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Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention

Systematic Review

April 2020

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Executive Summary

Background

Calcitonin gene-related peptide (CGRP) is a neuropeptide that is thought to play a role in migraine and cluster headache pathophysiology; thus, blocking CGRP has been studied as a mechanism for preventing and treating headache.[1,2] CGRP inhibitors can take the form of monoclonal antibodies administered subcutaneously (SC) or intravenously (IV) that target the CGRP receptor (erenumab) or CGRP ligand (eptinezumab, fremanezumab, and galcanezumab), or oral small molecule inhibitors (rimegepant, ubrogepant) that target the CGRP receptor. The U.S. Food and Drug Administration (FDA) has approved 6 CGRP inhibitors (eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant). We completed a report for the Drug Effectiveness Review Project (DERP) in October 2018 that assessed 4 drugs (eptinezumab, erenumab, fremanezumab, galcanezumab) for the prevention of chronic and episodic migraine headache.[3] This report makes updates to the previous report and expands its scope to include 2 additional drugs (rimegepant, ubrogepant) for the treatment of acute migraine headache, as well as an additional indication for the use of CGRP inhibitors for the prevention of cluster headache.

PICOS and Key Questions

This report focuses on adults with episodic or chronic migraines or cluster headaches, and identified randomized controlled trials (RCTs) or prospective cohort studies that evaluated the effectiveness of CGRP inhibitors compared to: 1) each other; 2) other migraine preventive or acute treatment medications; or 3) a placebo. Outcomes of interest are migraine events and symptoms, including function, disability, and quality of life (QoL); employment-related outcomes; use of rescue therapies; health care utilization; and adverse events (AEs). The following are the key questions for this review:

1. What is the effectiveness of CGRP inhibitors for:
   a. Prevention of chronic migraine headache?
   b. Prevention of episodic migraine headache?
   c. Acute treatment of migraine headache?
   d. Prevention of cluster headache?
2. What is the frequency of adverse events with CGRP inhibitors for the prevention and treatment of episodic and chronic migraine or cluster headache, and for the acute treatment of migraine?
3. Are there subgroups of people based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which CGRP inhibitors differ in effectiveness or harms?
4. What are the characteristics of ongoing studies of CGRP inhibitors for the prevention and treatment of episodic and chronic migraine and cluster headache or the acute treatment of migraine?

Methods

We describe our complete methods in Appendix A. Briefly, we searched MEDLINE via PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and several other websites from database inception through October 31, 2020 to identify eligible studies. We conducted active surveillance of the literature through March 31, 2020. We rated the methodological quality of eligible RCTs using

standard instruments adapted from national and international quality standards.[4,5] We rated the quality of the body of evidence (QoE) for each drug and indication (chronic and episodic migraine prevention, acute migraine treatment, cluster headache prevention) for up to 5 outcomes (migraine or headache days per month or pain relief for acute migraine, functional outcomes, QoL, serious adverse events [SAEs], discontinuations due to AEs), when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[6,7] We used OpenEpi (version 3.0.1) to calculate mean differences, risk differences (RD) and risk ratios (RR) for various outcomes when these data were not provided by study authors.

Key Findings

We identified 27 placebo-controlled RCTs[8-38]; 14 RCTs[8-20,24,32,35,38] were new to the current report. Six placebo-controlled RCTs reported on 4 drugs (eptinezumab,[11] erenumab,[34] fremanezumab,[12,36,37] galcanezumab[13]) for the prevention of chronic migraine; 13 RCTs reported on 4 drugs (eptinezumab,[21,38] erenumab,[8,9,22,23,25] fremanezumab,[26,27] galcanezumab[28-30,33]) for the prevention of episodic migraines; 7 RCTs reported on 2 drugs (rimegepant,[14-16] ubrogepant[17-20]) for the acute treatment of migraine; and 1 RCT reported on 1 drug (galcanezumab[10]) for the prevention of cluster headache. We identified no studies that compared one CGRP inhibitor to another. We rated all but one study as of fair methodological quality, primarily because of the risk of bias from industry sponsorship and extensive manufacturer involvement in study design, conduction, analysis, and preparation of manuscripts; the other study[20] we rated as of poor methodological quality because the relevant study groups were not blinded, and because of a high potential for selection bias due to an extension trial design with recruitment restricted to participants completing 1 of 2 previous trials.

Effectiveness of CGRP Inhibitors for Chronic Migraine Prevention (Key Question 1a)

- Compared to a placebo, eptinezumab, erenumab, fremanezumab, and galcanezumab resulted in a statistically significant decrease in migraine days per month at 12 weeks; the differences from a placebo ranged from -1.8 days to -3.5 days (moderate QoE).[11-13,34,36,37]
- Compared to placebo, eptinezumab, erenumab, and fremanezumab were more effective at improving functioning at 12 weeks as measured by the 6-item Headache Impact Test (HIT-6); the difference from placebo ranged from 1.1 to 4.2 points across 4 RCTs (moderate QoE)[11,12,34,35,37]; galcanezumab 120-mg was also more effective at improving functioning as measured by the Migraine-specific Quality of Life score (MSQL); the mean difference was 8.7 points compared to placebo in 1 RCT (moderate QoE).[13]

Effectiveness of CGRP Inhibitors for Episodic Migraine Prevention (Key Question 1b)

- Compared to a placebo, eptinezumab, erenumab, fremanezumab, and galcanezumab resulted in a statistically significant decrease in migraine days per month for episodic migraine at 12 to 24 weeks; the difference from placebo ranged from -0.7 days to -2.8 days across 13 RCTs (moderate QoE).[8,9,22,23,25-30,33,38]
- Compared to placebo, erenumab (moderate QoE) was more effective at improving functioning as measured by the HIT-6 (range of effects in mean difference 1.0 to 2.3 points); [8,22,24,25] fremanezumab and galcanezumab were more effective at improving functioning as measured by the Migraine Disability Assessment (MIDAS; range of effects in mean difference 5.2 to 15.2 points; moderate QoE for both agents).[26,27,29,33] Eptinezumab was no different than placebo as measured by the HIT-6 (low QoE).[21]

Effectiveness of CGRP Inhibitors for Acute Migraine Treatment (Key Question 1c)

- Compared to placebo, a statistically significantly higher percentage of participants randomized to rimegepant (3 RCTs) or ubrogepant (3 RCTs) achieved freedom from pain within 2 hours post-dose; the difference compared to placebo in the percentage of participants achieving this outcome ranged from 6.4 to 16.6 percentage points higher for active doses (moderate QoE). [14-19]

Effectiveness of CGRP Inhibitors for Cluster Headache Prevention (Key Question 1d)

- Compared to placebo, galcanezumab resulted in statistically significantly fewer cluster headache attacks per week during weeks 1 through 3 of follow-up (3.5 fewer attacks per week; 95% confidence intervals [CI], -0.2 to -6.7) but was no different than placebo at week 8 (1.3 more attacks per week; 95% CI, -1.2 to 3.8; low QoE).[10]

Adverse Events From CGRP Inhibitors (Key Question 2)

- The frequency of AEs, SAEs, and discontinuations because of AEs in active treatment groups was similar to placebo at 12 to 24 weeks across nearly all drugs and dosages.[8-39] We evaluated the body of evidence on SAEs and discontinuations because of AEs as having very low QoE for nearly all drugs and indications. This was due to study limitations from manufacturer involvement, and serious or very serious imprecision because SAEs and discontinuations due to AEs were rare.
- Treatment-related liver injury was uncommon and similar between active treatment and placebo groups.[8-37,39]

Subgroup Differences in Efficacy and Adverse Events (Key Question 3)

- Few studies reported findings by subgroups. Three studies (all on fremanezumab for migraine prevention) reported similar efficacy among participants who were not taking concomitant preventive medication compared to the full study population, which also included participants taking concomitant preventive medication. [26,27 37]

Ongoing Studies (Key Question 4)

We identified 19 ongoing studies of CGRP inhibitors, most of which are blinded, placebo-controlled randomized trials. However, 1 RCT is evaluating erenumab compared to topiramate, and 1 open-label RCT is comparing erenumab to oral prophylactic medications.

- 2 studies are for eptinezumab (1 chronic migraine prevention, 1 acute migraine treatment)
- 6 studies are for erenumab (1 chronic migraine prevention, 4 episodic migraine prevention, 1 combined chronic and episodic migraine prevention)
- 5 studies are for fremanezumab (1 chronic migraine prevention, 1 episodic migraine prevention, 3 combined chronic and episodic migraine prevention)
- 4 studies are for galcanezumab (2 episodic migraine prevention, 1 combined chronic and episodic migraine prevention, 1 cluster headache prevention)
- 2 studies are for rimegepant (1 migraine prevention, 1 acute treatment)
- No ongoing studies were identified for ubrogepant
- Most studies of migraine prevention have follow-up periods of at 12 and 24 weeks; some studies with primary safety endpoints have follow-up periods up to 1.5 years; acute migraine treatment studies have follow-up periods of 2 hours

Conclusions

The evidence showed that in short-term follow-up, eptinezumab, erenumab, fremanezumab, and galcanezumab were more effective than a placebo for chronic and episodic migraine prevention (based on moderate-quality evidence); these agents reduce the number of migraine days per month from 0.7 to 3.5 days compared to placebo.[8,9,11-13,22,23,25-30,33,34,36-38] SAEs occurred rarely in active drug and placebo groups so a relationship cannot be determined (based on very-low-quality evidence for eptinezumab, erenumab and galcanezumab, and on low-quality evidence for fremanezumab).[8,9,22,23,25-30,33,38] Rimegepant and ubrogepant were more effective than placebo for acute migraine treatment (based on moderate-quality evidence); the proportion of participants achieving freedom from pain at 2 hours post dose ranged from 6.4 to 16.6 percentage points higher for active doses compared to placebo. SAEs in rimegepant and ubrogepant studies were rare; thus, no relationship can be determined (based on very-low-quality evidence).[14-19] Galcanezumab was more effective in the very short term (1 to 3 weeks) for cluster headache prevention, but longer-term effectiveness was unclear (based on low-quality evidence).[10] Two head-to-head trials and 18 additional placebo-controlled studies of CGRP inhibitors are in progress, but none will report efficacy outcomes at follow-up longer than 6 months or harms at follow-up longer than 1.5 years.

List of Brand Name and Generic Drugs

Table 1 describes current calcitonin gene-related peptide (CGRP) inhibitors and U.S. Food and Drug Administration (FDA) approval status.

Table 1. List of CGRP Inhibitors

Generic Drug (Brand/Alternative Names)	Manufacturer	Dosage(s); Form	Frequency	FDA Status	Approved Indication
Eptinezumab (Vyepti, ALD403)	Alder Biopharmaceuticals, Inc.	100-mg, 300-mg[a]; IV	Every 3 months	BLA approved February 21, 2020	Migraine prevention
Erenumab (Aimovig, AMG 334)	Amgen, Inc./ Novartis	70-mg, 140-mg; SC	Every month	BLA approved May 17, 2018	Migraine prevention
Fremanezumab[b] (Ajovy, TEV-48125, LBR-101)	Teva Pharmaceutical Industries, Ltd.	225-mg or 675-mg; SC	Every month (225-mg) or 3 months (675-mg)	BLA approved September 14, 2018	Migraine prevention
Galcanezumab (Emgality, LY2951742)	Eli Lilly and Company	Migraine headache: 120-mg; SC[c] Cluster headache: 300-mg; SC[d]	Every month	Initial BLA approved September 27, 2018; additional indication approved June 4, 2019	• Migraine prevention • Cluster headache prevention
Rimegepant (Zydis, BHV3000)	Biohaven Pharmaceuticals	75-mg[e]; PO[f]	Single dose upon migraine attack	BLA approved February 27, 2020	Acute migraine treatment
Ubrogepant (Ubrelvy, MK-1602)	Allergan USA, Inc.	50-mg, 100-mg; PO	Single and repeat dose upon migraine attack	BLA approved December 23, 2019	Acute migraine treatment

Notes. [a] These are the dosages that are being evaluated in the most recent phase 3 trial. [b] Various doses and dosing regimens were evaluated in phase 2 and 3 studies. The FDA-approved label dosage is 225-mg every month or 675-mg every 3 months. [c] The FDA-approved label dosage is an initial loading dose of 240-mg followed by a monthly dose of 120-mg. [d] Administered at onset of cluster period and then monthly until the end of the cluster period. [e] As used in phase 3 studies. [f] Oral and rapidly dissolving tablets. Abbreviations. BLA: biologic license application; CGRP: calcitonin gene-related peptide; FDA: U.S. Food and Drug Administration; IV: intravenous; NDA: new drug application; PO: per os (orally); SC: subcutaneous.

Background

State Medicaid program administrators are interested in a review of the evidence of the efficacy and adverse events (AEs) of calcitonin gene-related peptide (CGRP) inhibitors, to aid in decision making regarding this new drug class. A Drug Effectiveness Review Project (DERP) report completed in October 2018 reviewed the evidence for 4 CGRP drugs (eptinezumab, erenumab, fremanezumab, galcanezumab) for the prevention of chronic and episodic migraine headache.[3] This current report makes updates to the previous report and expands its scope to include 2 additional drugs (rimegepant, ubrogepant) for the treatment of acute migraine headache and an additional indication, the prevention of cluster headache.

CGRP Inhibitors in Migraine Prevention

CGRP is a 37-amino acid neuropeptide that is hypothesized to play a role in migraine pathophysiology through vasodilation of cerebral and dural vessels; thus, blocking CGRP has been studied as a mechanism for preventing migraine headaches.[40-42] Unlike other available preventive treatments (e.g., antihypertensive agents, antidepressants, antiepileptics), CGRP inhibitors were developed specifically for use in migraines.

The FDA approved the first CGRP inhibitor for migraine prevention (erenumab) in May 2018, and subsequently approved fremanezumab and galcanezumab in September 2018 and eptinezumab in February 2020. Eptinezumab, fremanezumab, and galcanezumab are humanized monoclonal antibodies that target the CGRP ligand; erenumab is a fully human monoclonal antibody that binds to the CGRP receptor.[43]

The definition of migraine is based on the International Classification of Headache Disorders (3rd edition) and is divided into migraine with or without aura (e.g., sensory disturbances such as light flashes, blind spots, and tingling).[44] Migraine without aura requires at least 5 attacks with headache lasting 4 to 72 hours without treatment or without successful treatment, at least 2 characteristics (unilateral location, pulsating quality, moderate-to-severe pain, aggravated by activity), and at least 1 symptom of nausea/vomiting or sensitivity to light or sound. Migraine with aura requires at least 2 attacks with presence of aura, and at least 2 characteristics (aura symptoms spread gradually over at least 5 minutes, aura symptoms last 45 to 60 minutes, at least 1 aura symptom is unilateral, a headache accompanies the aura or follows within 60 minutes). Chronic migraines are characterized by the occurrence of 15 or more headache days per month for at least 3 months.[43] Migraines that cannot be categorized as chronic are considered episodic, which can include various definitions of headache frequency (typically 4 to 14 migraine days per month).

CGRP Inhibitors in Acute Migraine Treatment

In addition to the role of CGRP inhibitors in migraine prevention, research has also focused on the role of these agents for the acute treatment of migraine attacks;[2] specifically, oral, small molecule inhibitors referred to as the "gepant" class of compounds. This class is the first new drug class for the acute treatment of migraine in over 20 years. Unlike other acute migraine treatments (e.g., triptans), CGRP inhibitors do not constrict blood vessels.[1] Relative to the monoclonal antibody CGRP inhibitors, the gepants have lower target specificity, shorter circulating half-life, and higher risk for drug-drug interactions and off-target AEs.[1] Like other

acute medications for migraine attacks, these agents should be taken early in the course of a migraine headache attack for optimal effectiveness.

To date, 6 compounds in the gepant class have been developed; however, the development of 3 agents was discontinued and the status of a fourth agent is unknown.[2] Thus, rimegepant and ubrogepant are the only agents currently remaining in this class. The FDA approved ubrogepant for acute migraine treatment in December 2019 at dosages of 50-mg and 100-mg. The FDA approved rimegepant in February 2020 at a dosage of 75 mg.

CGRP Inhibitors in Cluster Headache Prevention

In addition to use in migraine headache, CGRP inhibitors may be effective for the prevention of cluster headaches.[1] Cluster headache is less common than the other primary headache syndromes and affects more men than women.[45] Cluster headache attacks are characterized by severe, unilateral pain, often located around the eye and associated with conjunctival injection, tearing, runny nose, sweating, miosis, and ptosis on the same side as the pain.[45,46] These headaches can also be associated with agitation and restlessness.[45,46] Cluster attacks are generally short-lived but may recur multiple times, even within the course of a single day. This headache syndrome is called 'cluster' because of the typical presentation of multiple headaches occurring within a period of days to weeks to months (referred to as cluster periods). Like migraine headaches, cluster headache syndromes can be classified as episodic or chronic. The criteria for episodic cluster headache include at least 2 cluster periods (lasting from 7 days to 1 year) of headaches that are separated by a pain-free remission period of at least 3 months. Chronic cluster headache is characterized by the lack of a sustained remission in between cluster periods. The pathophysiology underlying cluster headaches is complex and researchers have demonstrated CGRP involvement in cluster headache attacks, thus prompting the evaluation of CGRP inhibitors as a preventive therapeutic option.[1,46]

Unlike use in migraine prevention, which involves regular use unrelated to the occurrence of migraine headache, the use of medications for prevention of cluster headaches involves administration at the onset of a cluster period followed by regular doses until the end of the cluster period.[1] Currently available preventive treatments include verapamil, steroids, ergots, topiramate, lithium, and nerve blocks.[47] Trials of potential preventive agents are designed to align with the natural history of cluster headaches, which is characterized by abrupt onset and termination of cluster periods. The FDA approved galcanezumab for cluster headache prevention in June 2019. Fremanezumab had been under development for episodic and chronic cluster headache, but the manufacturer suspended its development in April 2019 after results from futility analyses in two phase 3 trials suggested that it was not likely to meet its primary endpoints.

