to inform of differences in efficacy between the age groups.

## Hepatic Impairment

Hepatic impairment is not expected to affect pharmacokinetics of erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), or galcanezumab-gnlm (Emgality). No dedicated clinical studies to evaluate the impact of hepatic impairment have been conducted for these agents.

No dosage adjustment of atogepant and rimegepant is needed in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Their use should be avoided in patients with severe impairment (Child-Pugh C) due to increased drug plasma concentrations.

Higher degrees of hepatic impairment are associated with higher ubrogepant levels. Dose adjustments of ubrogepant are not required for mild to moderate hepatic impairment but are recommended for patients with severe hepatic impairment (Child-Pugh Class C).

Lasmiditan has not been studied in patients with severe hepatic impairment (Child-Pugh C); therefore, use in this patient population is not recommended. A dose adjustment is not required for patients with mild or moderate hepatic impairment (Child-Pugh A or B).

## Renal Impairment

Renal impairment is not expected to affect pharmacokinetics of CGRP inhibitors. No formal clinical studies to evaluate the impact of renal impairment have been conducted for erenumab-aooe, fremanezumab-vfrm, or galcanezumab-gnlm.

Dosage adjustment of atogepant is not recommended for patients with mild (creatinine clearance [CrCl], 60 to  $< 90$  mL/min) or moderate (CrCl, 30 to  $< 60$  mL/min) renal impairment. In patients with severe renal impairment (CrCl, 15 to 29 mL/min) and end-stage renal disease (ESRD) (CrCl  $< 15$  mL/min), the recommended dose of atogepant is limited to 10 mg daily. Administer atogepant dose after dialysis.

No dosage adjustment of rimegepant is needed in patients with mild, moderate, or severe renal impairment. Its use has not been evaluated in those with ESRD or on dialysis; it should be avoided in patients with ESRD.

No dose adjustments for ubrogepant are required in patients with mild to moderate renal impairment. Dose adjustments are recommended in those with severe renal impairment, and use should be avoided if ESRD is present.

No dose adjustment of lasmiditan is required based on renal function.

## DOSAGES<sup>82,83,84,85,86,87,88</sup>

Drug	Indication	Dosage	Availability
<b>Calcitonin gene-related peptide receptor antagonists</b>			
atogepant (Qulipta)	Preventive treatment of episodic migraine	10 mg, 30 mg, or 60 mg orally once daily	10 mg, 30 mg, and 60 mg tablets
erenumab-aooe (Aimovig)	Preventive treatment of migraine	70 mg SC once monthly; some patients may benefit 140 mg SC once monthly	70 mg/1 mL and 140 mg/1 mL single-dose prefilled syringe or SureClick® autoinjector (carton contains 1 syringe or autoinjector)
fremanezumab-vfrm (Ajovy)	Preventive treatment of migraine	225 mg once SC monthly or 675 mg every 3 months (administer as 3 consecutive 225 mg injections) When switching dosage options, administer the first dose of the new regimen on the next scheduled date of administration	225 mg/1.5 mL single-dose prefilled syringe or autoinjector (packages contain 1 syringe/ autoinjector or 3 autoinjectors)
galcanezumab-gnlm (Emgality)	Preventive treatment of migraine	240 mg SC (administered as 2 consecutive 120 mg injections) once as a loading dose, followed by 120 mg SC once monthly	120 mg/1 mL single-dose prefilled syringe and single-dose prefilled pen (carton contains 1 prefilled syringe or pen)
	Treatment of episodic cluster headache	300 mg SC (administered as 3 consecutive 100 mg SC injections) at the onset of symptoms, followed by 300 mg SC monthly through the end of the cluster period	100 mg/1 mL single-dose prefilled syringe (carton contains 3 prefilled syringes)
rimegepant (Nurtec ODT)	Preventive treatment of episodic migraine	75 mg orally every other day; place tablet on or under the tongue	75 mg orally disintegrating tablets (ODTs); package of 8
	Acute treatment of migraine	75 mg orally as needed; place tablet on or under the tongue Do not exceed 75 mg in a 24-hour period; safety of > 18 doses in a 30-day period has not been established	
ubrogepant (Ubrovelvy)	Acute treatment of migraine	50 mg or 100 mg orally with or without food as needed for migraine; if needed, a second dose may be taken ≥ 2 hours after the initial dose; maximum dose per 24-hour period is 200 mg The safety of treating ≥ 8 migraines in a 30-day period has not been established	50 mg and 100 mg tablets; package of 10

