

Therapeutic Class Overview

Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015*).
 - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
 - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
 - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2017, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016*).
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 4 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm and galcanezumab-gnlm are 2 humanized monoclonal antibodies that target and potently bind the CGRP ligand, in most cases both the α and β isoforms. Ubrogепant is the only oral CGRP inhibitor (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
 - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of

olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- Two investigational CGRP inhibitors with near-term anticipated approvals include rimegepant, an oral tablet and oral disintegrating tablet CGRP inhibitor, and eptinezumab, an IV formulation that could be funded under the medical benefit. Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019, Staines 2019*).
- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently in early phase studies for the indication of cluster headache (*Clinicaltrials.gov 2019*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene-related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab-aooe)	-
Ajovy (fremanezumab-vfrm)	-
Emgality (galcanezumab-gnlm)	-
Ubrovelvy (ubrogepant)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab-aooe)	Ajovy (fremanezumab-vfrm)	Emgality (galcanezumab-gnlm)	Ubrovelvy (ubrogepant)
Acute treatment of migraine with or without aura in adults	⦿	⦿	⦿	✓*
Preventive treatment of migraine in adults	✓	✓	✓	⦿
Treatment of episodic cluster headache in adults	-	-	✓	⦿

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2019, Ajovy 2018, Emgality 2019, Ubrovelvy 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 open-label extension (OLE) trial in unpublished formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and

Data as of December 30, 2019 LMR/AKS

Page 2 of 15

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).

- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Erenumab-aooe

- The STRIVE trial was a 6-month, double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab-aooe 70 mg (mean change vs placebo, -1.4; 95% confidence interval [CI], -1.9 to -0.9; p < 0.001) and erenumab-aooe 140 mg (mean change vs placebo, -1.9; 95% CI, -2.3 to -1.4; p < 0.001). Erenumab-aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab-aooe was also associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference for 70 mg vs placebo, -0.9; difference for 140 mg vs placebo, -1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab-aooe 70 mg (mean change vs placebo, -1.0; 95% CI, -1.6 to -0.5; p < 0.001). Compared to placebo, erenumab-aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab-aooe was also associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference, -0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab-aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab-aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, -1.61; 95% CI, -2.70 to -0.52; p = 0.004). Erenumab-aooe was also associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference, -1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, -1.5; 95% CI, -2.0 to -0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, -1.3; 95% CI, -1.8 to -0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, -1.3) and 675 mg (mean change vs placebo, -1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference for 225 mg vs placebo, -1.4; difference for 675 mg vs placebo, -1.3) (*Dodick et al 2018[b]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanzumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanzumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanzumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanzumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
 - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanzumab-gnlm 120 mg (mean change vs placebo, -1.9; 95% CI, -2.5 to -1.4; p < 0.001) and galcanzumab-gnlm 240 mg (mean change vs placebo, -1.8; 95% CI, -2.3 to -1.2; p < 0.001). Galcanzumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanzumab-gnlm 120 mg and 9.4% more treated with galcanzumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanzumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference for 120 mg vs placebo, -1.8; difference for 240 mg vs placebo, -1.6) (*Stauffer et al 2018*).
 - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanzumab-gnlm 120 mg (mean change vs placebo, -2.0; 95% CI, -2.6 to -1.5; p < 0.001) and galcanzumab-gnlm 240 mg (mean change vs placebo, -1.9; 95% CI, -2.4 to -1.4; p < 0.001). Galcanzumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanzumab-gnlm 120 mg and 8.1% more treated with galcanzumab-gnlm 240 mg reported migraine cessation. Galcanzumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference for 120 mg vs placebo, -1.8; difference for 240 mg vs placebo, -1.7) (*Skljarevski et al 2018*).
 - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanzumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanzumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanzumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of chronic migraine