PICOS

Populations

- Adults with episodic or chronic migraines with no previous treatment history, or adults who have not responded to other migraine therapies
- Adults with episodic or chronic cluster headache with no previous treatment history, or adults who have not responded to other migraine therapies
- Adults with acute migraine headache

Comparators

- CGRP inhibitors compared to each other (head-to-head)
- Pharmacological agents aimed at treating or preventing migraines or cluster headaches (e.g., amitriptyline, ergotamine, onabotulinumtoxinA)
- Sham or placebo

Outcomes

- Migraine events (including frequency, intensity, and duration)
- Pain (including intensity, duration, and pain scale range)
- Other symptoms (e.g., nausea, vomiting, photophobia, phonophobia)
- Functional ability (including cognitive)
- Disability
- Quality of life (QoL)
- Other patient-reported outcomes (e.g., depression, anxiety, and difficulties in interpersonal relationships)
- Employment-related outcomes (e.g., unemployment, work productivity loss, and absenteeism)
- Use of rescue therapies
- Number of emergency department and/or primary care provider visits
- Tolerability
- AEs
- Serious adverse events (SAEs)
- Discontinuations due to AEs

Study Designs

- Randomized controlled trials (RCTs)
- Prospective cohort studies

Key Questions

1. What is the effectiveness of CGRP inhibitors for:
   a. Prevention of chronic migraine headache?
   b. Prevention of episodic migraine headache?
   c. Acute treatment of migraine headache?
   d. Prevention of cluster headache?
2. What is the frequency of AEs with CGRP inhibitors for the prevention and treatment of episodic and chronic migraine and cluster headache and for the acute treatment of migraine?
3. Are there subgroups of people based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which CGRP inhibitors differ in effectiveness or harms?
4. What are the characteristics of ongoing studies of CGRP inhibitors for the prevention and treatment of episodic and chronic migraine and cluster headache or the acute treatment of migraine?

Methods

We describe our complete methods in Appendix A. Briefly, we searched MEDLINE via PubMed, Embase, the Cochrane Library, clinicaltrials.gov, and several other websites through October 31, 2019 to identify eligible studies. We did not limit the search by date, to accommodate the expansion in scope for the current report. However, we removed citations identified in the previous report and only screened newly identified citations. We conducted active surveillance of the literature through March 31, 2020.

We rated the methodological quality of eligible RCTs or systematic reviews using standard instruments adapted from national and international quality standards.[4,5] We rated the quality of evidence (QoE) for each drug and indication (chronic and episodic migraine prevention, acute migraine treatment, cluster headache prevention) for up to 5 outcomes (migraine or headache days per month or pain relief for acute migraine, functional outcomes, QoL, SAEs, and discontinuations due to AEs) when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[6,7] For continuous efficacy measures, we extracted the difference between the intervention and the control reported by studies or calculated the difference based on data provided in the study, when not reported by authors. For categorical efficacy measures, we extracted the measures of effect reported by studies (typically frequencies, percentages, risk ratios [RRs], or odds ratios [ORs]) and used OpenEpi (version 3.0.1) to calculate risk differences (RDs), RRs, and associated 95% confidence intervals (CI) based on data provided in the study, when not reported by authors. We also conducted two-tailed testing when authors only reported one-tailed testing. For harm outcomes, we extracted frequencies and percentages.

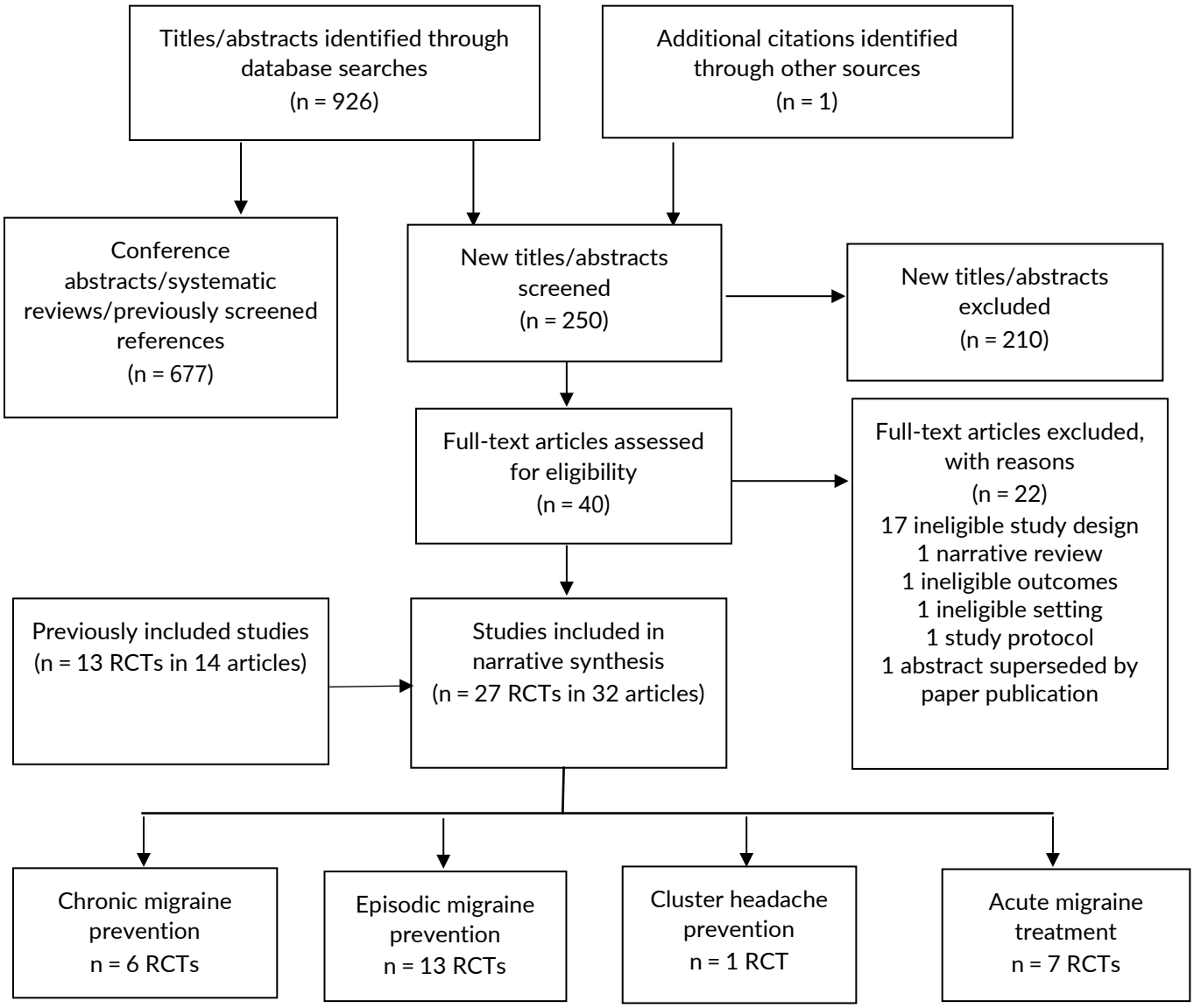
Findings

Overall, we included 27 RCTs (published in 32 articles; Figure 1 and Appendix D).[8-37,39] Of those, 14 RCTs are new to the current report.[8-20] Six placebo-controlled RCTs reported on 4 drugs (eptinezumab,[11] erenumab,[34] fremanezumab,[12,36,37] galcanezumab[13]) for the prevention of chronic migraine. Thirteen RCTs reported on 4 drugs for the prevention of episodic migraine (eptinezumab,[21,38] erenumab,[8,9,22,23,25] fremanezumab,[26,27] galcanezumab[28-30,33]). Seven RCTs reported on 2 drugs (rimegepant,[14-16] ubrogepant[17-20]) for the acute treatment of migraine, and 1 RCT reported on 1 drug (galcanezumab[10]) for the prevention of cluster headache. We also identified 4 articles reporting additional findings from previously included RCTs on chronic[35] and episodic[24,32,39] migraine prevention. Pharmaceutical manufacturers sponsored all trials included in this review, and we rated the methodological quality of all but 1 included studies as fair, primarily because of industry sponsorship and the risk of bias from extensive manufacturer involvement in study design, conduction, analysis, and preparation of manuscripts. The remaining study[20] we rated as of poor methodological quality because the relevant study groups were not blinded, and because of a high potential for selection bias due to an extension trial design with recruitment restricted to participants from previous trials. Articles that we reviewed at the full-text stage but ultimately excluded are detailed in Appendix E.

In the rest of this section, we summarize the efficacy (Key Question 1) by indication (chronic migraine prevention, episodic migraine prevention, acute migraine treatment, cluster headache prevention) and by drug, including findings for subgroups of interest (Key Question 3) where

relevant. Next, we summarize AEs (Key Question 2) and last, we describe ongoing studies (Key Question 4).

Figure 1. Literature Flow Diagram



Abbreviation. RCT: randomized controlled trial.

Chronic Migraine Prevention

Table 2 provides the summary of findings (GRADE) for the evidence for chronic migraine prevention. For migraine days per month, days with acute medication use per month, and percentage of participants with at least a 50% reduction in migraine days, all 4 drugs (erenumab, fremanezumab, galcanezumab, eptinezumab) were more effective than placebo. We rated the evidence as of moderate quality. We downgraded this quality rating because of industry sponsorship and concerns about risk of bias from extensive manufacturer involvement in the trials. No statistically significant differences in SAEs or discontinuations due to AEs were observed; we rated this evidence as very low quality for erenumab, fremanezumab, and

eptinezumab, and as low quality for galcanezumab, as compared to placebo. We downgraded these quality ratings for the same study quality concerns and because of serious or very serious imprecision from infrequent events, which precludes a definitive conclusion about the relationship.

Table 2. Summary of Findings (GRADE) for CGRP Inhibitors for Chronic Migraine Prevention

Outcome	Quality of Evidence	Relationship	Rationale
Eptinezumab vs. Placebo			
Migraine days per month (1 RCT[11])	Moderate ●●●○	Statistically significant improvements with 300-mg or 100-mg dosage compared to placebo.	Downgraded 1 level for study limitations
Percentage with at least 50% reduction in number of migraine days per month (1 RCT[11])	Moderate ●●●○		
Mean change in HIT-6 (1 RCT[11])	Moderate ●●●○	Statistically significant improvement for 300-mg dosage, but no significant difference for 100-mg dosage compared to placebo.	Downgraded 1 level for study limitations
Serious adverse events (1 RCT[11])	Very low ●○○○	Rare events, relationship cannot be determined.	Downgraded 1 level for study limitations and 2 levels for imprecision
Infusion interruptions due to adverse event (1 RCT[11])	Very low ●○○○		
Erenumab vs. Placebo			
Migraine days per month (1 RCT[34])	Moderate ●●●○	Statistically significant improvements for both 70-mg and 140-mg dosages compared to placebo.	Downgraded 1 level for study limitations
Days with acute migraine medication use per month (1 RCT[34])	Moderate ●●●○		
Percentage with at least 50% reduction in number of migraine days per month (1 RCT[34])	Moderate ●●●○		
Mean change in HIT-6 (1 RCT[34,35])	Moderate ●●●○		
Serious adverse events (1 RCT[34])	Very low ●○○○	Rare events, relationship cannot be determined.	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuation due to adverse event (1 RCT[34])	Very low ●○○○		
Fremanezumab vs. Placebo			
Migraine days per month (3 RCTs[12,36,37])	Moderate ●●●○	Statistically significant improvements with active dosages compared to placebo.	Downgraded 1 level for study limitations
Days with acute headache medication use per month (3 RCTs[12,36,37])	Moderate ●●●○		

Outcome	Quality of Evidence	Relationship	Rationale
Percentage with at least 50% reduction in number of migraine days per month (2 RCTs[12,37])	Moderate ●●●○		
Mean change in HIT-6 (2 RCTs[12,37])	Moderate ●●●○		
Serious adverse events (3 RCTs[12,36,37])	Low ●●○○	Rare events, relationship cannot be determined.	Downgraded 1 level for study limitations and 1 level for imprecision
Discontinuations due to adverse event (3 RCTs[12,36,37])	Low ●●○○		
Galcanezumab vs. Placebo			
Migraine days per month (1 RCT[13])	Moderate ●●●○	Statistically significant improvements with 120-mg and 240-mg dosages compared to placebo.[a]	Downgraded 1 level for study limitations
Percentage with at least 50% reduction in number of migraine days per month (1 RCT[13])	Moderate ●●●○		
Days with acute headache days per month (1 RCT[13])	Moderate ●●●○		
Mean change in MSQL (1 RCT[13])	Moderate ●●●○		
Serious adverse events (1 RCT[48])	Very low ●○○○	Rare events, relationship cannot be determined.	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (1 RCT[48])	Very low ●○○○		

Note. [a] Finding for change in MIDAS was not statistically significant for the 240-mg dosage. Abbreviations. CGRP: calcitonin gene-related peptide inhibitors; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; HIT-6: 6-item Headache Impact Test; MSQL: Migraine-specific Quality of Life score; RCT: randomized controlled trial.

Table 3 summarizes the study characteristics, primary study endpoint findings, SAEs, and discontinuations because of AEs for the 6 placebo-controlled trials that reported on the use of erenumab,[34] fremanezumab,[36,37] galcanezumab,[13] or eptinezumab.[11] Three RCTs are new to the current report,[11-13] and 1 previously included study had additional outcomes reported in a new publication.[35] These studies predominantly enrolled women; the mean number of migraine headache days at baseline ranged from 14.1 days to 19.6 days across studies. Detailed evidence tables are in Appendix B, Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes).

Table 3. Summary of Evidence: Placebo-Controlled RCTs of CGRP Inhibitors for Chronic Migraine Prevention

Study Trial Number Trial Name	Dose, Form, Frequency,[a] Number (n and N) Randomized	Primary Endpoint; Difference From Placebo (95% CI)	N (%) With at Least 1 SAE[b]	N (%) With AE Leading to Discontinuation
Eptinezumab				
Dodick et al., 2019[11] NCT02275117	300-mg IV single dose = 131 100-mg IV single dose = 133 30-mg IV single dose = 134 10-mg IV single dose = 133 Placebo IV = 134 Total N = 665	Percentage of patients with a 75% or greater reduction in the mean number of migraine headache days per month from baseline at weeks 1 to 12; 100-mg: 37 (31.4) (*P* = .07)[c] 300-mg: 38 (33.3) (*P* = .03)[c] Placebo: 24 (20.7)	100-mg: 4 (3.3) 300-mg: 7 (5.8) Placebo: 1 (0.8)	AE leading to infusion interruption: 100-mg: 2 (1.6) 300-mg: 4 (3.3) Placebo: 0 (0)
Erenumab				
Tepper et al., 2017[34] Lipton et al., 2019 [35] NCT02066415	70-mg SC = 191 140-mg SC = 190 Placebo SC = 286 Total N = 667	Mean change in migraine days per month from baseline at weeks 9 to 12; 70-mg: -2.5 (-3.5 to -1.4)[d] 140-mg: -2.5 (-3.5 to -1.4)[d]	70-mg: 6 (3) 140-mg: 2 (1) Placebo: 7 (2)	70-mg: 0 (0) 140-mg: 2 (1) Placebo: 2 (< 1)
Fremanezumab				
Bigal et al., 2015[36] NCT02021773	225-mg[e] SC = 88 900-mg SC = 87 Placebo SC = 89 Total N = 264	Mean change in headache hours per month from baseline during weeks 9 to 12[f]; 225-mg: -22.7 (-44.3 to -1.2)[d] 900-mg: -30.4 (-51.9 to -9.0)[d]	225-mg: 1 (1) 900-mg: 2 (2) Placebo: 1 (1)	225-mg: 4 (5) 900-mg: 3 (4) Placebo: 1 (1)
Silberstein et al., 2017[37] NCT02621931 HALO CM	225-mg[e] SC =379 675-mg quarterly SC = 376 Placebo SC = 375 Total N = 1,130	Mean change in headache days per month[g] from baseline during weeks 9 to 12; 225-mg: -2.1 (*P* < .001) 675-mg: -1.8 (*P* < .001)	225-mg: 5 (1) 675-mg: 3 (< 1) Placebo: 6 (2)	225-mg: 7 (2) 675-mg: 5 (1) Placebo: 8 (2)
Ferrari et al., 2019[12] NCT03308968 FOCUS	225-mg SC (episodic) and 675-mg SC (chronic) initial dose, then 225-mg monthly: 283 675-mg SC quarterly: 276	Mean change from baseline in the monthly average number of migraine days over weeks 1 to 12; Monthly: -3.5 (-4.2 to -2.8)[d] Quarterly: -3.1 (-3.8 to -2.4)[d]	Monthly: 4 (1) Quarterly: 2 (< 1) Placebo: 4 (1)	Monthly: 4 (1) Quarterly: 1 (< 1) Placebo: 3 (1)