SC = subcutaneously

## Dosages (continued)

Drug	Indication	Dosage	Availability
<b>Serotonin (5-HT) 1F receptor agonist</b>			
lasmiditan (Reyvow)	Acute treatment of migraine	50 mg, 100 mg or 200 mg orally with or without food as needed for migraine; no more than 1 dose should be taken in a 24-hour period; the safety of treating > 4 migraine attacks per 30 days has not been established  Do not take < 8 hours before driving or operating machinery; a second dose has not been shown to be effective for the same migraine attack	50 mg and 100 mg tablets; package of 8

Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm should be administered by SC injection only and may be self-administered with proper training. Inject in the abdomen, thigh, or upper arm. Do not inject into skin that is tender, bruised, red, or hard.

Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm should be stored under refrigeration and placed at room temperature for at least 30 minutes prior to administration.

Components of the erenumab-aooe (Aimovig) prefilled syringe and autoinjector contain dry natural rubber (a derivative of latex), which may cause allergic reactions in latex-sensitive individuals.

Rimegepant ODT should be taken immediately after opening the blister pack.

Dose modifications of atogepant are required if used concurrently with certain medications and in patients with renal impairment.

- Severe renal impairment and end-stage renal disease (CrCl < 30 mL/min): 10 mg once daily
- Strong CYP3A4 inhibitors: 10 mg once daily
- Strong and moderate CYP3A4 inducers: 30 mg or 60 mg once daily
- OATP inhibitors: 10 mg or 30 mg once daily

Dose modifications of ubrogepant are required if used concurrently with certain medications and in patients with hepatic/renal impairment.

- Severe hepatic impairment (Child-Pugh Class C): 50 mg initial dose, 50 mg second dose
- Severe renal impairment (CrCl 15 to < 30 mL/min): 50 mg initial dose, 50 mg second dose
- Moderate CYP3A4 inhibitors: 50 mg initial dose, avoid administering the second dose within 24 hours of the first dose.
- Weak CYP3A4 inhibitors: 50 mg initial dose, 50 mg second dose
- Weak and moderate CYP3A4 inducers: 100 mg initial dose, 100 mg second dose
- BCRP and/or P-gp inhibitors: 50 mg initial dose, 50 mg second dose

## CLINICAL TRIALS

### Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized,

comparative, controlled trials performed in the US comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in US, single-blind or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

## Migraine

### ***atogepant (Qulipta) versus placebo***

Two randomized, multicenter, double-blind, placebo-controlled studies (Study 1, n=910 [NCT03777059]; Study 2, n=652 [NCT02848326]) enrolled adults with  $\geq 1$ -year history of migraine with or without aura, as based on the International Classification of Headache Disorders (ICHD-3) diagnostic criteria.<sup>89,90</sup> Eligible patients experienced 4 to 14 monthly migraine days (MMD). The mean MMD at baseline was 8 days in each study. Mean age was 42 years (Study 1) and 40 years (Study 2). The majority of patients were female. In both studies, patients were randomized (Study 1, 1:1:1:1; Study 2, 1:2:2:2) to atogepant 10 mg, 30 mg, or 60 mg or placebo once daily. Acute migraine treatment (e.g., triptans, ergotamine derivatives, NSAIDs, opioids, acetaminophen) was allowed as needed; use of other CGRP-targeted therapies was not permitted. The primary efficacy endpoint in both studies was the change from baseline in the mean MMD during the 12-week treatment period. The mean change from baseline in MMD for atogepant 10 mg, 30 mg, and 60 mg and placebo in Study 1 was -3.7, -3.9, -4.2, and -2.5 days, respectively ( $p < 0.001$  for all doses versus placebo), and in Study 2 was -4, -3.8, -3.6, and -2.8 days, respectively ( $p = 0.024$ ,  $p = 0.039$ , and  $p = 0.039$ , respectively, versus placebo). Similarly, significant changes in monthly headache days were seen with atogepant in each study compared to placebo. In Study 1, significant improvement in other secondary endpoints were also seen with all doses of atogepant compared to placebo; these endpoints included monthly acute medication use, percentage of responders that achieved  $\geq 50\%$  reduction in MMD, and quality of life measures.