Erenumab-aooe

Data as of December 30, 2019 LMR/AKS

Page 4 of 15

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Erenumab-aooe was studied in a 12-week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab-aooe 70 mg (n = 191), or erenumab-aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab-aooe 70 mg and erenumab-aooe 140 mg (mean change for both doses vs placebo, -2.5; 95% CI, -3.5 to -1.4; p < 0.0001). Erenumab-aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab-aooe 70 mg (difference, -1.9) and erenumab-aooe 140 mg (difference, -2.6) significantly reduced the mean acute migraine-specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose-dependent (*Tepper et al 2017*).
 - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab-aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab-aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, -2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, -1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference for 225 mg vs placebo, -2.3; difference for 675 mg vs placebo, -1.8) (*Silberstein et al 2017*).
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, -2.1; 95% CI, -2.9 to -1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, -1.9; 95% CI, -2.7 to -1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine-specific medication treatment days (difference for 120 mg vs placebo, -2.5; difference for 240 mg vs placebo, -2.1) (*Detke et al 2018*).
 - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (\geq 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2019, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n = 1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for \geq 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
 - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the most bothersome symptom (MBS) freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
 - Pain-free at 2 hours: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
 - MBS-free at 2 hours: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
 - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
 - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (\leq 2.5% for all arms) and dizziness (\leq 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to \geq 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, 308 patients completed 1 year of open-label (OL) treatment. For the \geq 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
 - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days

(mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, 65% (n = 184) of episodic migraine patients achieved a $\geq 50\%$ reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.

- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
 - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a $\geq 50\%$ reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
 - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence $\geq 15.0\%$) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2019, Ubrelvy prescribing information 2019*).
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
 - Established efficacy:
 - Triptans
 - Ergotamine derivatives
 - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
 - Opioids (butorphanol, although use is not recommended)
 - Combination medications
 - Probably effective
 - Ergotamine or other forms of DHE
 - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)

- Magnesium IV
- Isometheptene compounds
- Combination medications (codeine/APAP, tramadol/APAP)
- Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
- Ubrogепant was reviewed by the AHS prior to FDA-approval for recommendation. The AHS recommend it may have a role in patients with cardiovascular (CV) conditions or in cases of triptan contraindications. Further recommendations include patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
 - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
 - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence-based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
 - Level A (established efficacy and > 2 Class I trials):
 - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
 - Beta blockers: metoprolol, propranolol, and timolol
 - Triptans (for menstrual related migraine [MRM]): for short-term prophylaxis, frovatriptan
 - Level B (probably effective and 1 Class I or 2 Class II trials):
 - Antidepressants: amitriptyline and venlafaxine
 - Beta blockers: atenolol and nadolol
 - Triptans (for MRM): for short-term prophylaxis, naratriptan and zolmitriptan
 - Level C (possibly effective and 1 Class II trial):
 - Angiotensin-converting enzyme (ACE) inhibitors: lisinopril
 - Angiotensin II receptor blockers (ARBs): candesartan
 - Alpha agonists: clonidine and guanfacine
 - Antiepileptic drugs: carbamazepine
 - Beta blockers: nebivolol and pindolol
 - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
 - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
 - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
 - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).

- Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
 - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
 - Level A (established efficacy and ≥ 2 Class I trials):
 - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
 - Oxygen
 - Level B (probably effective and 1 Class I or 2 Class II trials):
 - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
 - Sphenopalatine ganglion stimulation
 - Level C (possibly effective and 1 Class II trial):
 - Cocaine/lidocaine nasal spray
 - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
 - Level A (established efficacy and ≥ 2 Class I trials):
 - Suboccipital steroid injection
 - Level B (probably effective and 1 Class I or 2 Class II trials):
 - Civamide nasal spray (not marketed in the US)
 - Level C (possibly effective and 1 Class II trial):
 - Lithium
 - Verapamil
 - Warfarin
 - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. In cases of serious or severe reactions, treatment should be discontinued.
- Erenumab-aooe has an additional warning and precaution associated with constipation with serious complications noted post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
- For the prevention of migraine, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. The most common adverse reactions observed in CGRP inhibitor prevention studies included injection site reactions (all agents) and constipation (erenumab-aooe only).
- For the treatment of episodic cluster headache, galcanezumab-gnlm was evaluated for 2 months in trials and the safety profile was similar to those adverse events observed in migraine prevention trials. Two patients discontinued DB treatment due to adverse events.
- For the treatment of acute migraines, the safety of ubrogepant was evaluated for up to 1 year in an OLE in patients who had ≥ 2 attacks/month. The most common adverse events were nausea (2 to 4%) and somnolence (2 to 3%). The most common adverse reaction resulting in discontinuation in the OLE was nausea.

- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration. No additional concerns were raised within the OLE at ≥ 3 years, including any CV events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with the 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Clinicaltrials.gov [NCT02873221] 2019, Eli Lilly and Company [data on file] 2018, Stauffer et al 2017, Tepper et al 2018*).
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab-aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self-administered by patients in the abdomen, thigh, or back of upper arm. Latex-sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab-vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self-administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab-gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	<i>Prevention of migraine:</i> 2 consecutive injections (120 mg each) as a loading dose, then once monthly	May be self-administered by patients in the abdomen, thigh, back of upper arm or buttocks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			<i>Episodic cluster headache:</i> 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Ubrovelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	<i>Acute migraine treatment:</i> As needed. A second dose may be taken at least 2 hours after the initial dose. Max dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food

See the current prescribing information for full details

Abbreviations: CrCL = creatinine clearance; PO = oral; SC = subcutaneous

Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Ubrogepant is indicated for acute treatment of migraine with or without aura. Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
 - Current evidence-based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti-seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
 - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
 - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics.

Recent AHS guidelines state that ubrogepant may have a role in patients with CV conditions or in cases of triptan contraindications. It is also noted that other CGRP inhibitors may shortly be FDA-approved for use.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
 - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
 - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 1.0 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 3.1 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
 - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders ($\geq 50\%$ reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo ($p = 0.046$).
 - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, ubrogepant has a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children. Based on current data, the safety profiles of the CGRP inhibitors are generally mild with the most common adverse effects observed being injection site reactions in SC formulations and nausea in oral formulations.
- Overall, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm represent another therapy option in the prevention of episodic or chronic migraine. Fremanezumab-vfrm is the only agent in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches and ubrogepant is the only CGRP inhibitor indicated for acute treatment of migraines and also the only oral formulation. The frequency of administration (and route or dose) vary by indication. Further long-term study is warranted.

APPENDICES

• Appendix A. AAN levels of evidence classification (AAN 2017, Gronseth et al 2011)

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal

	potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b–e).
Class III	Controlled trials (including well-defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

Appendix B. AAN/AHS levels of evidence classification (Oskoui et al 2019[b])

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

REFERENCES

- Aimovig [package insert], Thousand Oaks, CA: Amgen, Inc. and Novartis Pharmaceuticals Corp.; October 2019.
- Ajovy [package insert], North Wales, PA: Teva Pharmaceuticals, Inc.; September 2018.
- American Academy of Neurology. Quality measurement manual: 2017 update. 2017. <https://www.aan.com/siteassets/home-page/policy-and-guidelines/quality/quality-measures/how-measures-are-developed/17qualitymeasuredevprocmanualfinal.pdf>. Accessed December 30, 2019.
- American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59(1):1-18.
- American Migraine Foundation (AMF). Non-invasive neuromodulation devices. December 14, 2017. Web site. <https://americanmigraine.org/resource-library/non-invasive-neuromodulation-devices/>. Accessed December 30, 2019.
- Amgen. Aimovig. [data on file]. September 2018.
- Ashina M, Dodick D, Goadsby PJ, et al. Erenumab–aooe (AMG 334) in episodic migraine. *Neurology*. 2017;89:1237–43.
- Ashina M, Dodick D, Goadsby PJ, et al. Long-term safety and tolerability of erenumab: three-plus year results from an ongoing open-label extension study in episodic migraine. [abstract IOR-01]. Presented at the 60th Annual Scientific Meeting of the American Headache Society; San Francisco, CA. June 27 to July 1, 2018.
- Biohaven Pharmaceuticals. Biohaven Pharmaceuticals reports third quarter 2019 financial results and recent business developments. Press release. November 1, 2019. <https://finance.yahoo.com/news/biohaven-pharmaceuticals-reports-third-quarter-201500946.html>. Accessed December 30, 2019.
- Burgos-Vega C, Moy J, Dussor G. Meningeal afferent signaling and the pathophysiology of migraine. *Prog Mol Biol Transl Sci*. 2015;131:537–64.
- Clinicaltrials.gov. US National Library of Medicine. 2019. Web site. <https://www.clinicaltrials.gov/>. Accessed December 30, 2019.
- Clinicaltrials.gov. An extension study to evaluate the long-term safety and tolerability of ubrogepant in the treatment of migraine (NCT02873221). August 26, 2019. Web site. <https://clinicaltrials.gov/ct2/show/results/NCT02873221>. Accessed December 30, 2019.
- Clinicaltrials.gov. A study of galcanezumab in participants with episodic cluster headache (NCT02397473). Web site. September 9, 2019. <https://www.clinicaltrials.gov/ct2/show/NCT02397473?term=NCT02397473&rank=1>. Accessed December 30, 2019.
- Detke, H, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211–e2221.
- Dodick DW, Ashina M, Brandes JL, et al. ARISE: A phase 3 randomized trial of erenumab–aooe for episodic migraine. *Cephalalgia*. 2018[a];38(6):1026–37.
- Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial (HALO EM). *JAMA*. 2018[b];319(19):1999–2008.
- Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med*. 2019;381(23):2230–2241.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed December 30, 2019.
- Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache*. 2017;57 Suppl 2:47–55.
- Eli Lilly and Company. Emgality. [data on file]. October 2018.
- Emgality [dossier], Indianapolis, IN: Eli Lilly and Company; October 2018.
- Emgality [package insert], Indianapolis, IN: Eli Lilly and Company; December 2019.
- Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. *Eur J Neurol*. 2009 ;16(9):968-981.
- Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet*. 2019;394(10203):1030-1040.
- Förderreuther S, Zhang Q, Stauffer VL, et al. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. *J Headache Pain*. 2018;19(1):121.
- Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology*. 2010;75:463-473.