Study Trial Number Trial Name	Dose, Form, Frequency,[a] Number (n and N) Randomized	Primary Endpoint; Difference From Placebo (95% CI)	N (%) With at Least 1 SAE[b]	N (%) With AE Leading to Discontinuation
	Placebo SC: 279 Total N = 838			
Galcanezumab				
Detke et al., 2018[13] NCT02614261 REGAIN	120-mg SC (with 240-mg loading dose) = 279 240-mg SC = 279 Placebo SC = 559 Total N = 1,117	Mean change in migraine headache days per month from baseline at weeks 4 to 12; 120-mg: -2.1 (-2.9 to -1.3)[d] 240-mg: -1.9 (-2.7 to -1.1)[d]	120-mg: 1 (0.4) 240-mg: 4 (1.4) Placebo: 4 (0.7)	120-mg: 1 (0.4) 240-mg: 4 (1.4) Placebo: 6 (1.0)

Notes. [a] All doses are monthly unless otherwise specified. [b] Defined as death, life-threatening events, events requiring initial or prolonged hospitalization, events resulting persistent or significant disability or that required intervention to prevent permanent impairment or damage, congenital anomaly or birth defect, other events that do not fit any of the previous categories but that may jeopardize the patient or require medical or surgical intervention and are considered significant by the investigator. [c] Most studies report the proportion that achieved a 50% reduction in monthly migraine days; for this study this proportion was statistically significantly higher for both dosages (P < .001). [d] Indicates a statistically significant result based on an alpha equal to .05. [e] Patients in the 225-mg group received 675-mg at baseline and 225-mg at weeks 4 and 8. [f] This was the study's reported primary endpoint. This study also reported mean change in migraine days per month from baseline as a secondary endpoint; difference from placebo was -1.7 (95% CI, -3.7 to 0.2) for 225-mg and -2.0 (95% CI, -3.9 to -0.1) for 900-mg. [g] This study reported mean change in migraine days per month from baseline as a secondary endpoint; difference from placebo was -1.8 (SE 0.4) for 225-mg and -1.7 (SE 0.4) for 675-mg, both P < .001. Abbreviations. AE: adverse event; CGRP: calcitonin gene-related peptide inhibitors; CI: confidence interval; IV: intravenous; NCT: U.S. National Clinical Trial; RCT: randomized controlled trial; SAE: serious adverse event; SC: subcutaneous.

Eptinezumab

Study Characteristics

One new phase 2b RCT[11] conducted among 665 participants at multiple sites in the U.S., Australia, New Zealand, and the Republic of Georgia evaluated a single dose of 300-mg, 100-mg, 30-mg, or 10-mg intravenous infusion of eptinezumab compared to placebo, with follow-up over a 12-week period. This study enrolled adults aged 18 to 55 with a history of chronic migraine including at least 8 migraine days during the run-in phase. The study authors used the run-in phase to confirm study eligibility with respect to the number of headaches per month and to assess compliance with an electronic headache diary; no study medications were given during the run-in phase.[11] Study investigators allowed preventive medications for headache (including topiramate, beta-blockers, valproate, tricyclic antidepressants, but not including botulinum toxin), if the dosing was stable for at least 3 months before screening.[11]

Study Results

We focused on results from the 300-mg and 100-mg dosages, which are the dosages being evaluated in phase 3 trials (see Table 10). The study authors observed statistically significant differences in the percentage of patients with a 75% or greater reduction in the mean number of migraine headache days per month from baseline (primary study endpoint) for the 300-mg

dosage, but not for the 100-mg dosage (Table 3).[11] This was the only study included in the review with a primary endpoint of a 75% greater reduction in the mean number of migraine headache days per month; most other studies used an endpoint of 50% or greater reduction.[11] All secondary migraine and headache event efficacy endpoints (e.g., percentage of patients with a 50% reduction in migraine headache days per month, mean change in monthly headache days per month) showed statistically significant differences for both the 300-mg and 100-mg dosages compared with placebo.[11] The study authors also reported statistically significant decreases in the 6-item Headache Impact Test (HIT-6) for the 300-mg dosage group (mean difference form placebo, -4.2) but did not observe a statistically significant difference for the 100-mg dosage (mean difference from placebo, -1.1).[11] The study authors observed AEs in 64% of participants in the 300-mg dosage group and in 58% of participants in the 100-mg dosage group, compared to 56% of participants in the placebo group.[11] Further, authors observed SAEs in 6%, 3%, and less than 1% of participants, respectively. Discontinuations due to AEs were also infrequent (Table 3).[11] This study did not report any subgroup findings.[11]

Erenumab

Study Characteristics

We identified 1 new publication (Lipton et al.[35]) reporting additional results for a previously included phase 2 RCT (Tepper et al.[34]). This RCT was conducted among 667 participants at multiple sites in North America and evaluated 70-mg and 140-mg dosages of erenumab compared to placebo over 12 weeks.[34] This study enrolled adults aged 18 to 65 with a history of chronic migraine in the previous 3 months and during the 4-week run-in phase.[34] The study authors used the run-in phase to confirm study eligibility with respect to the number of headaches per month, and to assess compliance with an electronic headache diary; no study medications were given during the run-in phase.[34] The use of other drugs for migraine prevention was prohibited in the 2 months prior to run-in and during the treatment phase.[34] Study investigators allowed the use of non-study migraine prevention drugs if prescribed for non-migraine indications (e.g., depression, high blood pressure) and if the dose was stable in the month prior to screening.[34] Study investigators allowed participants to use acute migraine treatment during the study period.[34]

Study Results

The study authors observed the same statistically significant decrease in mean change in migraine days per month from baseline (primary study endpoint) for both dosages (-2.5 days; 95% CI, -3.5 to -1.4) compared to the placebo group (Table 3).[34] All secondary migraine and headache event efficacy endpoints (e.g., days of acute migraine medication use, percentage of participants with at least a 50% reduction in migraine headache days per month) demonstrated a similar effect, and all endpoints were statistically significant except for mean change in headache hours (of any severity) per month for the 70-mg dosage (Appendix B, Table B2).[34] In the new publication identified for the current report, Lipton et al. reported functioning and QoL outcomes using the Migraine-Specific Quality of Life Questionnaire (MSQL), the HIT-6, the Migraine Disability Assessment (MIDAS), and the Patient-Reported Outcomes Measurement Information System (PROMIS).[35] All functioning and QoL measures demonstrated a statistically significant favorable effect for both dosages compared to placebo, except for 1 of the 3 MSQL domains for the 70-mg dosage (Appendix B, Table B2).[35] AEs were comparable between the active treatment

groups (44% and 47%) and the placebo group (39%).[34] SAEs and discontinuations were infrequent.[34] (Table 3). This study did not report any subgroup findings.[34,35]

Fremanezumab

Study Characteristics

We identified 1 new phase 3b RCT (FOCUS[12]) evaluating fremanezumab, conducted among 838 participants at multiple sites in the U.S. and Europe that; 61% of participants in this study met criteria for chronic migraine whereas 39% met criteria for episodic migraine. The previous review included 1 phase 2b RCT (Bigal et al.[36]) conducted among 264 participants at multiple sites in the U.S., and 1 phase 3 RCT (HALO CM[37]) conducted among 1,130 participants at multiple sites in North America and Europe. FOCUS compared 2 dosage regimens to placebo: a quarterly dose of 675-mg; or an initial dose of 225-mg for those with episodic migraine or an initial dose of 675-mg for those with chronic migraine, followed by a monthly dose of 225-mg.[12] Bigal et al. compared monthly doses of 225-mg and 900-mg with a placebo.[36] HALO CM compared monthly (225-mg) and quarterly (675-mg) doses to a placebo.[12,37] All studies used a 4-week run-in phase to confirm study eligibility and to assess compliance with an electronic headache diary; no study medications were administered during the run-in phase.[12,36,37] All studies used an active treatment phase of 12 weeks.[12,36,37] FOCUS[12] excluded patients using migraine preventive medications whereas Bigal et al.[36] and Halo CM[37] allowed 1 or 2 other migraine preventive drugs or devices if the participant's use was stable for at least 2 months prior to the run-in phase.

Study Results

All 3 RCTs reported statistically significant larger improvements in the primary efficacy endpoints (mean change in headache hours per month from baseline in Bigal et al.,[36] and mean change in headache days per month from baseline in HALO CM[37] and FOCUS[12]) for all dosages compared to the placebo (Table 3). The secondary and exploratory migraine and headache event efficacy endpoints reported in Bigal et al.[36] consistently demonstrated a favorable effect for both dosage groups when compared to a placebo, but not all findings were statistically significant.[36] For example, the authors observed a statistically significant change from placebo in mean change in migraine days per month for the 900-mg dosage (-2.0; 95% CI, -3.9 to -0.1), but not for the 225-mg dosage (-1.7; 95% CI, -3.7 to 0.2).[36] The secondary migraine or headache efficacy endpoints reported in HALO CM[37] (change in migraine days per month, days of acute headache medication use, proportion with 50% or more reduction in headache days per month) all demonstrated statistically significant differences, consistent with the primary study endpoint.[37] The secondary migraine and headache efficacy outcomes reported in FOCUS[12] (use of acute headache medication, days with nausea and vomiting, days with photophobia or phonophobia, proportion with 50% and 75% or more reduction in headache days per month) consistently demonstrated a favorable effect for both dosages when compared to placebo, except for the proportion of participants with a 100% reduction in headache days.[12] In a subgroup of participants not taking concomitant preventive therapy, HALO CM[37] reported similar findings for the outcome of change in acute headache days per month compared to the full study population that included participants taking concomitant preventive therapy.[37]

HALO CM[37] and FOCUS[12] reported statistically significant differences in change on the HIT-6 for both the monthly dose (mean difference from placebo, 2.4 and 3.8 points, respectively) and the quarterly dose (mean difference from placebo, 1.9 and 3.0 points, respectively).[37] FOCUS[12]

also reported statistically significant differences for the monthly and quarterly doses compared to placebo on the MIDAS, MSQL, and European Quality of Life 5-Dimension measure (EQ-5D) for both dosages compared to placebo, whereas the effect as measured by the Work Productivity and Activity Impairment Questionnaire (WPAI) was only statistically significant in the monthly group.[12] Bigal et al.[36] did not report any QoL or function outcomes.[36]

In Bigal et al.,[36] the percentage of participants with at least 1 treatment-emergent AE was 53% in the 225-mg dosage group, 48% in the 900-mg dosage group, and 40% in the placebo group.[36] These findings were similar to those reported in in HALO CM[37] (51% in the 225-mg group, 49% in the 675-mg group, and 42% in the placebo group) and in FOCUS[12] (45% in the 225-mg monthly group, 55% in the 675-mg quarterly group, and 48% in the placebo group). SAEs and discontinuations due to AEs were infrequent and comparable across all active dosages and placebo (Table 3).[12,36,37]

Galcanezumab

Study Characteristics

One new phase 3 RCT (REGAIN[13]) conducted among 1,117 participants at multiple sites in South America, North America, Europe, and Asia evaluated monthly 120-mg or 240-mg doses of galcanezumab compared to placebo over a 12-week period. We note the FDA-approved dosage is an initial loading dose of 120 mg followed by a monthly dose of 120 mg. The study enrolled adults aged 18 to 65 with a history of chronic migraine in the 3 months before screening. Similar to other included studies, study authors confirmed eligibility with a run-in phase; no study medications were given during the run-in phase.[13] Study investigators allowed the use of 2 preventive migraine treatments (topiramate or propranolol) if the participant's use was stable for at least 2 months prior to the run-in phase.

Study Results

The study authors observed similar statistically significant differences in mean change in migraine headache days per month from baseline (primary study endpoint) in the 120-mg group (-2.1; 95% CI, -2.9 to -1.3) and the 240-mg group (-1.9; 95% CI, -2.7 to -1.1) compared to placebo.[13] All secondary migraine and headache event efficacy endpoints (e.g., days of acute migraine medication use, percentage of participants with at least 50% reduction in migraine headache days per month) demonstrated a similar effect, and all endpoints were statistically significant compared to placebo except for percentage of participants with 100% or greater reduction in migraine headache days per month (Appendix B, Table B2).[13] Significantly larger improvements in QoL were observed for both active doses compared to placebo, the range of improvement was 5.1 to 7.0 points as measured by the MSQL scale across the 3 domains of the instrument and across doses. The study authors observed AEs in 58% of participants taking the 120-mg dosage, 57% of participants taking the 240-mg dosage, and in 50% of participants taking the placebo.[13] SAEs and discontinuations due to AEs were infrequent (Table 3).[13] This study did not report any subgroup findings.

Episodic Migraine Prevention

Table 4 provides the summary of findings (GRADE) for the evidence for episodic migraine prevention. We observed larger improvements for eptinezumab, erenumab, fremanezumab, and galcanezumab compared to placebo for mean migraine headache days per month. We rated the

evidence as of moderate quality. We downgraded the QoE because of concerns about study limitations from risk of bias because of manufacturer involvement. Active treatment was also more effective than placebo on other efficacy endpoints for eptinezumab, erenumab, fremanezumab, and galcanezumab, and we rated this evidence as of low to moderate quality. The frequency of SAEs and discontinuations because of AEs was similar between active treatment and placebo for all drugs, and we rated the evidence as very low quality. We downgraded this evidence because of study limitations from the risk of bias from manufacturer involvement and very serious imprecision.

Table 4. Summary of Findings (GRADE) for CGRP Inhibitors for Episodic Migraine Prevention

Outcome	Quality of Evidence	Relationship	Rationale
Eptinezumab			
Migraine days per month (2 RCTs[21,38])	Moderate ●●●○	Statistically significant improvements at 12 weeks compared to placebo in larger of the 2 studies	Downgraded 1 level for study limitations
Percentage with at least 50% reduction in number of migraine days per month (2 RCTs[21,38])	Moderate ●●●○	Statistically significant improvements at 12 weeks compared to placebo in larger of the 2 studies	
HIT-6 (1 RCT[21])	Low ●●○○	No significant difference compared to placebo	
Serious adverse events (2 RCTs[21,38])	Very low ●○○○	Rare events, relationship cannot be determined	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuation due to adverse event (2 RCTs[21,38])	Very low ●○○○	None observed in placebo or active treatment groups	
Erenumab			
Migraine days per month (5 RCTs[8,9,22,23,25])	Moderate ●●●○	Statistically significant improvements with active dosages compared to placebo[a]	Downgraded 1 level for study limitations
Days with acute migraine medication use per month (5 RCTs[8,9,22,23,25])	Moderate ●●●○		
Percentage with at least 50% reduction in number of migraine days per month (5 RCTs[8,9,22,23,25])	Moderate ●●●○		
HIT-6 (4 RCTs[8,22,24,25])	Moderate ●●●○		
Serious adverse events (5 RCTs[8,9,22,23,25])	Very low ●○○○	Rare events, relationship cannot be determined	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuation due to adverse event (5 RCTs[8,9,22,23,25])	Very low ●○○○		
Fremanezumab			
Migraine days per month	Moderate		

Outcome	Quality of Evidence	Relationship	Rationale
(2 RCTs[26,27])	●●●○	Statistically significant improvements with active dosages compared to placebo	Downgraded 1 level for study limitations
Days with acute headache medication use per month (2 RCTs[26,27])	Moderate ●●●○		
Percentage with at least 50% reduction in number of migraine days per month (2 RCTs[26,27])	Moderate ●●●○		
MIDAS score (2 RCTs[26,27])	Moderate ●●●○		
Serious adverse events (2 RCTs[26,27])	Very low ●○○○	Rare events, relationship cannot be determined	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (2 RCTs[26,27])	Very low ●○○○		
Galcanezumab			
Migraine days per month (4 RCTs[28-30,33])	Moderate ●●●○	Statistically significant improvements with active dosages compared to placebo	Downgraded 1 level for study limitations
Percentage with at least 50% reduction in number of migraine days per month (4 RCTs[28-30,33])	Moderate ●●●○		
MIDAS Score (2 RCTs[29,33])	Moderate ●●●○		
Serious adverse events (4 RCTs[28-30,33])	Very low ●○○○	Rare events, relationship cannot be determined	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (4 RCTs[28-31,33])	Very low ●○○○		

Note. [a] With 1 exception in 1 study, the difference in HIT-6 scores in the Sun et al.[25] study was not statistically different from placebo but was in the same direction as the other 3 studies. Abbreviations. CGRP: calcitonin gene-related peptide inhibitors; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; HIT-6: Headache Impact Test (6-item); MIDAS: Migraine Disability Assessment; RCT: randomized controlled trial.