### ***erenumab-aooe (Aimovig) versus placebo***

In the double-blind STRIVE study, 955 patients ages 18 to 65 years with episodic migraine (defined as 4 to 14 migraine days per month), with or without aura, were randomized 1:1:1 to erenumab-aooe 70 mg, erenumab-aooe 140 mg, or placebo administered SC monthly for 6 months.<sup>91</sup> At baseline, mean migraine days per month (MDM) was 8.3 in the overall study population. By months 4 to 6, the mean MDM (primary endpoint) was reduced by 3.2 days in the 70 mg group (difference from placebo, -1.4 [95% confidence interval {CI}, -1.9 to -0.9];  $p < 0.001$ ) and 3.7 days in the 140 mg group (difference from placebo, -1.9 [95% CI, -2.3 to -1.4];  $p < 0.001$ ) compared to 1.8 days in the placebo group. A reduction in mean MDM  $\geq 50\%$  was achieved in 43.3% of patients in the 70 mg group (odds ratio [OR], 2.13 [95% CI,

1.52 to 2.98];  $p < 0.001$ ) and 50% of patients in the 140 mg group (OR, 2.81 [95% CI, 2.01 to 3.94];  $p < 0.001$ ) versus 26.6% in the placebo group. Serious adverse events were similar between all groups.

In the double-blind ARISE study, 577 patients with episodic migraine were randomized 1:1 to placebo or 70 mg erenumab-aooe administered SC monthly for 3 months, and 570 patients were included in the efficacy analysis.<sup>92,93,94</sup> By 3 months, the mean MDM was reduced by 2.9 days in the treatment group compared to 1.8 days in the placebo group (treatment difference, -1 [95% CI, -1.6 to -0.5];  $p < 0.001$ ). A mean MDM  $\geq 50\%$  reduction was achieved in 39.7% of patients in the treatment group versus 29.5% of patients in the placebo group (OR, 1.59 [95% CI, 1.12 to 2.27];  $p = 0.01$ ). Safety and adverse events were similar between both groups.

The double-blind LIBERTY trial assessed erenumab-aooe in 246 adults with episodic migraine, with or without aura, who had failed 2 to 4 prophylactic migraine treatments in terms of efficacy and/or tolerability.<sup>95,96</sup> Patients were randomized 2:1 to SC erenumab-aooe 140 mg (two 70 mg injections) or placebo every 4 weeks for 12 weeks. At week 12, 30% of patients in the erenumab-aooe group achieved mean MD  $\geq 50\%$  reduction compared with 14% of patients in the placebo group (OR, 2.7 [95% CI, 1.4 to 5.2];  $p = 0.002$ ). Safety and adverse events were similar between both groups.

A double-blind study (NCT02066415) was conducted in 667 adults with a history of chronic migraine (defined as  $\geq 15$  headache days per month with  $\geq 8$  migraine days per month), with or without aura. Patients were randomized 3:2:2 to placebo, erenumab-aooe 70 mg, or erenumab-aooe 140 mg given SC monthly for 3 months.<sup>97</sup> At the end of the study, the mean MDM in both the 70 mg and 140 mg groups was reduced by 6.6 days compared to 4.2 days in the placebo group (treatment difference, -2.5 [95% CI, -3.5 to -1.4];  $p < 0.001$ ). A reduction in mean MDM  $\geq 50\%$  was achieved in 39.9% of patients in the 70 mg group and 41.2% of patients in the 140 mg group versus 23.5% of patients in the placebo group ( $p < 0.001$ ). Safety and adverse event profiles were similar between all groups.

