

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), opioids, **small molecule CGRP inhibitors, and a 5-hydroxytryptamine (5-HT)_{1F} receptor agonist**. 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] 2020, 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 **6** 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, eptinezumab-ijmr, and galcanezumab-gnlm** are humanized monoclonal antibodies that bind to the CGRP ligand and block its binding to the receptor. **Rimegepant and ubrogepant** are small molecule oral CGRP receptor antagonists (*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.

- o 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*).
- o 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 and eptinezumab-jjmr are not currently under clinical investigation for the indication of cluster headache** (*Clinicaltrials.gov 2020*).
- 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)	-
Nurtec ODT (rimegepant sulfate)	-
Emgality (galcanezumab-gnlm)	-
Ubrelvy (ubrogepant)	-
Vyepti (eptinezumab-jjmr)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab-aooe)	Ajovy (fremanezumab-vfrm)	Emgality (galcanezumab-gnlm)	Nurtec ODT (rimegepant)	Ubrelvy (ubrogepant)	Vyepti (eptinezumab-jjmr)
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 2020, Ajovy 2020, Emgality 2019, Nurtec ODT, Ubrelvy 2019, Vyepti 2020*)

- 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

- Rimegepant ODT has been studied as acute therapy in approximately 1466 patients in 1 Phase 3 trial of episodic migraine (with or without aura) patients and in 1 unpublished long-term safety trial. Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval; 2 trials

included approximately 2348 patients with episodic migraine, and 1 dose-ranging study included 885 patients randomized to 6 dose groups of rimegepant, sumatriptan 100 mg, or placebo.

- 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 unpublished, open-label extension (OLE) trial.
- Eptinezumab-jjmr has been studied in approximately 2019 patients across 2 trials in patients with episodic or chronic migraine subtypes for prevention, with data available in published 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 available 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 available 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 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

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo ($n = 222$), eptinezumab-jjmr 100 mg ($n = 221$), or eptinezumab-jjmr 300 mg ($n = 222$) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, -3.2 ; 100 mg, -3.9 , $p = 0.02$; 300 mg, -4.3 , $p = 0.0001$). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (Ashina *et al* 2020, Vyepti [dossier] 2020).

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 75\%$ 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*).

Galcanezumab-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), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-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 galcanezumab-gnlm 120 mg (mean change vs placebo, -1.9; 95% CI, -2.5 to -1.4; $p < 0.001$) and galcanezumab-gnlm 240 mg (mean change vs placebo, -1.8; 95% CI, -2.3 to -1.2; $p < 0.001$). Galcanezumab-gnlm significantly increased the proportion of patients achieving $\geq 50\%$ 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 galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. 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, -1.8; difference for 240 mg vs placebo, -1.6) (Stauffer et al 2018).
- In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, -2.0; 95% CI, -2.6 to -1.5; $p < 0.001$) and galcanezumab-gnlm 240 mg (mean change vs placebo, -1.9; 95% CI, -2.4 to -1.4; $p < 0.001$). Galcanezumab-gnlm significantly increased the proportion of patients achieving $\geq 50\%$ 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 galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. 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, -1.8; difference for 240 mg vs placebo, -1.7) (Skjarevski et al 2018).
- In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a $\geq 50\%$ response for ≥ 3 months, which was greater than placebo (21.4%; $p < 0.001$). Approximately 6% of galcanezumab-gnlm-treated patients maintained $\geq 75\%$ response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months ($< 1.5\%$) (Förderreuther et al 2018).

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo ($n = 366$), eptinezumab-jjmr 100 mg ($n = 356$), or eptinezumab-jjmr 300 mg ($n = 350$) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo -5.6; 100 mg -7.7, $p < 0.0001$; 300 mg -8.2, $p < 0.0001$). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (Lipton et al 2020).

Erenumab-aooe

- 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 $\geq 50\%$ 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 $\geq 50\%$ 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 (≥ 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] 2020, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking

preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).