Table 5 summarizes the study characteristics, primary study endpoint findings, serious AEs, and discontinuations because of AEs for the 13 placebo-controlled randomized trials that reported on the use of eptinezumab,[21,38] erenumab,[8,9,22,23,25] fremanezumab,[26,27] or galcanezumab.[28-31,33] Three RCTs[8,9,38] were new to the current report, and we identified 2 new articles[24,32] providing additional data for 2 previously included RCTs. These studies predominantly enrolled women; the mean number of migraine headache days at baseline ranged from 6.6 to 11.3 across studies. We assessed each study as of fair methodological quality because of the risk of bias from industry sponsorship and extensive manufacturer involvement; in addition, 1 RCT[21] had selective outcome reporting. Detailed evidence tables are in Appendix B, Table B4 (study characteristics), Table B5 (efficacy outcomes), and Table B6 (adverse event outcomes).

Table 5. Summary of Evidence: Placebo-Controlled RCTs of CGRP Inhibitors for Episodic Migraine Prevention

Study; Trial Number Trial Name	Dose, Form, Frequency,[a] and Number (n and N) Randomized	Primary Endpoint; Difference From Placebo (95% CI) or OR (95% CI)	N (%) With at Least 1 SAE[b]	N (%) With AE Leading to Discontinuation
Eptinezumab				
Ashina et al., 2020[38] NCT02559895 PROMISE-1	30-mg IV = 224 100-mg IV = 225 300-mg IV = 224 Placebo IV = 225 Total IV = 898	Mean change in migraine days per month from baseline at weeks 0 to 12; 30-mg: -0.8 (-1.4 to -0.3) 100-mg: -0.7 (-1.3 to -0.1) 300-mg: -1.1 (-1.7 to -0.5)	All treatment groups: 11 (1.7) Placebo: 6 (2.7)	30-mg: 12 (5.5) 100-mg: 6 (2.7) 300-mg: 5 (2.2) Placebo: 6 (2.7)
Dodick et al., 2014[21] NCT01772524	1,000-mg IV, 1 time = 86 Placebo IV = 88 Total N = 174	Mean change in migraine days per month from baseline at weeks 5 to 8; -1.0 (-2.0 to 0.1)[c]	1,000-mg: 2 (2.5) Placebo: 1 (1.2)	1,000-mg: 0 Placebo: 0
Erenumab				
Dodick et al., 2018[22] NCT02483585 ARISE	70-mg SC = 286 Placebo SC = 291 Total N = 577	Mean change in migraine days per month from baseline at weeks 9 to 12; -1.0 (-1.6 to -0.5)[d]	70-mg: 3 (1.1) Placebo: 5 (1.7)	70-mg: 5 (1.8) Placebo: 1 (0.3)
Goadsby et al., 2017[23] Buse et al., 2018[24] NCT02456740 STRIVE	70-mg SC = 317 140-mg SC = 319 Placebo = 319 Total N = 955	Mean change in migraine days per month from baseline at months 4 to 6; 70-mg: -1.4 (-1.9 to -0.9)[d] 140-mg: -1.9 (-2.3 to -1.4)[d]	70-mg: 8 (2.5) 140-mg: 6 (1.9) Placebo: 7 (2.2)	70-mg: 7 (2.2) 140-mg: 7 (2.2) Placebo: 8 (2.5)
Sun et al., 2016[25] NCT01952574	70-mg SC = 107 Placebo = 160 Total N = 483[e]	Mean change in migraine (or probable migraine) days per month from baseline at weeks 9 to 12; -1.1 (-2.1 to -0.2)[d]	70-mg: 1 (1) Placebo: 0 (0)	70-mg: 3 (3) Placebo: 2 (1)
Reuter et al., 2018[9] NCT03096834 LIBERTY	140-mg SC monthly = 121 Placebo SC =125 Total N = 246	Percentage of participants with 50% or greater reduction in the mean number of migraine headache days per month from baseline at weeks 9 to 12[f]; OR, 2.7 (1.4 to 5.2)[d]	140-mg: 2 (2) Placebo: 1 (1)	140-mg: 0 (0) Placebo: 1 (1)
Sakai et al., 2019[8] NCT01081795	70-mg SC = 135 140-mg SC = 137 Placebo SC = 136 Total N = 475[g]	Mean change in migraine days per month from baseline at months 4 to 6; 70-mg: -2.3 (-3.0 to -1.6)[d] 140-mg: -1.9 (-2.6 to -1.2)[d]	70-mg: 1 (0.7) 140-mg: 1 (0.7) Placebo: 4 (2.9)	70-mg: 2 (1.5) 140-mg: 0 (0) Placebo: 1 (0.7)

Study; Trial Number Trial Name	Dose, Form, Frequency,[a] and Number (n and N) Randomized	Primary Endpoint; Difference From Placebo (95% CI) or OR (95% CI)	N (%) With at Least 1 SAE[b]	N (%) With AE Leading to Discontinuation
Fremanezumab				
Bigal et al., 2015[26] NCT02025556	225-mg SC = 96 675-mg SC = 97 Placebo SC = 104 Total N = 297	Mean change in migraine days per month from baseline at weeks 9 to 12; 225-mg: -2.8 (-4.1 to -1.6)[d] 675-mg: -2.6 (-3.9 to -1.4)[d]	225-mg: 2 (2.0) 675-mg: 2 (2.0) Placebo: 0 (0)	225-mg: 4 (4.2) 675-mg: 2 (2.0) Placebo: 0 (0)
Dodick et al., 2018[27] Brandes et al., 2019[39] NCT02629861 HALO EM	225-mg SC = 290 675-mg SC quarterly = 291 Placebo SC = 294 Total N = 875	Mean change in migraine days per month from baseline at weeks 9 to 12; 225-mg: -1.5 (-2.0 to -0.93)[d] 675-mg: -1.3 (-1.8 to -0.72)[d]	225-mg: 3 (1.0) 675-mg: 3 (1.0) Placebo: 7 (2.4)	225-mg: 5 (1.7) 675-mg: 5 (1.7) Placebo: 5 (1.7)
Galcanezumab				
Dodick et al., 2014[28] NCT01625988	Every 2 weeks 150-mg SC = 108 Placebo SC = 110 Total N = 218	Mean change in migraine days per month from baseline at weeks 9 to 12; -1.2 (90% CI, -1.9 to -0.6)[d]	150-mg: 2 (1.9) Placebo: 4 (3.6)	150-mg: 0 (0) Placebo: 1 (0.9)
Skljarevski et al., 2018[30] Oakes et al., 2018[31] Ayer et al., 2018[32] NCT02163993	120-mg SC = 70 300-mg SC = 67 Placebo = 137 Total N = 410[h]	Mean change in migraine days per month from baseline at weeks 9 to 12[i]; 120-mg: -0.9 (*P* = .02) 300-mg: -0.9 (*P* = .02)	120-mg: 1 (1.4) 300-mg: 0 (0) Placebo: 0 (0)	120-mg: 0 (0) 300-mg: 1 (1.5) Placebo: 0 (0)
Stauffer et al., 2018[33] NCT02614183 EVOLVE-1	120-mg SC = 213 240-mg SC = 212 Placebo = 433 Total N = 862	Mean change in migraine days per month from baseline over 6 months; 120-mg: -1.9 (-2.5 to -1.4)[d] 240-mg: -1.8 (-2.3 to -1.2)[d]	120-mg: 6 (2.9) 240-mg: 0 (0) Placebo: 5 (1.2)	120-mg: 2 (1.0)[j] 240-mg: 0 (0)[j] Placebo: 2 (0.5)[j]
Skljarevski et al., 2018[29] NCT02614196 EVOLVE-2	120-mg SC[k] = 231 240-mg SC = 223 Placebo = 461 Total N = 915	Mean change in migraine days per month from baseline over 6 months; 120-mg: -2.0 (-2.6 to -1.5)[d] 240-mg: -1.9 (-2.4 to -1.4)[d]	120-mg: 5 (2.2) 240-mg: 7 (3.1) Placebo: 5 (1.1)	120-mg: 5 (2.2) 240-mg: 9 (4.0) Placebo: 8 (1.7)

Notes. [a] *All doses are monthly unless otherwise specified.* [b] *Defined as death, life-threatening events, events requiring initial or prolonged hospitalization, events resulting persistent or significant disability or that required intervention to prevent permanent impairment or damage, congenital anomaly or birth defect, other events that do not fit any of the previous categories but that may jeopardize the patient or require medical or surgical intervention and are considered significant by the investigator.* [c] *The study authors reported the P value associated with this comparison as .0306. Study authors also reported this outcome for 9 to 12 weeks: -1.0 (95% CI, -2.1 to 0.2); P = .065. We note that the clinical trials registration entry for this study listed safety outcomes as the primary study outcomes; this outcome was reported as the primary efficacy endpoint; however,*

all efficacy outpoints were considered secondary. [d] Indicates a statistically significant result based on an alpha equal to .05. [e] Study also included 7-mg and 21-mg dosage groups; these are not included because they are outside the FDA-approved dosing range. [f] This was the study's primary endpoint; the study also reported the change in mean migraine days per month: -1.6 (95% CI, -2.7 to -0.5). [g] Study also included 28-mg dosage groups; data are not included because this dosage is outside of the dosing range approved by the FDA. [h] Study also included 5-mg and 50-mg dosage groups; these are not included because they are outside of the FDA-approved dosing range. [i] This was a secondary endpoint; the primary endpoint was the posterior probability of greater improvement in migraine days of at least 95%compared to placebo for at least 1 dosage; this endpoint was met (posterior probability 99.6%). [j] Study only reported serious adverse events leading to discontinuation. [k] A loading dose of 240-mg was used for the first dose. Abbreviations. AE: adverse event; CGRP: calcitonin gene-related peptide inhibitors; CI: confidence interval; IV: intravenous; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; SAE: severe adverse event; SC: subcutaneous.

Eptinezumab

Study Characteristics

We identified 1 new phase 3 RCT (Promise-1[38]) conducted among 898 participants at multiple sites in the U.S. and the Republic of Georgia. The previous review included 1 phase 2 RCT (Dodick et al.[21]) conducted among 174 participants at multiple sites in the U.S. PROMISE-1 compared up to 4 intravenous doses of 30-mg, 100-mg, or 300-mg of eptinezumab every 12 weeks with a placebo. Dodick et al. compared a single 1,000-mg intravenous dose of eptinezumab with a placebo. Both studies used a 4-week run-in phase and a 12-week follow-up period for efficacy outcomes. PROMISE-1 used a 12-week follow-up period for safety outcomes and Dodick et al. used a 24-week follow-up period for safety outcomes.[21] PROMISE-1 allowed use of some medications to prevent and treat migraine if dosages were stable at the time of enrollment. Dodick et al. did not allow concomitant regular use of preventive migraine medication within 3 months prior to screening or during the study period.[21]

Study Results

PROMISE-1 was the only RCT with a primary efficacy outcome. The authors observed statistically significant reductions in mean change in migraine days per month from baseline (primary study endpoint) for all dosages (Table 5).[38] The mean difference from placebo ranged from -1.1 days (95% CI, -1.7 to -0.5) in the 300-mg dosage group to -0.7 days (95% CI, -1.3 to -0.1) in the 100-mg dosage group.[38] There was a statistically significant difference in the percentage of patients with a 50% or greater reduction in the mean number of migraine headache days per month from baseline for all dosage groups.[38] All efficacy outcomes reported by Dodick et al. were secondary study endpoints, including the outcome the authors reported as their primary efficacy endpoint (mean change in monthly migraine days from baseline at 5 to 8 weeks).[21] The study authors reported the mean difference from the placebo was -1.0 day (95% CI, -2.0 to 0.1); the authors reported this result as statistically significant (P = .03) using a one-tailed significance test.[21] Using data provided in the study, we calculated the CIs as -2.0 to 0.04 and calculated the P value as .06 using a two-tailed t-test. The authors observed a similar effect for this outcome at the 9- to 12-week follow-up time point (-1.0 day; 95% CI, -2.1 to 0.2); the authors reported this finding as not significant (P = .07).[21] The authors observed no statistically significant differences in the other reported efficacy outcomes (Appendix B, Table B5).[21]

The percentage of participants reporting AEs was similar in both RCTs. In PROMISE-1, the number of participants who experienced AEs was 129 (58%) in the 300-mg group, 141 (63%) in

the 100-mg group, and 132 (60%) in the placebo group.[38] The percentage of participants with serious treatment-emergent adverse events was 6 (3%) in the placebo group compared to 11 (2%) in all active-treatment groups combined.[38] The primary endpoints for Dodick et al. were safety outcomes.[21] A similar number of participants experienced AEs, 43 (52%) in the placebo group compared to 46 (57%) in the active treatment group.[21] The percentage of participants with SAEs and discontinuations due to AEs was similar between active treatment and placebo groups (Table 5).[21]

Erenumab

Study Characteristics

We identified 1 new phase 3b RCT (LIBERTY,[9] N = 246), 1 new phase 2 RCT (Sakai et al.,[8] N = 475), and 1 new publication (Buse et al.[24]) that reported additional functional and QoL measures for the previously included STRIVE RCT (N = 955).[23] The previous review also included an additional phase 3 RCT (ARISE,[22] N = 577) and 1 phase 2 RCT (Sun et al.,[25] N = 267) for a cumulative total of 5 included studies for this agent (total N = 2,520). LIBERTY, ARISE, STRIVE, and Sun et al. were conducted at multiple sites in North America and Europe, and Sakai et al. was conducted at multiple sites in Japan. Two studies[22,25] evaluated a monthly dose of 70 mg, 1 study[9] evaluated a monthly dose of 140 mg, and 2 studies[8,23] evaluated both dosages. Two studies also included study arms evaluating dosages of 7 mg, 21 mg, and 28 mg; these dosages are lower than the FDA-approved dosages of 70 mg and 140 mg, and we will not report findings from those study arms in this report. All studies used a 4-week run-in phase to confirm eligibility and assess compliance with the electronic headache diary; no study medications were administered during the run-in phase. The double-blind active treatment phase was 12 weeks in 3 studies[9,22,25] and 24 weeks in 2 studies.[8,23] ARISE,[22] STRIVE,[23] and Sakai et al.[8] allowed concomitant use of 1 migraine preventive treatment as long as use was stable prior to enrollment.

Study Results

All studies reported statistically significant differences favoring the active treatment groups compared to placebo for all primary efficacy endpoints (mean change in monthly migraine days from baseline, percentage of participants with 50% or great monthly reduction in migraine, Table 5).[8,9,22,23,25] For mean change in monthly migraine days, the treatment effect ranged from -1.0 to -2.3 days for the 70-mg dosage and -1.6 to -1.9 days for the 140-mg dosage.[8,9,22,23,25] All studies also demonstrated statistically significant differences for the active treatment groups compared to the placebo group for the mean change in days of acute migraine medication use (mean difference from placebo ranging from -0.6 to -1.7 days across dosages and studies) and in the percentage of participants with a 50% or greater reduction in mean number of migraine headache days per month (ORs ranging from 1.6 to 5.6 across dosages and studies).[8,9,22,23,25]

Across all studies, authors observed larger improvements in functioning and QoL for active treatments compared to placebo, but findings were mixed with respect to the number of outcomes reported and the precision and statistical significance of the estimates.[8,9,22,23,25] These outcomes were secondary outcomes in all studies, and the authors designed studies with sample sizes for adequate statistical power on the primary study endpoints.[8,9,22,23,25] Four[8,9,22,23] of the 5 studies consistently found statistically significant improvements across 1 or more reported measure; the exception was Sun et al.,[25] which did not find any statistically significant findings

though estimates were consistent in direction with the other studies but lower in magnitude of effect. Four studies reported on HIT-6[8,22,24,25] and the difference in improvement between groups was 1.0 to 2.3 points. Four studies[8,9,22,24] reported using the Migraine Physical Function Impact Diary (MPFID); the difference in improvement in scores between groups across domains was 1.1 to 3.9 points. Three studies[22,24,25] reported using the MSQL; the difference in improvements between groups across studies and domains was 0.5 to 6.7 points. Finally, 3 studies[22,24,25] reported using the MIDAS; the difference in improvement in total score ranged from 1.7 to 5.3 points across studies. Detailed findings are in Appendix B, Table B5.