### ***fremanezumab-vfrm (Ajovy) versus placebo***

The double-blind HALO EM study (NCT02629861) assessed the safety and efficacy of fremanezumab-vfrm in 1,875 patients with episodic migraine (defined as  $< 15$  headache days per month).<sup>98</sup> Patients were randomized 1:1:1 to fremanezumab-vfrm 225 mg monthly, fremanezumab-vfrm 675 mg every 3 months, or placebo monthly for 3 months. At baseline, mean MDM was 8.9, 9.3, and 9.1 in the fremanezumab-vfrm 225 mg and 675 mg groups and placebo group, respectively. By month 3, the mean MDM was reduced by 3.7 days in the 225 mg group and 3.4 days in the 675 mg group compared to 2.2 days in the placebo group ( $p < 0.001$  for each dose versus placebo). A reduction in mean MDM  $\geq 50\%$  was achieved in 47.7% of patients in the 225 mg group (difference from placebo, 19.8%;  $p < 0.001$ ) and 44.4% of patients in the 675 mg group (difference from placebo, 16.5%;  $p < 0.001$ ) versus 27.9% in the placebo group. Serious adverse events were similar between all groups.

In the HALO CM study (NCT02621931), 1,130 adults with a history of chronic migraine (defined as  $\geq 15$  headache days per month) were randomized 1:1:1 to fremanezumab-vfrm 675 mg initially followed by 225 mg monthly, fremanezumab-vfrm 675 mg given every 3 months, or placebo once monthly for 3 months total.<sup>99</sup> The results showed that the mean number of MDM in the 225 mg group and the 675 mg group were reduced by 4.6 days and 4.3 days, respectively, compared to 2.5 days in the placebo group ( $p < 0.001$  for both doses versus placebo). A reduction in mean MDM  $\geq 50\%$  was achieved in 40.8% of patients in the 225 mg group and 37.6% of patients in the 675 mg group versus 18.1% of patients with placebo ( $p < 0.001$  for both doses).

### ***galcanezumab-gnlm (Emgality) versus placebo***

The 6-month, double-blind EVOLVE-1 (n=858) and EVOLVE-2 (n=915) studies evaluated efficacy and safety of galcanezumab-gnlm in adults with episodic migraine.<sup>100,101</sup> Patients were randomized 2:1:1 to monthly SC placebo, galcanezumab-gnlm 120 mg, or galcanezumab-gnlm 240 mg. Patients in the 120 mg galcanezumab-gnlm arm received a 240 mg loading dose. The mean baseline migraine frequency in the studies was 9 MDM. In both trials, the primary endpoint of mean change from baseline in the number of MDM over 6 months was met for both galcanezumab-gnlm doses. In EVOLVE-1, treatment with galcanezumab-gnlm significantly reduced the mean MDM by 4.7 days (120 mg dose) and 4.6 days (240 mg dose), compared with placebo (2.8 days) ( $p < 0.001$  for both doses versus placebo); in EVOLVE-2, mean MDM were reduced by 4.3 days (120 mg) and 4.2 days (240 mg dose), and 2.3 days with placebo ( $p < 0.001$  for both doses versus placebo). Galcanezumab-gnlm was well tolerated.

The 3-month, double-blind REGAIN trial evaluated treatment with galcanezumab-gnlm in 1,113 adults with chronic migraine (defined as  $\geq 15$  headache days per month, of which  $\geq 8$  were migraines).<sup>102</sup> Patients were randomized 2:1:1 to monthly placebo, galcanezumab-gnlm 120 mg, or galcanezumab-gnlm 240 mg. All patients in the 120 mg galcanezumab-gnlm arm received a 240 mg loading dose. At baseline, mean number of monthly migraine headache days at baseline was 19.4. The primary endpoint of mean change from baseline in the number of monthly migraine headache days over 3 months was met for both galcanezumab-gnlm doses: reduction of 4.8 days (120 mg dose), 4.6 days (240 mg dose), compared to 2.7 days for placebo ( $p < 0.001$  for both doses versus placebo). Galcanezumab-gnlm was well tolerated.

An 8-week, double-blind study (NCT02397473) evaluated the efficacy and safety of galcanezumab-gnlm in adults with episodic cluster headache.<sup>103</sup> Patients (n=106) were required to have with an attack frequency of a minimum of 1 attack every other day and at least 4 total attacks with no greater than 8 attacks each day for 7 consecutive days and a CH period of at least 6 weeks duration. Patients were randomized 1:1 to placebo or galcanezumab-gnlm 300 mg given SC at month 0 and month 1. At baseline, the mean number of CH attacks per week was similar between the 2 study groups (17.8 with galcanezumab versus 17.3 with placebo). The primary endpoint of overall mean change from baseline in the number of weekly CH attacks from week 1 through 3 was met for galcanezumab-gnlm: reduction of 8.7 attacks per week, compared to 5.2 attacks for placebo ( $p = 0.04$ ). Galcanezumab-gnlm was well tolerated.