- The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
 - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo ($p < 0.0001$)
 - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo ($p = 0.0009$)
- Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
- The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
 - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [$n = 27/86$] vs 15.3% [$n = 31/203$]; $p = 0.002$). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).
 - A MC, DB, PC, Phase 3 trial ($n = 1072$ in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; $p < 0.001$). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; $p < 0.001$). Nausea and urinary tract infection were the only AEs reported in $> 1\%$ of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain ($n = 1$) (*Lipton et al 2019[c], Nurtec ODT [dossier] 2020*).
 - A MC, DB, PC, Phase 3 trial ($n = 1084$ in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; $p = 0.03$). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; $p = 0.002$). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).

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 ≥ 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 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 (≤ 2.5% for all arms) and dizziness (≤ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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] 2020, Ubrelvy prescribing information 2019*).

- Rimegepant 75 mg was evaluated in an unpublished interim analysis of a long-term safety study which evaluated 1784 patients for up to 52 weeks. The most frequently reported adverse events were upper respiratory tract infection (8.5%) and nasopharyngitis (6.4%). There were no deaths, and the rates of serious adverse events and adverse events leading to discontinuation of rimegepant were low (2.5% and 2.7%, respectively). No clinically relevant trends in laboratory abnormalities were observed on-treatment or during follow up (*Nurtec ODT dossier 2020*).
- 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)
 - The AHS recommends that rimegepant and ubrogepant may have a role in 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

- Ubrogепant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant 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. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions. Erenumab-aooe has additional warnings and precautions associated with the following:
 - Constipation with serious complications: Constipation with serious complications has been reported 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.
 - Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.
- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogепant was associated with somnolence, and both ubrogепant and rimegepant were associated with 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 (a fatal arteriosclerosis event and a myocardial ischemia event 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. In a safety study of eptinezumab-jjmr in which 90.2% of patients were exposed to the drug for ≥ 6 months and 47.7% were exposed for ≥ 12 months, the most common adverse events observed were nasopharyngitis and hypersensitivity. A total of 9 patients reported serious adverse events with ubrogепant 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 ubrogепant 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. In an interim analysis of an OL, 52-week safety study of rimegepant, the most frequently reported adverse events were upper respiratory tract infection and nasopharyngitis. There were no deaths, and the rates of serious adverse events and adverse events leading to discontinuation of rimegepant were low. 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] 2020, Eli Lilly and Company [data on file] 2018, Nurtec ODT [dossier] 2020, Stauffer et al 2017, Tepper et al 2018, Vyepti prescribing information 2020*).
- 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

Data as of May 1, 2020 AVD/AKS

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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.

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)	<p>May be self-administered by patients in the abdomen, thigh, or back of upper arm.</p> <p>Latex-sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe.</p> <p>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.</p>
Ajovy (fremanezumab-vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	<p>May be self-administered by patients in the abdomen, thigh, or back of upper arm.</p> <p>The prefilled syringe cap is not made with natural rubber latex.</p> <p>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.</p>
Emgality (galcanezumab-gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	<p><i>Prevention of migraine:</i> 2 consecutive injections (120 mg each) as a loading dose, then once monthly</p> <p><i>Episodic cluster headache:</i> 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period</p>	<p>May be self-administered by patients in the abdomen, thigh, back of upper arm or buttocks.</p> <p>The cap is not made with natural rubber latex.</p> <p>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.</p>
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	<i>Acute migraine treatment:</i> As needed. Maximum dose: 75 mg in 24 hours.	<p>The safety of treating > 15 migraines in a 30-day period has not been established.</p> <p>Avoid concomitant administration with strong inhibitors of CYP3A4, moderate or strong inducers of CYP3A, or P-gp or BCRP inhibitors.</p>
Ubrelvy (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	The safety of treating > 8 migraines in a 30 day period has not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			initial dose. Maximum dose: 200 mg in 24 hours.	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
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

See the current prescribing information for full details

Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; BCRP = breast cancer resistance protein; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; 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.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. The injectable CGRP inhibitors eptinezumab-jjmr, 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. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.
- 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 rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.
- 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 0.7 to 3.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 5.8 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 and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not.
 - Rimegepant ODT demonstrated efficacy compared to placebo in a Phase 3, DB, RCT which evaluated acute response to migraine treatment after 2 hours. Patients were not allowed a second dose of study treatment (placebo or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant 75 mg were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval.
 - 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, rimegepant and ubrogepant have 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.
- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.

- Overall, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents 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. Dosage and administration vary by product and 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

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Publication Date: May 18, 2020