The incidence of AEs in placebo groups across the 5 studies ranged from 54% to 67%.[8,9,22,23,25] The incidence of AEs across all active dosage groups in the 5 studies ranged from 48% to 70%.[8,9,22,23,25] SAEs and discontinuations due to AEs were infrequent and comparable across active dosages and placebo (Table 5).[8,9,22,23,25] No studies reported findings for any subgroups of interest to this review.[8,9,22,23,25]

Fremanezumab

Study Characteristics

We identified 1 new publication (Brandes et al.[39]) providing additional data for a phase 3 RCT (HALO EM[27]) that was previously included. The previous review also included 1 other RCT (Bigal et al.[26]) for a cumulative total of 2 included studies (total N = 1,172) in the current report. Bigal et al.[26] was conducted among 297 participants at multiple U.S. sites, and HALO EM[27] was conducted among 875 participants at multiple sites in 9 countries. Bigal et al. evaluated a monthly dose of 225 mg and a monthly dose of 675 mg compared to a placebo.[26] HALO EM evaluated a monthly dose of 225 mg and a quarterly dose of 675 mg.[27] Both studies used a 4-week run-in phase to confirm study eligibility and assess compliance with an electronic headache diary; no study medications were administered during the run-in phase.[26,27] In both studies, the double-blind active treatment phase was 12 weeks and both studies allowed concomitant use of 1 migraine preventive treatment if use was stable prior to enrollment.[26,27]

Study Results

Both studies reported statistically significant differences in the primary efficacy endpoint (mean change in monthly migraine days from baseline) for active treatment compared to placebo (Table 5).[26,27] The mean difference from the placebo ranged from -1.3 days to -2.8 days across dosages.[26,27] The authors of both studies reported a statistically significant difference in days of acute headache medication use; the mean difference from the placebo across active dosages ranged from -1.3 days to -1.8 days.[26,27] HALO EM[27] reported a higher percentage of participants with a reduction of 50% or more in migraine headache days per month for active treatment compared to placebo (RD, 19.8%; 95% CI, 12.1% to 27.6%, for monthly dose; RD, 16.5%; 95% CI, 8.9% to 24.1%, for quarterly dose).[26] Both studies demonstrated statistically significant improvements in other secondary headache event or symptom endpoints such as reduction in days with nausea and vomiting, photophobia, and phonophobia (Appendix B, Table B5).[26,27] Both studies reported the mean change in acute headache days among the subgroup of participants not taking concomitant preventive medication and findings were similar to results in the full study population.[26,27]

HALO EM[27] and Bigal et al.[26] both reported changes in QoL and function using the MIDAS instrument. The authors of both studies observed a statistically significant difference in improvement in the MIDAS overall score across all dosages compared to placebo, though the magnitude of improvement compared to placebo was larger in Bigal et al.[26] (14.5 and 15.2 points across dosages) compared to HALO EM[27] (5.4 and 7.0 points across dosages).

The percentage of participants reporting AEs was 56%[26] and 58%[27] in the placebo groups, and ranged from 46%[26] to 66%[27] across active dosage groups.[26,27] SAEs and discontinuations due to AEs were infrequent and comparable between placebo and active dosage groups (Table 5).[26,27]

Galcanezumab

Study Characteristics

We identified 1 new article (Ayer et al.[32]) providing additional results for a phase 2b RCT (Skljarevski et al.,[30] N = 410) that was included in the previous report. The previous report also included another phase 2 RCT (Dodick et al.,[28] N = 218) and two phase 3 RCTs (EVOLVE-1,[33] N = 862; EVOLVE-2,[29] N =915) for a total of 4 included studies (total N = 2,269) in the current report. Two RCTs[28,30] were conducted at multiple sites in the U.S., 1 RCT[33] was conducted at multiple sites in North America, and 1 RCT[29] was conducted at multiple sites in North America, Europe, South America, and Asia. Dodick et al.[28] evaluated 150-mg doses every 2 weeks and Skljarevski et al.[30] evaluated 5-mg, 50-mg, 120-mg, and 300-mg doses every month but did not report migraine or headache event efficacy outcomes for the 300-mg dosage. We do not report on findings from the 5-mg and 50-mg dosages because they are lower than the FDA-approved dosage, which is a 240-mg initial loading dose followed by a monthly dose of 120-mg. EVOLVE-1 and EVOLVE-2 evaluated 120-mg and 240-mg doses every month.[29,33] Similar to other included studies, all studies used a run-in phase (range 28 to 40 days) during which no study medications were administered.[28-30,33] The double-blind active treatment phase was 12 weeks in 2 studies[28,30] and 6 months in 2 studies.[29,33] No studies allowed concomitant migraine prevention treatment.

Study Results

All 4 studies[28-30,33] reported statistically significant differences in the mean change in monthly migraine days from baseline, which was the primary efficacy endpoint in 3 of the studies (Table 5).[28,29,33] However, we note that 1 study[28] reported findings using 90% CIs.[28] Across the 4 studies, the mean difference from a placebo ranged from -0.9 days to -2.0 days across dosages.[28-30,33] All studies also reported a statistically significantly higher percentage of participants reporting a 50% or greater reduction in migraine days for all active dosages compared to a placebo.[28-30,33] Dodick et al.[28] reported an OR of 2.9 (90% CI, 1.8 to 4.7); we calculated the RR with a 95% CI as 1.6 (1.2 to 2.0).[28] EVOLVE-1[33] and EVOLVE-2[29] reported a similar treatment effect as Dodick et al.,[28] for both the 120-mg and 240-mg dosages (Appendix B, Table B5).[29,33] The fourth study, Skljarevski et al.,[30] reported the percentage of participants with at least a 50% reduction in migraine days as 76% in the 120-mg dosage group compared to 62% in the placebo group; the authors reported this difference as statistically significant (*P* = .03).[30] We calculated the RR as 1.2 (95% CI, 1.01 to 1.5). EVOLVE-1[33] and EVOLVE-2[29] reported the change in days of acute headache medication use from baseline; both reported statistically significant differences compared to placebo with reductions ranging from 1.6 to 1.8 days.[29,33] All studies also demonstrated statistically significant improvements in other secondary

headache event or symptom endpoints (Appendix B, Table B5) with 1 exception (Skljarveski et al.,[30] mean change in headache days per month for the 120-mg dosage).

Across these 4 studies,[28-30,33] the authors reported various QoL and functional outcomes as well as mixed findings with respect to precision and statistical significance of estimates (Appendix B, Table B5). These outcomes were secondary outcomes in all studies, and the authors designed studies with sample sizes for adequate statistical power on the primary study endpoints.[28-30,33] EVOLVE-1[33] and EVOLVE-2[29] reported statistically significant improvements on the MSQL (overall and domain-specific scores), the MIDAS, and the Patient Global Impression Survey (PGI-S) for both active dosages compared to a placebo.[29,33] As part of exploratory efficacy endpoints, Dodick et al.[28] reported larger improvements in both the MSQL (domain-specific scores) and the HIT-6, but they did not perform formal statistical tests, and we were unable to generate CIs for the estimates using available data. Skljarevski et al.[30] reported no significant difference in the MSQL overall score between either the 120-mg or 300-mg dosage at weeks 9 to 12 compared to a placebo (actual mean difference from the placebo not reported). There was a statistically significant improvement on the HIT-6 for the 120-mg dosage (*mean difference from placebo -2.7*; *P = .04*) but not for the 300-mg dosage (mean difference not reported and we were unable to calculate it using available data). Ayer et al.[32] reported additional post-hoc analyses of patient-reported outcomes for this study. The authors reported statistically significant improvements in the MSQL overall score and all domain scores from baseline to 12 weeks in the 120-mg dosage compared to placebo but did not find a statistically significant improvement on the HIT-6 from baseline to 12 weeks (Appendix B, Table B5).[32] This post-hoc analysis focused only on the 120-mg dosage and did not conduct analyses for the other dosages.[32]

Across placebo groups, the percentage of participants with AEs was 51% to 67% and the range was 51% to 72% across active dosage groups.[28-30,33] SAEs and discontinuations due to AEs were infrequent and comparable across groups (Table 5).[28-30,33] No studies reported findings for any subgroups of interest to this review.[28-30,33]

Acute Migraine Treatment

The evaluation of CGRP inhibitors for the acute treatment of migraine is new to the current report. Table 6 provides the summary of findings (GRADE) for these agents. We observed that both ubrogepant and rimegepant were more effective compared to placebo for both freedom from pain and freedom from the most bothersome symptoms at 2 hours post-dose. We rated the evidence as of moderate quality. We also rated the evidence as of moderate quality for larger improvements in function for active treatment compared to placebo for both agents. We rated the evidence as of very low quality for SAEs since few to no events were reported across dosages and studies; thus, we were unable to determine a relationship for this outcome.

Table 6. Summary of Findings (GRADE) for CGRP Inhibitors for Acute Migraine Treatment

Outcome	Quality of Evidence	Relationship	Rationale
Rimegepant vs. Placebo			
Freedom from pain at 2 hours post-dose (3 RCTs[14-16])	Moderate ●●●○	Active treatment significantly more	Downgraded 1 level for study limitations

Outcome	Quality of Evidence	Relationship	Rationale
Freedom from most bothersome symptom at 2 hours post-dose (2 RCTs[15,16])	Moderate ●●●○	effective than placebo.	
Ability to function normally within 2 hours post-dose (2 RCTs[15,16])	Moderate ●●●○		
Serious adverse events (3 RCTs[14-16])	Very low ●○○○	Rare events, relationship cannot be determined.	Downgraded 1 level for study limitations and 2 levels for imprecision
Ubrogepant vs. Placebo			
Freedom from pain at 2 hours post-dose (3 RCTs[17-19])	Moderate ●●●○	Active treatment significantly more effective than placebo.	Downgraded 1 level for study limitation
Freedom from most bothersome symptom at 2 hours post-dose (2 RCTs[18,19])	Moderate ●●●○		
Ability to function normally within 2 hours post-dose (1 RCT[18])	Moderate ●●●○		
Serious adverse events (4 RCTs[17-20])	Very low ●○○○	Rare events, relationship cannot be determined.	Downgraded 1 level for study limitations and 2 levels for imprecision

Abbreviations. CGRP: calcitonin gene-related peptide; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RCT: randomized controlled trial.

Table 7 summarizes the study characteristics, primary study endpoint findings, SAEs, and discontinuations because of AEs for the 7 placebo-controlled trials that reported on the use of rimegepant[14-16] or ubrogepant.[17-20] We assessed all studies as of fair methodological quality because of industry sponsorship and extensive manufacturer involvement in study design, execution, and reporting, except for one study[20] that was assessed as poor quality because of the relevant treatment groups were not blinded and a high potential for selection bias was present. Detailed evidence tables are in Appendix B, Table B7 (study characteristics), Table B8 (efficacy outcomes), and Table B9 (adverse event outcomes).

Table 7. Summary of Evidence: Placebo-Controlled RCTs of CGRP Inhibitors for Acute Migraine Treatment

Study Trial Number Trial Name	Dose Number (n and N) Randomized	Primary Endpoint; Risk Difference From Placebo (95% CI)	N (%) With at Least 1 SAE[a]	N (%) With AE Leading to Discontinuation
Rimegepant				
Croop et al., 2019[15] NCT03461757	75-mg = 732 Placebo = 734 Total N = 1,466	Freedom from pain at 2 hours post-dose: 10.4% (6.5% to 14.2%)[b] Freedom from most bothersome symptoms at 2 hours post-dose: 8.3% (3.4% to 13.2%)[b]	75-mg: 0 (0) Placebo: 0 (0)	NR
Lipton et al., 2019[16] NCT03237845	75-mg = 594 Placebo = 592 Total N = 1,186	Freedom from pain at 2 hours post-dose: 7.6% (3.3% to 11.9%)[b] Freedom from most bothersome symptoms at 2 hours post-dose: 12.4% (6.9% to 17.9%)[b]	75-mg: 1 (0.2) Placebo: 2 (0.4)	NR
Marcus et al., 2014[14] NCT01430442	75-mg = 91 Sumatriptan = 109 Placebo = 229 Total N = 885[c]	Freedom from pain at 2 hours post-dose: 75-mg vs. placebo: 16.2% (5.2% to 27.1%)[b] 75-mg vs sumatriptan: -3.6% (-17.2 to 9.9%)[b]	2 events NR by group (neither treatment-related)	75-mg: 0 (0) Sumatriptan: 0 (0) Placebo: 0 (0)
Ubrogepant				
Ailani et al., 2020[20] NCT02873221	50-mg = 404 100-mg = 409 Placebo = 417 Total N = 1,230	NR, this was an open-label extension to ACHIEVE-I & II for safety outcomes	50-mg: 9 (2) 100-mg: 12 (3)	50-mg: 9 (2) 100-mg: 11 (3)
Dodick et al., 2019[18] NCT02828020 ACHIEVE-I	50-mg = 556 100-mg = 557 Placebo = 559 Total N = 1,672	Freedom from pain at 2 hours post-dose: 50-mg: 7.4% (2.6% to 12.1%)[b] 100-mg: 9.4% (4.6% to 14.2%)[b] Absence of most bothersome symptoms: 50-mg: 10.8% (4.6 to 17.0)[b] 100-mg: 10.0% (3.9 to 16.1)[b]	50-mg: 3 (0.6) 100-mg: 2 (0.4) Placebo: 0 (0)	50-mg: 0 (0) 100-mg: 0 (0) Placebo: 0 (0)
Lipton et al. 2019[19] NCT02867709 ACHIEVE-II	50-mg = 562 Placebo = 563 Total N = 1,686[d]	Freedom from pain at 2 hours post-dose: 50-mg: 7.5% (2.6 % to 12.5%; *P* = .01) Freedom from most bothersome symptom at 2 hours post-dose: 50-mg: 11.5% (5.4% to 17.5%; *P* = .01)	50-mg: 0 (0) Placebo: 0 (0)	50-mg: 0 (0) Placebo: 0 (0)

Study Trial Number Trial Name	Dose Number (n and N) Randomized	Primary Endpoint; Risk Difference From Placebo (95% CI)	N (%) With at Least 1 SAE[a]	N (%) With AE Leading to Discontinuation
Voss et al., 2016[17] NCT01613248	50-mg = 139 100-mg = 140 Placebo = 139 Total N = 418	Freedom from pain at 2 hours post-dose: 50-mg: 12.0% (2.6 to 21.4)[b] 100-mg: 16.6% (12.4 to 22.4)[b] Headache response at 2 hours post-dose: 50-mg: 12.5% (-0.7% to 25.7%) 100-mg: 14.2% (0.9% to 27.5%)[b]	50-mg: 0 (0) 100-mg: 0 (0) Placebo: 0 (0)	NR

Notes. Calculated values are in italics. [a] Defined as death, life-threatening events, events requiring initial or prolonged hospitalization, events resulting persistent or significant disability or that required intervention to prevent permanent impairment or damage, congenital anomaly or birth defect, other events that do not fit any of the previous categories but that may jeopardize the patient or require medical or surgical intervention and are considered significant by the investigator. b Indicates a statistically significant result based on an alpha equal to .05. [c] Study also included 10-mg, 25-mg, 150-mg, 300-mg, and 600-mg dose rimegepant dosage groups. [d] This study also included a 25-mg dosage group; we do not report on this group as it is outside of the FDA-approved dosing range. Abbreviations. AE: adverse event; CGRP: calcitonin gene-related peptide; CI: confidence interval; NCT: U.S. National Clinical Trial; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event.

Rimegepant

Study Characteristics

Two phase 3 RCTs (Croop et al.,[15] N = 1,466; Lipton et al.,[16] N = 1,186) and 1 double-blind dose-ranging RCT (Marcus et al.,[14] N = 429), all conducted at multiple sites in the U.S., evaluated a 75-mg dosage of rimegepant compared to placebo. Marcus et al.[14] also evaluated other dosages of rimegepant compared to placebo but for this report we focus only on the 75-mg dosage because that is the dosage subsequently selected for use in the phase 3 trials. Marcus et al.[14] also included a study arm evaluating 100-mg of sumatriptan. Across the 3 studies, enrolled participants had on average 4.0 to 4.6 migraines per month. All studies had a 45-day acute treatment window during which participants treated a single, moderate-to-severe migraine attack with the study drug to which they were randomized. Participants used an electronic diary to enter information about their symptoms before and after using the medication and attended a follow-up visit within 7 days of treatment. The study authors discontinued participants who did not have a migraine attack during the treatment window. All 3 studies allowed participants to take ongoing preventive therapy if the participant's dosage was stable for 3 months prior to study.

Study Results

All 3 studies reported statistically significant differences between rimegepant compared to placebo for being pain-free at 2 hours post-dose (RD range, 7.6 to 16.2 percentage points), which was the primary or co-primary efficacy endpoint in all studies (Table 7).[14-16] Croop et al.[15] and Lipton et al.[16] also included the co-primary endpoint of freedom from most bothersome

symptoms at 2 hours post-dose, and both found 75 mg of rimegepant to be statistically significantly more effective than placebo for this endpoint (Appendix B, Table B8). All secondary migraine and headache event endpoints (e.g., sustained pain relief, sustained pain freedom, freedom from photophobia and phonophobia) that authors assessed for statistical significance favored active treatment except for freedom from nausea in Croop et al. (RD, 5.9; 95% CI, −0.9 to 12.7; *P* > .05).[15]

Croop et al.[15] reported ability to function normally at 60 minutes, 90 minutes, and 2 hours, sustained ability to function normally at 2 to 24 hours and 2 to 48 hours, and found a statistically significant favorable effect for rimegepant compared to placebo at all time points. Lipton et al.[16] included ability to function normally at 2 hours post-dose, but did not assess the statistical significance of this endpoint based on the study's hierarchical gate-keeping plan (RD, 9.2%; 95% CI, 3.9% to 14.6%). Marcus et al.[14] did not include any functioning or QoL endpoints.