### ***lasmiditan (Reyvow) versus placebo***

The randomized, double-blind, SAMURAI trial (NCT02439320) compared lasmiditan 100 mg and 200 mg to placebo in patients  $\geq 18$  years of age with a diagnosis of migraine with or without aura as defined by the International Headache Society (IHS) diagnostic criteria.<sup>104</sup> Patients were eligible for inclusion if they had a diagnosis of disabling migraine for  $\geq 1$  year, a Migraine Disability Assessment Score of  $\geq 11$ , a migraine onset before 50 years of age, and 3 to 8 migraine attacks per month ( $< 15$  headache days per month). Patients enrolled in the SAMURAI trial (n=2,231) were randomized 1:1:1 to receive lasmiditan 200 mg, lasmiditan 100 mg, or placebo for the treatment of their next migraine attack. Patients were instructed to take the study medication within 4 hours of the onset of headache and recorded their responses using an electronic diary. The primary endpoint was the proportion of patients who were headache pain-free 2 hours after the first dose of study medication (200 mg lasmiditan versus placebo). Secondary endpoints included the proportion of patients who were headache pain-free 2 hours after the first dose of study medication (100 mg lasmiditan versus placebo) and the proportion of the patients who were free of the

most bothersome symptom (MBS) 2 hours after the first dose of study medication (200 mg versus placebo and 100 mg versus placebo). More patients treated with lasmiditan 200 mg were headache pain-free 2 hours after the first dose compared to placebo (32.2% versus 15.3%, respectively; odds ratio [OR], 2.6; 95% CI, 2 to 3.6;  $p < 0.001$ ). Likewise, more patients treated with lasmiditan 100 mg were headache pain-free 2 hours after the first dose compared to placebo (28.2% versus 15.3%, respectively; OR, 2.2; 95% CI, 1.6 to 3;  $p < 0.001$ ). Additionally, more patients receiving lasmiditan 200 mg compared to placebo were free of their MBS 2 hours after the first dose (40.7% versus 29.5%, respectively; OR, 1.6; 95% CI, 1.3 to 2.1;  $p < 0.001$ ) and lasmiditan 100 mg (40.9%; OR, 1.7; 95% CI, 1.3 to 2.2;  $p < 0.001$ ).

The randomized, double-blind, SPARTAN trial (NCT02605174) compared lasmiditan 50 mg, 100 mg, and 200 mg to placebo in patients  $\geq 18$  years of age with a diagnosis of migraine with or without aura as defined by the IHS diagnostic criteria.<sup>105</sup> Patients were eligible for inclusion if they had a diagnosis of disabling migraine for  $\geq 1$  year, a Migraine Disability Assessment Score of  $\geq 11$ , a migraine onset before 50 years of age and 3 to 8 migraine attacks per month ( $< 15$  headache days per month). Patients enrolled in the SPARTAN trial ( $n=3,005$ ) were randomized 1:1:1:1 to receive lasmiditan 200 mg, lasmiditan 100 mg, lasmiditan 50 mg, or placebo for the treatment of their next migraine attack. Patients recorded their responses using an electronic diary. The primary endpoints for the SPARTAN trial were the proportion of patients who were headache pain-free and MBS-free at 2 hours post dose for each treatment arm. A greater proportion of patients treated with lasmiditan were headache pain-free 2 hours after the first dose compared to 21.3% with placebo (lasmiditan 200 mg: 38.8% [OR versus placebo, 2.3; 95% CI, 1.8 to 3.1;  $p=0.001$ ]; 100 mg: 31.4% [OR versus placebo, 1.7; 95% CI, 1.3 to 2.2;  $p < 0.001$ ]; 50 mg: 28.6% [OR, 1.5; 95% CI, 1.1 to 1.9;  $p=0.003$ ]). Additionally, a greater percentage of lasmiditan-treated patients experienced freedom from MBS at 2 hours post dose compared to 33.5% of those treated with placebo (lasmiditan 200 mg, 48.7% [OR, 1.9; 95% CI, 1.4 to 2.4;  $p < 0.001$ ]; 100 mg, 44.2% [OR, 1.6; 95% CI, 1.2 to 2;  $p < 0.001$ ]; 50 mg, 40.8% [OR, 1.4; 95% CI, 1.1 to 1.8;  $p=0.009$ ]).