- Global Burden of Disease (GBD) 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545–602.
- Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab–aooe for episodic migraine (STRIVE). *N Engl J Med*. 2017;377(22):2123–32.
- Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med*. 2019;381(2):132-141.
- Gronseth GS, Woodroffe LM, Getchius TS, et al; for the American Academy of Neurology. Clinical Practice Guideline Process Manual, 11th edition. 2011. Available at: <http://tools.aan.com/globals/axon/assets/9023.pdf>. Accessed December 30, 2019.
- International Headache Society (IHS). Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
- Jackson JL, Coqbill E, Santana–Davila R, et al. A comparative effectiveness meta–analysis of drugs for the prophylaxis of migraine headache. *PLoS One*. 2015;10(7):e0130733.
- Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep*. 2012;16(1):86-92.
- Lipton RB, Manack Adams A, Buse DC, et al. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache–related disability. *Headache*. 2016;56:1280–9.
- Lipton RB, Dodick DW, Allani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: The ACHIEVE II randomized clinical trial. *JAMA*. 2019[a];322(19):1887-1898.
- Lipton RB, Tepper SJ, Reuter U, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. *Neurology*. 2019[b];92(19):e2250-e2260.
- Ljubisavljevic S, Zidverc Trajkovic J. Cluster headache: pathophysiology, diagnosis and treatment. *J Neurol*. 2019;266(5):1059-1066.
- Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. *Curr Pain Headache Rep*. 2011;15:70–8.
- Marmura MJ, Silberstein SD, Schwedt TJ, et al. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed December 30, 2019.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019[a];93(11):487-499.
- Oskoui M, Pringsheim T, Billingham L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Headache*. 2019[b];59(8):1144-1157.
- Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018[a];392(10161):2280-7.
- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache*. 2016;56(7):1093-106.
- Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
- Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine (HALO CM). *N Engl J Med*. 2017;377(22):2113-22.
- Silberstein SD, Holland S, Freitag F, et al. Evidence–based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337–45. Reaffirmed July 18, 2015.
- Silberstein SD, Tfelt–Hansen P, Dodick DW, et al; for the Task Force of the International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia*. 2008;28(5):484–95.
- Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818–26.
- Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38(8):1442-54.
- Staines R. Alder gears up for migraine showdown with eptinezumab filing. April 24, 2019. <https://pharmaphorum.com/news/alder-gears-up-for-migraine-showdown-with-eptinezumab-filing/>. Accessed December 30, 2019.
- Starling AJ and Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc*. 2015;90(3):408–14.
- Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75(9):1080-8.
- Stauffer VL, Sides R, Camporeale A, et al. A Phase 3, long-term, open-label safety study of self-administered galcanezumab injections in patients with migraine. [abstract PO-01-184]. Presented at the 18th Congress of the International Headache Society; Vancouver, CA. September 7 to 10, 2017.
- Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15(4):382-90.
- Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab–aooe for preventive treatment of chronic migraine: a randomised, double–blind, placebo–controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425–34.
- Tepper S, Ashina M, Reuter U, et al. Assessment of the long-term safety and efficacy of erenumab during open-label treatment in subjects with chronic migraine. [poster PF115LB]. Presented at the 60th Annual Scientific Meeting of the American Headache Society; San Francisco, CA. June 27 to July 1, 2018.



- Teva Pharmaceutical press release. Teva bails on fremanezumab in cluster headache. April 23, 2019. <https://seekingalpha.com/news/3452826-teva-bails-fremanezumab-cluster-headache>. Accessed December 30, 2019.
- Ubrelvy [package insert], Madison, NJ: Allergan; December 2019.
- Walker CS and Hay DL. CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amyline receptors? *Br J Pharmacol.* 2013; 170(7):1293-307.

Publication Date: January 2, 2020