The proportion of participants with AEs in the placebo groups was 11%[15] and 14%[16] in 2 studies, and was 13%[15] and 17%[16] in the active dosage groups. The authors of the third study reported that AEs were "comparable across groups."[14] No SAEs were reported in Croop et al.[15]; Marcus et al.[14] reported 2 SAEs but neither were considered to be treatment-related and the authors did not specify in which groups these events occurred. Lastly, Lipton et al.[16] reported 2 SAEs in the placebo group and 1 SAE in the active treatment group. Discontinuations due to AE were only reported by 1 study;[14] and no events were reported.[14] All 3 studies monitored liver enzymes for hepatotoxicity; the study authors observed no differences between placebo and active treatment groups.[14-16]

In terms of comparative effectiveness, Marcus et al.[14] also included a sumatriptan study group, but the authors did not conduct any statistical significance testing between the rimegepant and sumatriptan groups. Thirty-one percent of participants taking rimegepant had freedom from pain at 2 hours post-dose compared to 35% of participants taking sumatriptan.[14] We calculated the RD for this comparison to be -3.6 percentage points (95% CI, -17.2% to 9.9%), which suggested no statistically significant differences. Rimegepant and sumatriptan had comparable findings on all other efficacy measures reported (Appendix B, Table B8).[14] The study authors reported the incidence of overall AEs between placebo, rimegepant, and sumatriptan as comparable across groups.[14]

Ubrogepant

Study Characteristics

Two phase 3 RCTs (ACHIEVE-I,[18] N = 1,672; ACHIEVE-II,[19] N = 1,686) and 1 phase 2b RCT (Voss et al.,[17] N = 418) evaluated ubrogepant compared to placebo. In addition, a phase 3, open-label extension RCT (Ailani et al.,[20] N = 1,230) evaluated the long-term safety of ubrogepant among participants who participated in the ACHIEVE-I and II trials. We rated this study as of poor methodological quality for several reasons. In this study, participants who agreed to continue to participate after the main trials ended were randomized to usual care, 50 mg, or 100 mg of ubrogepant. Although the dosages of ubrogepant were blinded, allocation to ubrogepant vs. usual care was not blinded. The usual care group was prescribed acute migraine medication as directed by their usual care physician, which was not described by study authors. We note this type of study design has a selection bias since patients experiencing AEs or no effect of

treatment may elect not to continue into the extension phase. The ACHIEVE trials were conducted at multiple U.S. sites; Voss et al.,[17] did not report study locations. All studies compared 50-mg and 100-mg dosages of ubrogepant to placebo, except for ACHIEVE-II,[19] which compared 25-mg and 50-mg dosages to placebo. We focus on the FDA-approved dosages of 50-mg and 100-mg for this report. ACHIEVE-I[18] and ACHIEVE-II[19] used electronic diaries to capture symptoms before and after treatment, while Voss et al.[17] used a paper diary. All studies allowed the use of preventive medications. Treatment windows ranged from 2 months to 52 weeks. ACHIEVE-I[19] did not report a treatment window. Follow-up time ranged from 2 to 7 days, to 52 weeks post-dose.

Study Results

Ubrogepant was statistically significantly more effective than placebo in ACHIEVE-I,[18] ACHIEVE-II,[19] and in Voss et al.[17] for all dosages as measured by the co-primary endpoint, the proportion of participants with freedom from pain at 2 hours post-dose (Table 7). The range of effects was between 7.4 and 16.6 percentage points higher for achieving freedom from pain across dosages and studies compared to placebo.[17-19] The other ACHIEVE-I[18] and ACHIEVE-II[19] co-primary endpoint was freedom from the most bothersome symptoms at 2-hours post-dose, and both studies observed statistically significant favorable effects for all dosages (10.8 and 11.4 percentage points higher for treatment compared to placebo, respectively). The other co-primary endpoint reported by Voss et al.[17] was the proportion of participants with headache response, defined as a reduction in pain severity from moderate or severe to mild or no pain. We calculated a statistically significant favorable effect for the 100-mg dosage (RD, 14.2%; 95% CI, 0.9% to 27.5%) but not for the 50-mg dosage (RD, 12.5%; 95% CI, -0.7% to 25.7%) compared to placebo. The secondary and exploratory migraine and headache event endpoints assessed for statistical significance by ACHIEVE-I[18] and ACHIEVE-II[19] (pain relief at 2 hours post-dose, sustained pain relief and sustained freedom from pain at 2 to 24 hours, absence of photophobia and phonophobia) all demonstrated statistically significant, favorable differences, consistent with the primary study endpoint, except for absence of nausea in the 50-mg dosage group in ACHIEVE-II (Appendix B, Table 8). Voss et al.[17] did not assess the statistical significance of secondary endpoints but the direction and magnitude of the results on all secondary endpoints (e.g., absence of photophobia, sustained pain freedom, sustained pain relief) was consistent with the primary endpoint and endpoints from the other RCTs.

ACHIEVE-I[18] was the only study to report functional outcomes. ACHIEVE-I had a significantly higher proportion of participants who reported “no disability, able to function normally” on the Functional Disability Scale for both the 50-mg dosage (OR, 1.7; 95% CI, 1.2 to 2.3) and 100-mg dosage (OR, 1.9; 95% CI, 1.4 to 2.6) compared to placebo.[18]

The percentage of participants with AEs within 48 hours in the placebo groups from the 3 double-blind RCTs ranged from 10% to 25%, and the percentage with AEs in the active treatment dosages ranged from 9% to 29%.[17-19] Both ACHIEVE trials also reported AEs within 30 days; the incidence was higher across all groups compared to the proportion of AE reported at 48 hours.[18,19] No SAEs or discontinuations due to AEs were reported within 48 hours post-dose in the 3 double-blind RCTs.[17-19] Both ACHIEVE trials also reported SAEs within 30 days; none were reported in ACHIEVE-II[19] and 5 were reported in ACHIEVE-1,[18]all in the active treatment groups (2 appendicitis, 1 pericardial effusion, 1 seizure, 1 spontaneous abortion).[18] The 3 double-

blind RCTs also monitoring liver enzymes for hepatotoxicity; no differences were observed between placebo and treatment groups.[17-19]

The open-label long-term extension trial to the ACHIEVE trials reported by Ailani et al.[20] observed AEs over 52 weeks. In this study, 404 participants treated 10,323 migraine attacks with 1 or more 50-mg doses of ubrogepant (15,536 doses total) and 409 participants treated 11,131 migraine attacks with 1 or more 100-mg doses of ubrogepant (16,432 doses total).[20] Thus, study participants treated an average of 13.2 (50 mg) and 14.8 (100 mg) attacks with 1 dose of ubrogepant and an average of 12.3 (50 mg) and 12.4 (100 mg) attacks with 2 or more doses.[20] Study authors observed 9 (2.2%) SAEs in the 50-mg dosage group and 12 (2.9%) in the 100-mg dosage group and similar rates of discontinuations due to AEs over the course of 52 weeks of follow-up.[20] The incidence of participants with AEs was 66% and 73%, depending on dosage.[20] Overall AEs, SAEs, and discontinuations due to AEs were not reported for the usual care group in this study.[20] Over 52 weeks, Ailani et al.[20] observed 20 participants with liver enzymes that were 3 times or more the upper limit of normal. A blinded panel determined if elevations were study related. This panel determined that 4 cases in the usual care group were unlikely to be study related, 3 cases in the 50-mg dosage group were unlikely to be study related and 2 were possibly related, and 10 cases in the 100-mg dosage group were unlikely to be related and 1 case was determined to be probably related.[20]

Cluster Headache Prevention

The evaluation of CGRP inhibitors for cluster headache prevention is new to the current report. Table 8 provides the summary of findings (GRADE) for these agents. Compared to placebo, we observed larger reductions with galcanezumab for the frequency of cluster headache attacks and proportion of participants with at least a 50% reduction in attacks over weeks 1 to 3 after enrollment. We rated the evidence as of low quality. We rated the evidence as of very low quality for SAE and discontinuations due to AE; few to no events occurred, thus a relationship could not be determined.

Table 8. Summary of Findings (GRADE) for CGRP Inhibitors for Cluster Headache Prevention

Outcome	Quality of Evidence	Relationship	Rationale
Galcanezumab vs. Placebo			
Change in cluster headache attacks per week (1 RCT[10])	Low ●●○○	Statistically significant improvements over weeks 1 to 3; no difference at week 8[a]	Downgraded 1 level for study limitations and 1 level for imprecision
Percentage with at least 50% reduction in number of cluster headache attacks per week (1 RCT[10])	Low ●●○○		
Serious adverse events (1 RCT[10])	Very low ●○○○	No events in either group, relationship cannot be determined	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (1 RCT[10])	Very low ●○○○	Rare events, relationship cannot be determined	

Note. [a] *The primary study endpoint was designated as outcomes over weeks 1 to 3 because spontaneous improvement and remission are typical in the natural trajectory of this headache condition. Abbreviations. CGRP: calcitonin gene-related peptide; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RCT: randomized controlled trial.*

One RCT reported on galcanezumab compared to placebo for cluster headache prevention.[10] This study is summarized in Table 9, with detailed evidence tables in Appendix B, Table B10 (study characteristics), Table B11 (efficacy outcomes), and Table B12 (adverse event outcomes).

Table 9. Summary of Evidence: Placebo-Controlled RCTs of CGRP Inhibitors for Cluster Headache Prevention

Study Trial Number	Dose, Form Number (n and N) Randomized Frequency	Primary Endpoint; Difference From Placebo (95% CI)	N (%) With at Least 1 Serious Adverse Event[a]	N (%) With Adverse Event Leading to Discontinuation
Galcanezumab				
Goadsby et al., 2019[10] NCT02397473	300-mg SC = 49 Placebo SC = 57 Total N = 106[b] Dose at month 0 and 1 following beginning of cluster period	Mean change in frequency of cluster headache attacks per week from baseline at weeks 1 to 3: -3.5 (-0.2 to -6.7; *P* = .04)	Placebo: 0 (0) 300-mg: 0 (0)	Placebo: 1 (2) 300-mg: 2 (4)

Notes. [a] *Defined as death, life-threatening events, events requiring initial or prolonged hospitalization, events resulting persistent or significant disability or that required intervention to prevent permanent impairment or damage, congenital anomaly or birth defect, other events that do not fit any of the previous categories but that may jeopardize the patient or require medical or surgical intervention and are considered significant by the investigator.* [b] *Trial stopped early due to low participant accrual. Abbreviations. CGRP: calcitonin gene-related peptide; CI: confidence interval; NCT: U.S. National Clinical Trial; RCT: randomized controlled trial; SC: subcutaneous.*

Study Characteristics

One phase 3 RCT (Goadsby et al.[10]) conducted among 106 participants at multiple sites in Europe and North America evaluated a 300-mg dosage of galcanezumab at month 0 and month 1 following the beginning of a cluster headache period, compared with placebo over 8 weeks.[10] The study enrolled adults aged 18 to 65 years with a history of episodic cluster headache. The study authors used a 10- to 15-day run-in period with an 8-week follow-up period for efficacy and safety outcomes; no study medications were given during the run-in period. No concomitant use of preventive medication was permitted.[10] We note that the sponsor stopped this trial early because of low participant accrual that resulted because fewer participants entered active cluster headache periods than was anticipated. We note that the FDA-approved dosage for cluster headache is 300-mg at onset of the cluster period, then 300-mg monthly until end of the cluster period.

Study Results

The study authors observed a statistically significant difference in mean change in cluster headache attacks per week from baseline to weeks 1 to 3 (primary study endpoint: -3.5; 95% CI, -0.2 to -6.7) for galcanezumab compared to placebo.[10] However, from baseline to week 8, the mean change in cluster headache attacks per week increased compared to placebo (1.3; 95% CI, -1.2 to 3.8), but this increase was not statistically significant.[10] A statistically significantly greater proportion of the galcanezumab group had a 50% or greater reduction in frequency of cluster headache attacks per week at week 3 (71% vs. 53%; *P* = .046) compared to placebo.[10] At 8 weeks, there was no significant difference in the percentage of participants with 50% greater

reduction in the frequency of cluster headache attacks per week (74% vs. 88%; OR, 0.4; 95% CI, 0.1 to 1.3) compared with placebo.[10]

The percentage of participants with at least 1 AE was 43% in the galcanezumab group and 33% in the placebo group.[10] Neither group had any SAEs.[10] Two participants in the galcanezumab group and 1 participant in the placebo group discontinued treatment due to AEs.[10] Three participants in the treatment group and 2 participants in the placebo group experienced treatment-related liver injury (i.e., alanine aminotransferase, aspartate aminotransferase, or total bilirubin above upper limit of normal).[10]

Ongoing Studies

We identified 19 ongoing phase 2, 3, or 4 studies of CGRP inhibitors (Table 10). One study is a blinded head-to-head RCT comparing erenumab to topiramate, and one is an open-label RCT comparing erenumab to oral preventive medications. The rest are placebo-controlled RCTs. Most studies of migraine or cluster headache prevention have follow-up at 12 or 24 weeks, but some were longer. Compared to studies with primary efficacy end points, some studies with primary safety end points had longer follow-up periods (up to 1.5 years). Two acute migraine treatment studies had follow-up at 2 hours. Two studies are on eptinezumab (1 for chronic migraine prevention, 1 for acute migraine treatment), 6 studies are on erenumab (1 for chronic migraine prevention, 4 for episodic migraine prevention, 1 for chronic and episodic migraine prevention), 5 are on fremanezumab (1 for chronic migraine prevention, 1 for episodic migraine prevention, 3 for chronic and episodic migraine prevention), 4 on galcanezumab (2 for episodic migraine prevention, 1 for chronic and episodic migraine prevention, 1 for cluster headache prevention), and 2 on rimegepant (1 for acute treatment, 1 for chronic and episodic migraine prevention). No ongoing studies were identified for ubrogepant. Sixteen studies have a primary endpoint that is an efficacy outcome and 3 studies have a primary endpoint that is a safety outcome.

Table 10. Ongoing Studies of CGRP Inhibitors for Migraine Headache

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Eptinezumab				
NCT02974153 Evaluation of ALD403 (Eptinezumab) in the Prevention of Chronic Migraine (PROMISE 2) Phase 3	Dose 1, 2, placebo; Blinded	N = 1,121 (Actual) 12 to 36 weeks	April 2018 (Actual)	Change in frequency of migraine days at 12 weeks
NCT04152083 Evaluate Efficacy & Safety of Eptinezumab Administered Intravenously in Subjects Experiencing Acute Attack of Migraine (RELIEF)	100 mg, placebo; Blinded	N=450 (Estimated) 2 hours	September 2020 (Estimated)	Time to headache pain freedom; Time to absence of most bothersome symptom

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Phase 3				
Erenumab				
NCT03333109 Study of Efficacy and Safety of AMG 334 in Adult Episodic Migraine Patients (EMPOwER) Phase 3	Dose 1, 2, placebo; Blinded	N = 900 (Actual) 12 weeks to 24 weeks	February 2020 (Estimated)	Change in mean monthly migraine days from baseline to 12 weeks
NCT03828539 Head-to-head Study of Erenumab Against Topiramate in Patients With Episodic Migraine (HER-MES) Phase 4	70 mg, 140 mg, 50-100 mg topiramate; Blinded	N=770 (Estimated) 24 weeks	June 2020 (Estimated)	Number of patients discontinuing treatment due to adverse event during the double-blind epoch of the study at 24 weeks
NCT03812224 A Controlled Trial of Erenumab in Migraine Prevention Phase 3	Dose 1, placebo; Blinded	N=261 (Actual) 67 weeks	November 2020 (Estimate)	Mean monthly migraine days at 67 weeks
NCT03912337 Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Phase 4	Dose 1, placebo; Blinded	N=340 (Estimated) 6 months	April 2021 (Estimated)	Sum of monthly changes from baseline in modified Migraine Disability Assessment at 6 months
NCT03927144 Study of Sustained Benefit of Erenumab in Adult Episodic Migraine Patients Phase 4	Dose 1, 2, oral prophylactic; Open label	N=600 (Estimated) 12 months	July 2021 (Estimated)	Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at 12 months
NCT03867201 Study of Efficacy and Safety of Erenumab in Adult Chronic Migraine Patients (DRAGON) Phase 3	Dose 1, placebo; Blinded	N=550 (Estimated) 12 weeks	April 2022 (Estimated)	Change from baseline in monthly migraine days during the last 4 weeks of the 12-week treatment period

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Fremanezumab				
NCT02638103 Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine (HALO) Phase 3	Dose 1, 2, placebo; Blinded	N = 1,890 (Actual) NR (efficacy and safety outcomes assessed at 533 ± 15 days)	December 2018 (Actual)	Percentage of participants with adverse events at 533 ± 15 days
NCT03303092 Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Episodic Migraine Phase 2 and 3	225 mg, 675 mg, placebo; Blinded	N = 330 (Estimated) 12 weeks	November 2019 (Estimated)	Change in mean monthly migraine days from baseline to 12 weeks
NCT03303079 Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Chronic Migraine Phase 2 and 3	225 mg, 675 mg, placebo; Blinded	N = 540 (Estimated) 12 weeks	November 2019 (Estimated)	Change in mean monthly headache days of at least moderate severity from baseline to 12 weeks
NCT03303105 Long-term Safety and Tolerability of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine Phase 3	225 mg, 675 mg, placebo; Blinded	N = 40 (Estimated) NR (efficacy outcomes assessed at 337 days, safety outcomes assessed at 562 days)	June 2020 (Estimated)	Percentage of participants with adverse events at 562 days
NCT04041284 A Study to Evaluate the Efficacy and Safety of Fremanezumab for Preventive Treatment of Migraine in Patients With Major Depressive Disorder Phase 4	225 mg, placebo; Blinded	N=340 (Estimated) 12 weeks	August 2021 (Estimated)	Mean change in monthly average number of migraine days at 12 weeks
Galcanezumab				

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
NCT02959177 A Study of LY2951742 (Galcanezumab) in Japanese Participants With Episodic Migraine Phase 2	Dose 1, 2, placebo; Blinded	N = 451 (Estimated) 6 months	January 2019 (Actual)	Change in monthly migraine days from baseline to month 6
NCT02438826 A Study of Galcanezumab in Participants With Chronic Cluster Headache Phase 3	300 mg, placebo; Blinded	N=240 (Actual) 12 weeks	August 2019 (Actual)	Overall mean change from baseline in weekly cluster headache attack frequency at 12 weeks
NCT03559257 A Study of Galcanezumab (LY2951742) in Adults With Treatment-Resistant Migraine (CONQUER) Phase 3	Dose 1, placebo; Blinded	N=463 (Actual) 12 weeks	September 2019 (Actual)	Mean change from baseline in the number of monthly migraine headache days at 3 months
NCT03963232 A Study of Galcanezumab (LY2951742) in Participants With Episodic Migraine Phase 3	Dose 1, placebo; Blinded	N=486 (Estimated) 12 weeks	November 2021 (Estimated)	Mean change from baseline in the number of monthly migraine headache days at 3 months
Rimegepant				
NCT03235479 Safety and Efficacy Study in Adult Subjects With Acute Migraines Phase 3	75 mg, placebo; Blinded	N=1,485 (Actual) 2 hours	January 2018 (Actual)	Number of participants reporting no pain at 2 hours post-dose; Number of participants reporting the absence of their most bothersome symptom at 2 hours post-dose.
NCT03732638 Efficacy and Safety Trial of Rimegepant for Migraine Prevention in Adults Phase 2 and 3	75 mg, placebo; Blinded	N=1,629 (Actual) 12 weeks	January 2021 (Estimated)	Change from baseline in mean number of migraine days per month at 12 weeks
Ubrogepant				
None identified				

Note. [a]As indicated on Clinicaltrials.gov. Abbreviations. CGRP: calcitonin gene-related peptide; NCT: U.S. National Clinical Trial; NR: not reported.