### ***rimegepant (Nurtec ODT) versus placebo***

A randomized, double-blind, placebo-controlled trial (NCT03461757) evaluated the efficacy of rimegepant for the acute treatment of migraine with and without aura in adults.<sup>106,107</sup> Patients were randomized to 75 mg ( $n=732$ ) or placebo ( $n=734$ ) and instructed to treat a migraine of moderate to severe headache pain intensity with a one dose. Rescue medication, such as NSAIDs, acetaminophen, and/or an antiemetic, was allowed 2 hours after the initial treatment; triptans were not allowed within 48 hours of initial treatment. At baseline, approximately 14% of patients were taking preventive medications, and no patients were taking agents that act on the CGRP pathway. The percentage of patients who were free of headache pain at 2 hours post dose was significantly higher with rimegepant than placebo (21.2% versus 10.9%, respectively;  $p < 0.001$ ). The proportion of patients free of the most bothersome migraine symptom (MBS) (e.g., photophobia, phonophobia, nausea) was significantly higher with rimegepant than placebo (35.1% versus 26.8%, respectively;  $p=0.001$ ). In addition, rimegepant treatment compared to placebo, respectively, resulted in significantly more patients who demonstrated pain relief at 2 hours (59.3% versus 43.3%;  $p < 0.001$ ) and sustained pain freedom at 2 to 48 hours (13.5% versus 5.4%;  $p < 0.001$ ), significantly fewer patients using rescue medication within 24 hours (14.2% versus 29.2%;  $p < 0.001$ ), and significantly more patients reporting normal function at 2 hours (38.1% versus 25.8%;  $p < 0.001$ ).

### ***rimegepant tablet versus placebo***

A double-blind, placebo-controlled trial randomized 747 adult patients with a history of migraine for at least 1 year to every other day oral administration of rimegepant 75 mg *tablet* or placebo.<sup>108,109,110</sup> At baseline, the average headache days per a 28-day observational period was 10.9, including an average of 10.2 migraine days. Medication for acute treatment for headache (aspirin, acetaminophen, NSAIDs, antiemetics, muscle relaxants, triptans) was allowed in the trial if needed. At baseline, 10% of enrollees were on a preventive medication for migraine other than a CGRP agent. During weeks 9 through 12, the reduction in the primary efficacy endpoint of change in mean MMD from baseline was significantly greater with rimegepant compared to placebo (4.3 versus 3.5, respectively; difference, 0.8; 95% CI, 1.46 to 0.2; p=0.01). In addition, significantly more patients on rimegepant compared to placebo achieved at least a 50% reduction in moderate to severe MMDs from baseline (49.1% versus 41.5%, respectively; difference, 7.6%; p=0.044). Two percent of patients in the rimegepant group discontinued therapy due to an adverse event compared to 1% in the placebo group. Rimegepant tablet is not an FDA-approved dosage formulation but has demonstrated bioequivalence to the rimegepant orally disintegrating tablet (ODT).<sup>111</sup>