Discussion

In this report, we summarize findings from placebo-controlled trials of CGRP inhibitors for episodic and chronic migraine prevention, acute migraine treatment, and cluster headache prevention. We identified no head-to-head studies.

Migraine Prevention

For both chronic and episodic migraine, we have moderate-quality evidence suggesting a favorable treatment effect for eptinezumab, erenumab, fremanezumab, and galcanezumab compared to a placebo through at least 12 weeks of follow-up and longer in some studies. All 4 agents appear safe for use in migraine prevention, with relatively few serious AEs and discontinuations because of AEs (very-low-quality evidence). Liver toxicity was not common and did not occur more frequently with treatment compared to a placebo. However, safety outcomes for these CGRP inhibitors have limited follow-up, generally of no more than 12 to 24 weeks.

The magnitude of the treatment effect of CGRP inhibitors for migraine prevention is modest across all studies, generally between 0.7 to 3.5 days reduction compared to placebo. The magnitude of the treatment effect of CGRP inhibitors is similar to the treatment effects of other available migraine preventive agents.[43] Providers, patients, or both are likely to view the clinical significance of this magnitude of treatment effect differently, depending on the severity and disability of their headache condition, their ability to tolerate other preventive medications, the relative success of previously tried migraine prevention medications, and other factors. For the HIT-6 instrument, a between-group minimally important difference is 1.5 points based on a study evaluating clinically relevant changes among primary care populations with migraine headache.[49] Ten of the 11 identified studies reporting this outcome have between-group differences of 1.9 points or more for the active drug compared to a placebo, suggesting a clinically important improvement on this measure.

Across the body of evidence, all studies were of fair methodological quality. The studies shared many of the same design features and characteristics, including criteria for inclusion, outcomes, and outcome ascertainment methods, which is likely because of the substantial overlap in authors across the body of evidence. The main design feature on which the studies differed is whether participants using preventive therapy could enroll and how many prior preventive treatments had been tried, which is potentially useful information for clinical edit development. Some studies allowed concomitant preventive therapy and other studies did not. In the few studies that reported findings by concomitant preventive therapy, similar treatment effects to the full study population were observed for participants not taking concomitant therapy, but these findings were limited to studies of fremanezumab.

Findings from Systematic Reviews-Migraine Prevention

Several systematic reviews offer additional information about the use of CGRPs for migraine prevention.[43] The Institute for Clinical and Economic Review (ICER) published an evidence report with a network metaanalysis in May 2018 that included 11 trials for chronic migraine (1 for erenumab, 2 for fremanezumab, 8 for onabotulinumtoxinA or topiramate) and 16 trials for episodic migraine (3 for erenumab, 2 for fremanezumab, 1 for galcanezumab, 10 for other preventive therapies).[43] A network metaanalysis allows for an indirect comparison of therapies for which no head-to head trials may be available. In 2019, Huang et al. published a meta-

analysis of effectiveness of CGRP inhibitors compared to placebo that included 16 trials for migraine prevention reporting on 9,439 participants.[50]

For the prevention of chronic migraine, the ICER report study authors conducted a network metaanalysis for the outcomes of: change in monthly migraine days per month; days using acute medications; and monthly headache days.[43] Detailed findings from this analysis are provided in Appendix C, Table C1. The authors observed greater reductions in monthly migraine days, days using acute medications, and monthly headache days for all active treatments relative to a placebo, and most were statistically significant.[43] The magnitude of reductions relative to the placebo was similar for CGRP inhibitors compared to the other migraine preventive therapies that were included in the analysis, and no significant indirect comparisons between CGRP inhibitors and other drugs were observed for the efficacy outcomes that were evaluated.[43]

For the prevention of episodic migraine, the ICER report study authors conducted a network metaanalysis for the outcomes of: change in monthly migraine days per month; days using acute medications; and percentage of participants reporting a 50% or more reduction in monthly migraine days.[43] Detailed findings are presented in Appendix C, Table C2. Overall, the authors observed greater reductions in monthly headache days and days of acute medication use, and a higher percentage of participants achieving a 50% reduction in monthly migraine days for all active treatments, relative to a placebo; most were statistically significant.[43] The observed benefits relative to the placebo were generally similar for CGRP inhibitors compared to other migraine preventive therapies. In indirect comparisons to topiramate 50-mg, erenumab 70-mg (-1.10 days; 95% CI, -2.14 to -0.02), erenumab 140-mg (-1.75 days; 95% CI, -3.00 to -0.47), galcanezumab 120-mg (-1.71 days; 95% CI, -3.24 to -0.16), and fremanezumab 225-mg (-1.44 days; 95% CI, -2.76 to -0.20) had statistically significantly decreases in monthly migraine days.[43] No significant indirect comparisons between CGRP inhibitors and other drugs were observed for the percentage of participants reporting a 50% reduction in migraine days or for days of acute medication use.[43]

The ICER report authors also conducted network metaanalyses for all-cause discontinuations, discontinuations for AEs, and frequency of SAEs.[43] Discontinuations because of AEs ranged from 0% to 30% between 4 and 26 weeks among participants in the placebo group and from 0% to 5% between 12 and 24 weeks for the CGRP inhibitor group, and from 0% to 49% for other migraine preventive medications.[43] The ICER report authors also conducted network metaanalyses for: all-cause discontinuations; discontinuations for AEs; and frequency of SAEs.[43] No significant differences from a placebo in all-cause discontinuation were observed for any drug (CGRP or other).[43] Participants allocated to topiramate (100 mg or 200 mg daily), amitriptyline (75 to 150 mg per day), or onabotulinumtoxinA (100 to 200 units quarterly) were statistically significantly more likely to discontinue treatment because of AEs compared to the placebo group (ORs ranged from 2.6 to 3.7).[43] Participants allocated to CGRP inhibitors, propranolol, and 50 mg of topiramate per day had no significant differences in the frequency of discontinuation compared to the placebo group (ORs ranged from 1.0 to 1.7).[43] Amitriptyline was the only drug with a significantly higher frequency of SAEs compared to the placebo.[43] No significant differences between CGRP inhibitors and other active drugs were observed in indirect comparisons for all-cause discontinuations in chronic migraine.[43] For episodic migraine, erenumab 70-mg and 140-mg had statistically significantly less frequent all-cause

discontinuations compared to topiramate 200-mg in indirect comparisons.[43] For both chronic and episodic migraine, CGRP inhibitors had no statistically significant differences with other active treatments for discontinuations because of AEs or in the frequency of SAEs in indirect comparisons.[43] We note some of the limitations of network meta-analysis including that not all available treatments can be compared because of limited studies within the network. Further, important assumptions about the studies included must be met for results from a network meta-analysis to be valid including similar study and intervention characteristics among studies within the network and consistency between direct and indirect evidence.

The Huang et al. analysis pooled data across all studies of eptinezumab, erenumab, fremanezumab, and galcanezumab that involved participants with chronic migraine or episodic migraine.[50] The pooled RR comparing CGRP inhibitors to placebo for the incidence of achieving a 50% reduction in monthly migraine days in the 8 RCTs that reported findings by month (n = 2,516 participants) was 1.99 (95% CI, 1.59 to 2.49; I^2 = 55%) in the first month of follow up, and the RR was 1.48 (95% CI, 1.26 to 1.75; I^2 = 67%) in the third month of follow up.[50] In 9 RCTs that reported effects using cumulative 3-month responses (n = 5,406), the RR comparing CGRP inhibitors to placebo was 1.78 (95% CI, 1.54 to 2.05; I^2 = 56%).[50] This analysis did not report any head-to-head indirect comparisons or any AE outcomes.

Acute Migraine Treatment

We have moderate-quality evidence that rimegepant and ubrogepant are more effective than placebo for acute migraine treatment, with very low-quality evidence for no difference in harms, since SAEs and discontinuations due to AEs were very rare events, even over a longer follow-up period, as reported in the 1 open-label extension study followed for up to 52 weeks.[20] Across the body of evidence, all but 1 study were of fair methodological quality. The studies in this body of evidence shared similar design features and participant selection criteria, though most excluded participants with significant cardiovascular or cerebrovascular disease, which may limit generalizability, particularly given the positioning of these agents as alternatives to triptan agents, which are not recommended for persons with cardiovascular disease. One ongoing study of rimegepant for acute migraine treatment will provide additional efficacy and safety data when completed.

Findings from Systematic Reviews-Acute Migraine Treatment

The ICER published an Evidence Report in January 2020 on acute treatment for migraine that included a network metaanalysis for the comparative effectiveness of different drugs.[51] The network of studies included 3 placebo-controlled trials of lasmiditan, 4 placebo-controlled trials of rimegepant, 3 placebo-controlled trials of ubrogepant, 18 placebo-controlled trials of sumatriptan, 3 placebo-controlled trials of eletriptan, and 2 head-to-head trials comparing sumatriptan to eletriptan. We note the study authors included only trials of oral triptan agents, and included 1 trial of rimegepant that only reported findings in a conference abstract; findings from this study were not included in this current DERP report.

The authors reported quantitative results from indirect comparisons the following effectiveness outcomes: freedom from pain at 2 hours, pain relief at 2 hours, sustained pain freedom at 24 hours, freedom from most bothersome symptom at 2 hours, ability to function normally at 2 hours. Detailed findings are provided in Appendix C, Table C3. In brief, rimegepant and

ubrogepant were not significantly different from each other for any effectiveness outcome. Rimegepant and ubrogepant were significantly less effective than sumatriptan and eletriptan on freedom from pain at 2 hours and were also significantly less effective than eletriptan on pain relief at 2 hours. Although rimegepant and ubrogepant were less effective at sustained pain freedom at 24 hours compared to either sumatriptan or eletriptan, the findings for this outcome were not statistically significant. Comparisons related to freedom from most bothersome symptoms at 2 hours and the ability to function normally at 2 hours were not available for comparing the CGRP inhibitors to the triptan agents. Although lasmiditan demonstrated a higher likelihood of achieving effectiveness outcomes compared to either rimegepant or ubrogepant on all but 1 of the efficacy outcomes, none of those findings were statistically significant.

With respect to AEs as reported in single-attack RCTs, rimegepant (OR, 1.25; 95% credible interval, 0.83 to 1.87) and ubrogepant (OR, 1.11; 95% credible interval 0.73 to 1.71) and eletriptan (OR, 1.07; 95% credible interval, 0.76 to 1.52) were not statistically different compared to placebo, while sumatriptan (OR,1.82; 95% credible interval, 1.48 to 2.27) had significantly higher incidence compared to placebo. The rate of discontinuation due to AEs in open-label extension trials was 2.7% for rimegepant and 2.2% to 2.7% for ubrogepant. The rate of SAEs in open-label extension trials was 2.5% for rimegepant and 2.2% to 2.9% for ubrogepant.

Cluster Headache Prevention

We have low-quality evidence from only 1 RCT for the effectiveness of galcanezumab compared to placebo for cluster headache prevention, and very low-quality evidence for harms, given rare events. Further, the study was stopped early because of low participant accrual since not as many participants entered cluster headache periods as had been anticipated. The natural history of cluster headaches (e.g., abrupt onset and remission of cluster periods) makes preventive treatment challenging. Unlike preventive medication for migraine, preventive medication for cluster headache is only started once an active cluster period has been entered. Although galcanezumab was effective through the first 3 weeks of treatment, the authors observed no difference in cluster headache attacks by week 8, which might reflect the lack of efficacy of the agent, but may also reflect spontaneous remission of attacks, typical of the course for cluster headaches. These features of the cluster headache syndrome may make conducting and interpreting findings in future studies challenging.

Limitations of the Evidence

All studies were industry-sponsored, some authors were employed by the manufacturer, and nonemployee authors disclosed financial interests. Although the extent to which the manufacturer's involvement influenced study execution or reporting is not definitively known for this body of evidence, findings from a Cochrane systematic review suggest that industry sponsorship is associated with more favorable results than sponsorship by other sources.[52]

Most of the included trials of migraine prevention were only 12 weeks in duration; thus, durability of treatment effect and safety over a longer term and after patients discontinue taking the drug is not known. Further, in the acute migraine treatment studies, only use for single migraine attacks was assessed. Whether effectiveness persists with longer-term and repeated use needs to be established.

Nearly all studies required compliance with an electronic headache diary during a run-in phase; thus, generalizability of findings to a less selective population is uncertain. Further, most studies excluded patients with clinically significant psychiatric or medical conditions, including pregnancy; thus, whether similar findings would be observed in less selective populations is also uncertain. Females comprised the majority of the study populations in the migraine studies; most studies did not report race and ethnicity information. We did not identify any head-to-head trials that directly compared CGRP inhibitors to each other or to other migraine or cluster headache prevention drugs. One study of rimegepant included a sumatriptan comparator group, but the study was not designed for this comparison. Few studies reported findings among subgroups of interest to this review. Lastly, no studies reported outcomes related to employment or health care utilization.

Limitations of this Review

We included only studies published in English. We did not include data presented in press releases of conference abstracts; thus, this report might not reflect all known data on the efficacy or safety of CGRP inhibitors. When reviewing this report, state Medicaid administrators might consider using the findings and conclusions as a tool in their evidence-based decision-making process, such as clarifying place-in-therapy for CGRP inhibitors. Currently, the body of direct evidence is limited to placebo-controlled trials, which could hinder determining program placement. Consideration of indirect evidence may be warranted until direct head-to-head comparisons of CGRP inhibitors are available.

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Appendix A. Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify systematic reviews (with and without meta-analyses), technology assessments, randomized controlled trials (RCTs), and prospective cohort studies using the terms *eptinezumab*, *erenumab*, *fremanezumab*, *galcanezumab*, *ALD403*, *Aimovig*, *AMG 334*, *TEV-48125*, *LBR-101*, *LY2951742*, *rimegepant*, *ubrogepant*, *BHV3000*, *MK-1602*, and *CGRP inhibitors*. We did not limit searches of evidence sources by any dates because of the expansion in the scope of the current report to include acute migraine treatment and cluster headache prevention.