### ***ubrogepant (Ubrovelvy) versus placebo***

In the ACHIEVE I study (NCT02828020), patients 18 to 75 years of age with  $\geq 1$  year history of migraine with or without aura as defined by the International Classification of Headache Disorders were randomized 1:1:1 to placebo (n=559), ubrogepant 50 mg (n=556), or ubrogepant 100 mg (n=557). Patients were instructed to treat a migraine with moderate to severe headache pain intensity.<sup>112</sup> Two to 48 hours after the first dose of study medication, patients with persistent or recurrent moderate or severe headache were allowed to take an optional second dose of study drug or their own rescue therapy. Patients in the placebo group were given 2 tablets of placebo for the optional second dose, whereas patients in the ubrogepant arms were re-randomized to either receive the second dose as 2 placebo tablets or the same dose of ubrogepant they had previously received. If a patient utilized the optional second dose, rescue medication was not allowed until at least 2 hours following the second dose of study drug. The coprimary efficacy endpoints were evaluated at 2 hours following the first dose of ubrogepant or placebo and included freedom from migraine pain (change in the severity of headache pain from moderate or severe pain prior to the initial dose to no pain) and absence of the most bothersome migraine symptom (MBS) (photophobia, phonophobia, or nausea). At 2 hours post-dose, a significantly greater number of patients in the 50 mg (19.2%; p=0.002 versus placebo) and 100 mg (21.2%; p<0.001 versus placebo) ubrogepant groups exhibited freedom from migraine pain compared to placebo (11.8%). Absence of the MBS was also significantly improved with ubrogepant 50 mg (38.6%; p=0.002 versus placebo) and 100 mg (37.7%; p=0.002 versus placebo) compared to placebo (27.8%). In addition, significantly more patients in the ubrogepant groups than in the placebo group exhibited improvements in the secondary endpoints of pain relief at 2 hours and had sustained pain relief from 2 to 24 hours (p=0.002 versus placebo for both endpoints for the 50 mg and 100 mg ubrogepant groups). As there was not a statistically significant difference between the 50 mg ubrogepant and placebo for the sustained freedom from pain from 2 to 24 hours or for the 100 mg group and placebo for the absence of phonophobia at 2 hours, no further assessment of secondary endpoints was performed due to the hierarchical testing design. Overall, the types of adverse events as well as proportion of patients who experienced side effects were comparable across study groups. The most common adverse events determined to be related to the trial drug and occurring in  $\geq 2\%$  of patients in any group were nausea, somnolence, and dry mouth.

In the ACHIEVE II study (NCT02867709), adults with moderate to severe migraine headache with or without aura experiencing 2 to 8 migraine attacks per month were randomized 1:1:1 to placebo (n=563), ubrogepant 25 mg (n=561), or ubrogepant 50 mg (n=562).<sup>113</sup> Other inclusion criteria were identical to ACHIEVE I. The coprimary efficacy endpoints were the same as in the ACHIEVE I study and were evaluated at 2 hours after taking the medication for a migraine attack of moderate or severe pain intensity. Beginning 2 to 48 hours after the first dose of medication, an optional second dose or rescue therapy was permitted with placebo patients receiving placebo for the second dose and ubrogepant-treated patients being randomized to receive the same dose of study drug as previously taken or placebo. Patients who decided not to take a second dose of study drug were eligible to receive rescue medication (e.g., acetaminophen, NSAIDs, opioids, antiemetics, triptans). At 2 hours post-dose, significantly more patients treated with ubrogepant 50 mg (21.8%; treatment difference 7.5%; 95% CI, 2.6% to 12.5%; adjusted p=0.01) and ubrogepant 25 mg (20.7%; treatment difference 6.4%; 95% CI, 1.5% to 11.5%; adjusted p=0.03) exhibited freedom from pain as compared to placebo (14.3%). Significantly more patients were absent of MBS at 2 hours post-dose in the ubrogepant 50 mg group (38.9%; treatment difference 11.5%; 95% CI, 5.4% to 17.5%; adjusted p=0.01) compared to placebo, but the ubrogepant 25 mg group (34.1%; treatment difference 6.7%; 95% CI, 0.6% to 12.7%; adjusted p=0.07) did not achieve a statistically significant improvement compared to placebo (27.4%). The proportion of treatment-emergent adverse effects were comparable between ubrogepant-treated patients and placebo patients with nausea being the most frequent event within the first 48 hours and within 30 days.

## Episodic Cluster Headache

### *galcanezumab-gnlm (Emgality) versus placebo*

A randomized, placebo-controlled trial enrolled 106 adults 19 to 65 years of age who met the International Classification of Headache disorders diagnostic criteria for episodic cluster headache.<sup>114</sup> Patients had  $\leq 8$  attacks per day,  $\geq 1$  attack every other day, and  $\geq 4$  attacks during the prospective 7-day baseline period. All patients were randomized in a 1:1 manner to receive once-monthly SC galcanezumab 300 mg or placebo. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen, and NSAIDs during the study. The primary efficacy endpoint for study 4 was the mean change from baseline in weekly cluster headache attack frequency across weeks 1 to 3. A secondary endpoint was the percentage of patients who achieved a response (defined as a reduction from baseline of  $\geq 50\%$  in the weekly cluster headache attack frequency) at week 3. A total of 90 patients completed the 8-week double-blind phase. In the prospective baseline phase, the mean number of weekly cluster headache attacks was 17.5 and was similar across treatment groups. The mean reduction in the weekly frequency of cluster headache attacks across weeks 1 through 3 was 8.7 attacks in the galcanezumab group, as compared with 5.2 in the placebo group (difference, 3.5 attacks per week; 95% CI, 0.2 to 6.7; p=0.04). The percentage of patients who had a reduction of  $\geq 50\%$  in headache frequency at week 3 was 71% in the galcanezumab group and 53% in the placebo group. There were no substantial between-group differences in the incidence of adverse events, except that 8% of the patients in the galcanezumab group had injection-site pain.

## SUMMARY

Migraine is a complex neurological condition that can involve debilitating headache and sensory changes. Migraine attacks are usually episodic (< 15 headache days per month), but some migraine sufferers experience chronic daily headaches at least 15 days per month, often with migrainous features.

Triptans are the drugs of choice for treating acute migraine attacks with a response rate of about 60%. Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy. Indications for preventive therapy include  $\geq 4$  migraine attacks per month or  $\geq 8$  migraine days per month; acute medication overuse; and debilitating migraine. General first-line recommendations for either episodic or chronic migraine prophylaxis include oral medications such as select beta-blockers, anti-epileptics, and antidepressants; however, side effects and failure to completely eliminate headache pain result in low adherence to preventive therapy, estimated at 20% after 1 year of treatment. OnabotulinumtoxinA (Botox) injections are FDA-approved for chronic migraine prophylaxis only.

Calcitonin gene-related peptide (CGRP) may play a significant role in enhanced pain perception during a migraine attack. In 2018, the FDA approved 3 injectable anti-CGRP monoclonal antibodies, erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality). All 3 injectable agents are shown to be effective and well tolerated for the preventive treatment of episodic and chronic migraines. With proper training, each agent may be self-administered SC once monthly; galcanezumab-gnlm requires an initial loading dose. Fremanezumab-vfrm may also be dosed once every 3 months by administering 3 consecutive injections.

In late 2019 and early 2020, the FDA approved the first 2 oral small molecule CGRP inhibitors, ubrogepant (Ubrelvy) and rimegepant (Nurtec ODT), for the treatment of acute migraine on an as-needed basis. In May 2021, rimegepant became indicated also for the preventive treatment of episodic migraine in adults. In September 2021, the FDA approved atogepant (Qulipta) for the preventive treatment of episodic migraine in adults.

In 2019, the FDA also approved the oral selective 5-HT<sub>1F</sub> agonist lasmiditan (Reyvow) to treat acute migraine attacks. Lasmiditan has not been associated with vasoconstriction that is seen with triptan agents, which are selective 5-HT<sub>1B/D</sub> agonists. Due to significant impairment in the ability to drive or operate machinery with lasmiditan, patients should not take lasmiditan unless they are able to avoid driving or operating machinery for  $\geq 8$  hours after each lasmiditan dose. Lasmiditan is a schedule V controlled substance.

The American Headache Society (AHS) recommends incorporating injectable CGRP inhibitors in preventive migraine therapy in patients experiencing episodic or chronic migraine who cannot tolerate or have had an inadequate response to a 8-week trial of at least 2 oral prophylactic agents; alternatively, intolerance or inadequate response to at least 6 months of onabotulinumtoxinA is appropriate in patients with chronic migraine. Similarly, rimegepant and ubrogepant, CGRP inhibitors approved for the acute treatment of migraine, are recommended in patients who have failed  $\geq 2$  oral triptan agents or are not candidates for triptan therapy. AHS acknowledges that the oral CGRP receptor antagonists, atogepant and rimegepant are effective for preventive therapy for episodic migraine.

One of the 3 FDA approved anti-CGRP monoclonal antibodies, galcanezumab-gnlm (Emgality), is also approved for the treatment of episodic cluster headache (CH) based on data demonstrating a significant reduction in the number of CH attacks per week compared to placebo. CH attacks are extremely painful headaches on 1 side of the head accompanied by autonomic symptoms. The AHS guidelines for treating CH do not currently address the use of galcanezumab-gnlm due to the recent approval; however, galcanezumab-gnlm is the first FDA-approved therapy to decrease the frequency of episodic CH attacks.

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