We searched the following DERP evidence sources:

- Agency for Healthcare Research and Quality (AHRQ)
- Evidence-based Practice Centers (EPC) Reports
- Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE), Evidence
- MEDLINE via PubMed
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Embase

PubMed MEDLINE Search Strategy

Dates Searched: Inception through October 31, 2019

Migraine and Cluster Headache Prevention Scope

Search: ((((((((((eptinezumab[Text Word]) OR eptinezumab[Supplementary Concept]) OR ALD403[Text Word]) OR ALD 403[Text Word]) OR ALD-403[Text Word])) OR ((((((erenumab[Supplementary Concept]) OR erenumab[Text Word]) OR aimovig[Text Word]) OR AMG 334[Text Word]) OR AMG334[Text Word]) OR AMG-334[Text Word])) OR ((((((Galcanezumab[Supplementary Concept]) OR Galcanezumab[Text Word]) OR LY2951742[Text Word]) OR LY-2951742[Text Word]) OR LY 2951742[Text Word]) OR emgality[Text Word])) OR ((((((((((fremanezumab[Supplementary Concept]) OR fremanezumab[Text Word]) OR TEV-48125[Text Word]) OR TEV48125[Text Word]) OR TEV 48125[Text Word]) OR LBR-101[Text Word]) OR LBR101[Text Word]) OR LBR 101[Text Word])) OR ajovy[Text Word])) OR ((((Calcitonin Gene-Related Peptide Receptor Antagonists[MeSH Terms]) OR Calcitonin Gene-Related Peptide Inhibitors[Text Word]) OR Calcitonin Gene Related Peptide Inhibitors[Text Word]) OR CGRP Inhibitor*[Text Word])))) AND (((("Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Comparative Study"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh] OR "Pragmatic Clinical Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "randomized"[tiab] OR "trial"[tiab])) AND English[lang]) Filters: English

Acute Migraine Treatment Scope

Search: (Ubrogepant[Text Word] OR "ubrogepant"[Supplementary Concept] OR MK 1602[Text Word] OR MK-1602[Text Word] OR Rimegepant[Text Word] OR "(5S,6S,9R)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta(b)pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo(4,5-b)pyridin-1-yl)piperidine-1-carboxylate"[Supplementary Concept] OR BHV 3000[Text Word] OR BHV-3000[Text Word]) AND ("Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Comparative Study"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh] OR "Pragmatic Clinical Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "randomized"[tiab] OR "trial"[tiab]) Filters: English

Embase Search Strategy

Dates Searched: Inception through October 31, 2019

Migraine and Cluster Headache Prevention Scope

(eptinezumab:ti,ab,de OR 'eptinezumab'/exp OR ALD403:ti,ab,de OR 'ALD 403':ti,ab,de OR 'ALD-403':ti,ab,de OR 'erenumab'/exp OR erenumab:ti,ab,de OR aimovig:ti,ab,de,tn OR 'AMG 334':ti,ab,de OR AMG334:ti,ab,de OR 'AMG-334':ti,ab,de OR 'galcanezumab'/exp OR Galcanezumab:ti,ab,de OR LY2951742:ti,ab,de OR 'LY-2951742':ti,ab,de OR 'LY 2951742':ti,ab,de OR emgality:ti,ab,de,tn OR 'fremanezumab'/exp OR fremanezumab:ti,ab,de OR 'TEV-48125':ti,ab,de OR TEV48125:ti,ab,de OR 'TEV 48125':ti,ab,de OR 'LBR-101':ti,ab,de OR LBR101:ti,ab,de OR 'LBR 101':ti,ab,de OR ajovy:ti,ab,de,tn OR 'calcitonin gene related peptide receptor antagonist'/exp OR 'Calcitonin Gene-Related Peptide Inhibitors':ti,ab,de OR 'Calcitonin Gene Related Peptide Inhibitors':ti,ab,de OR (CGRP NEXT/1 Inhibitor*):ti,ab,de) AND ('controlled clinical trial'/exp OR 'phase 4 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'meta analysis'/exp OR 'comparative study'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'randomization'/exp OR 'pragmatic trial'/exp OR 'clinical trial'/exp OR 'randomized':ti,ab OR 'trial':ti,ab) AND [english]/lim

Acute Migraine Treatment Scope

(Ubrogepant:ti,ab,de OR 'ubrogepant'/exp OR 'MK 1602':ti,ab,de OR 'MK-1602':ti,ab,de OR Rimegepant:ti,ab,de OR 'rimegepant'/exp OR 'BHV 3000':ti,ab,de OR 'BHV-3000':ti,ab,de) AND ('controlled clinical trial'/exp OR 'phase 4 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'meta analysis'/exp OR 'comparative study'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'randomization'/exp OR 'pragmatic trial'/exp OR 'clinical trial'/exp OR 'randomized':ti,ab OR 'trial':ti,ab) AND [english]/lim

Cochrane Library Search Strategy

Database: Cochrane Reviews and Protocols through October 31, 2019

Migraine and Cluster Headache Prevention Scope

#1 MeSH descriptor: [Calcitonin Gene-Related Peptide Receptor Antagonists] explode all trees 35
#2 (eptinezumab OR ALD403 OR "ALD 403" OR "ALD-403" OR erenumab OR aimovig OR "AMG 334" OR AMG334 OR "AMG-334" OR Galcanezumab OR LY2951742 OR "LY-2951742"

OR "LY 2951742" OR emgality OR fremanezumab OR "TEV-48125" OR TEV48125 OR "TEV 48125" OR "LBR-101" OR LBR101 OR "LBR 101" OR ajovy OR "Calcitonin Gene-Related Peptide Inhibitors" OR "Calcitonin Gene Related Peptide Inhibitors" OR CGRP NEXT Inhibitor*):ti,ab,kw
#3 #1 OR #2

Acute Migraine Treatment Scope

#1 (Ubrogepant OR "MK 1602" OR "MK-1602" OR Rimegepant OR "BHV 3000" OR "BHV-3000"):ti,ab,kw 79
#2 ("Controlled Clinical Trial" OR "Clinical Trial, Phase IV" OR "Clinical Trial, Phase III" OR "Meta-Analysis" OR "Comparative Study" OR "Randomized Controlled Trial" OR "Pragmatic Clinical Trial" OR "Clinical Trial"):pt OR ("randomized" OR "trial"):ti OR ("randomized" OR "trial"):ab 1074169
#3 MeSH descriptor: [Single-Blind Method] explode all trees 19953
#4 MeSH descriptor: [Double-Blind Method] explode all trees 134139
#5 MeSH descriptor: [Random Allocation] explode all trees 20603
#6 #2 OR #3 OR #4 OR #5 1074257
#7 #1 AND #6 73

We searched the following DERP sources for ongoing studies using the search terms *eptinezumab*, *erenumab*, *fremanezumab*, *galcanezumab*, *ALD403*, *Aimovig*, *AMG 334*, *TEV-48125*, *LBR-101*, *LY2951742*, *rimegepant*, *BHV 3000*, *ubrogepant*, *MK 1602*, and *CGRP inhibitors*:

- ClinicalTrials.gov

Inclusion Criteria

Populations

- Adults with episodic or chronic migraines with no previous treatment history or adults who have not responded to other migraine therapies
- Adults with episodic or chronic cluster headache with no previous treatment history or adults who have not responded to other migraine therapies
- Adults with acute migraine headache

Comparators

- CGRP inhibitors compared to each other (head-to-head)
- Pharmacological agents aimed at treating or preventing migraines or cluster headaches (e.g., amitriptyline, ergotamine, onabotulinumtoxinA)
- Sham or placebo

Outcomes

- Migraine events (including frequency, intensity, and duration)
- Pain (including intensity, duration, and pain scale range)
- Other symptoms (e.g., nausea, vomiting, photophobia, and phonophobia)
- Functional ability (including cognitive)
- Disability
- Quality of life
- Other patient-reported outcomes (e.g., depression, anxiety, and difficulties in interpersonal relationships)

- Employment-related outcomes (e.g., unemployment, work productivity loss, and absenteeism)
- Use of rescue therapies
- Number of emergency department and/or primary care provider visits
- Tolerability
- Adverse events (AEs)
- Serious adverse events (SAEs)
- Discontinuations due to AEs

Study Designs

- RCTs
- Prospective cohort studies

Exclusion Criteria

We excluded studies if they were not published in English; we also excluded data in press releases, conference abstracts, or posted to trial registries without a corresponding published article.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, a third experienced researcher resolved the disagreement. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way. A second experienced researcher reviewed all the data entered. We attempted to resolve discrepancies through discussion. When discussion did not resolve the issue, a third experienced researcher settled disagreements.

Quality Assessment

Methodological Quality of Included Studies

We assessed the methodological quality of the included RCTs using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[4,5] One experienced researcher rated all included studies and a second experienced researcher reviewed ratings; disagreements were resolved through discussion.

Systematic Reviews and Randomized Controlled Trials

If a meta-analysis or network meta-analysis was conducted, the methodological quality of the analyses was considered in the overall rating for the systematic review. In brief, good-quality systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to assess study quality and select studies for inclusion (e.g., RCTs), and assessments of heterogeneity to determine whether a meta-analysis would be appropriate. Good-quality RCTs include a clear description of the population, setting,

intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality systematic reviews and RCTs have incomplete information about methods that might mask important limitations. Poor-quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[6,7] One independent experienced researcher assigned ratings, and a second experienced researcher reviewed the ratings with disagreements resolved through discussion. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Characteristics of Studies Evaluating CGRP Inhibitors for Chronic Migraine

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Bigal et al., 2015[36] NCT02021773 NR	Phase 2b, double-blind, parallel-assignment RCT Fremanezumab 225-mg[b] SC = 88 900-mg SC = 87 Placebo SC = 89 Total N = 264	Age: 40.7 (12.0) Female: 227 (86.3) Baseline migraine days per month: 16.8 (5.2) Inclusion: Men and women ages 18 to 65, diagnosed with chronic migraine according to ICHD-3, ≥80% compliance with electronic headache diary during run-in phase. Exclusion: Used onabotulinumtoxinA within 6 months, used opioid or barbiturates for > 4 days during run-in, used ≥ 3 preventive medications without efficacy, clinically significant medical or psychiatric conditions.	4 weeks 12 weeks 12 weeks Use of up to 2 preventive medications or devices if use was stable for 2 months prior to run-in.	62 sites in the U.S., including headache centers, neurology clinics, and primary care sites Teva Pharmaceuticals Fair
Detke et al., 2018[13] NCT02614261 REGAIN	Phase 3, double-blind, parallel-assignment RCT Galcanezumab 120-mg SC (with 240-mg loading dose) = 279 240-mg SC = 279	Age, by group: 120-mg: 39.7 (11.9) 240-mg: 41.1 (12.4) Placebo: 41.6 (12.1) Female, by group: 120-mg: 237 (85) 240-mg: 226 (82)	4 weeks 12 weeks 12 weeks The only preventive medications allowed were topiramate or propranolol if on a stable dosage in the 2 months before the run-in phase.	116 headache and clinical research centers in 12 countries: Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, the

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
	Placebo SC = 559 Total N = 1,117	Placebo: 483 (87) Baseline migraine days per month, by group: 120-mg: 19.4 (4.3) 240-mg: 19.2 (4.6) Placebo: 19.6 (4.6) Inclusion: Men and women ages 18 to 65 with a diagnosis of chronic migraine as defined by the ICHD-3 guidelines; migraine onset before age 50; at least 15 headache days per month, of which at least 8 were migraine for >3 months before screening and as assessed by the electronic headache diary during run-in phase; at least 1 headache-free day per month within 3 months before screening and during run-in; at least 80% compliant with electronic headache diary during run-in phase. Exclusion: Persistent daily headache, cluster headache; head or neck trauma within the past 6 months, possible posttraumatic headache, or primary headache other than chronic migraine; failure to respond to adequate trials of >3 different		United Kingdom, and the U.S. Eli Lilly and Company Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		preventive medication classes; use of therapeutic antibodies during or within 1 year; serious or unstable medical or psychiatric conditions; history of stroke; history of substance abuse or dependence in the past year; at risk for acute cardiovascular events.		
Dodick et al., 2019[11] NCT02275117 NR	Phase 2b, double-blind, parallel-assignment RCT Eptinezumab 300-mg IV single dose = 131 100-mg IV single dose = 133 30-mg IV single dose = 134 10-mg IV single dose = 133 Placebo IV = 134 Total N = 665	Age; by group: 300-mg: 37.2 (10.0) 100-mg: 36.7 (9.4) 30-mg: 35.7 (9.4) 10-mg: 36.4 (10.3) Placebo: 37.2 (9.2) Female, by group: 300-mg: 98 (81) 100-mg: 104 (85) 30-mg: 111 (91) 10-mg: 113 (87) Placebo: 109 (90) Baseline migraine days per month, by group: 300-mg: 16.5 (4.8) 100-mg: 16.9 (4.8) 30-mg: 16.2 (5.1) 10-mg: 16.4 (5.4)	4 weeks Single dose 12 weeks (efficacy)/ 49 weeks (safety) Hormone and preventive medications for headache (such as topiramate, beta-blockers, valproate, tricyclic antidepressants), except botulinum toxin, was allowed if the dosing has been stable for at least 3 months before screening and was maintained.	92 sites: 82 in the U.S., 4 in Australia, 3 each in New Zealand and the Republic of Georgia Alder Biopharmaceuticals, Inc. Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		Placebo: 16.4 (5.1) Inclusion: Men and women ages 18 to 55 with a diagnosis of chronic migraine as defined by the ICHD-3 guidelines; diagnosis at age ≤ 35, and at least 1 year history of chronic migraine; at least 15 headache days, during run-in phase including at least 8 migraine days. Exclusion: complicated migraine; chronic tension-type migraine, hypnic or cluster headache; specialized migraines; other pain syndromes; uncontrolled psychiatric conditions; temporomandibular disorders; current or previous malignancy; cardiovascular disease neurologic or cerebrovascular disease, diabetes, Raynaud's; BMI ≥ 39; history of substance abuse or other clinically significant medical conditions or laboratory abnormalities; botulinum toxin use with prior 4 months, monoclonal antibody use within 6 months.		

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Ferrari et al., 2019[12] NCT03308968 FOCUS	Phase 3b, double-blind, parallel-assignment RCT Fremanezumab 675-mg SC quarterly: 276 225-mg SC (episodic) and 675-mg SC (chronic) initial dose, then 225-mg monthly: 283 Placebo SC: 279 Total N = 838	Age; by group: Quarterly: 45.8 (11.0) Monthly: 45.9 (11.1) Placebo: 46.8 (11.1) Female, by group: Quarterly: 229 (83) Monthly: 238 (84) Placebo: 233 (84) Chronic migraine: *509 (60.7)* Episodic migraine: *329 (39.2)* Baseline migraine days per month, by group: Quarterly: 14.1 (5.6) Monthly: 14.1 (5.6) Placebo: 14.3 (6.1) Inclusion: Men and women ages 18 to 70 diagnosis of episodic or chronic migraine as defined by the ICHD-3 guidelines; diagnosis prior to age 50; history of migraine for at least 12 months before screening; documented failure of 2 to 4 migraine preventive medications within past 10 years.	4 weeks 12 weeks 12 weeks Ongoing preventive medications were not allowed.	104 sites across Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, the United Kingdom, and the U.S. Teva Branded Pharmaceutical Products, R&D Inc. Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		Exclusion: Use of migraine preventive medications; use of onabotulinumtoxinA during the prior 3 months; use of opioid- or barbiturates on more than 4 days during run-in; used interventions or devices for migraine during the 2 months before screening; used triptans or ergots as migraine preventive treatment; or used nonsteroidal anti-inflammatory drugs as a preventive treatment for migraine or on an almost daily basis for other indications, with the exception of low-dose aspirin for cardiovascular disease prevention; previous exposure to a monoclonal antibody targeting CGRP pathway; clinically significant disease or psychiatric issues; history of clinically significant cardiovascular disease or vascular ischemia or thromboembolic events.		
Silberstein et al., 2017[37] NCT02621931 HALO CM	Phase 3 double-blind, parallel-assignment RCT Fremanezumab 225-mg[b] SC = 379 675-mg quarterly SC = 376	Age; by group: 225-mg: 40.6 (12.0) 675-mg: 42.0 (12.4) Placebo: 41.4 (12.0) Female, by group: 225-mg: 330 (87) 675-mg: 331 (88)	4 weeks 12 weeks 12 weeks Use of 1 preventive medication if use was stable for 2 months prior to run-in; this was	132 sites in 9 countries, including academic neurology clinics, private practices, for-profit research clinics, specialty headache clinics, primary care

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
	Placebo SC = 375 Total N = 1,130	Placebo: 330 (88) Baseline migraine days per month, by group: 225-mg: 16.0 (5.2) 675-mg: 16.2 (4.9) Placebo: 16.4 (5.2) Inclusion: Men and women ages 18 to 70 with a history of migraine according to ICHD-3 for at least 12 months and fulfillment of chronic migraine criteria during run-in phase Exclusion: Used onabotulinumtoxinA within 4 months, used interventions or devices such as nerve blocks and transcranial magnetic stimulation for migraine within 2 months, used opioid or barbiturates for > 4 days during run-in, used ≥ 2 of 4 clusters of preventive medications without efficacy.	permitted for up to 30% of enrolled patients.	clinics, and other outpatient clinics Teva Pharmaceuticals Fair
Tepper et al., 2017[34] Lipton et al., 2019[35] NCT02066415	Phase 2 double-blind, parallel-assignment RCT Erenumab 70-mg SC = 191 140-mg SC = 190	Age, by group: 70-mg: 41.4 (11.3) 140-mg: 42.9 (11.1) Placebo: 42.1 (11.3) Female, by group: 70-mg: 166 (87) 140-mg: 160 (84)	4 weeks 12 weeks 12 weeks Migraine preventive drugs were prohibited in 2 months prior to run-in phase and during treatment phase.	69 sites in North America and Europe, including headache and clinical research centers Amgen

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
	Placebo SC = 286 Total N = 667	Placebo: 226 (79) Baseline migraine days per month, by group: 70-mg: 17.9 (4.4) 140-mg: 17.8 (4.7) Placebo: 18.2 (4.7) Inclusion: Male and female patients 18 years of age and older with at least a 1-year history of migraines (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition; age of onset prior to 50; migraine attacks that last about 4 - 72 hours; not more than 8 attacks of moderate or severe intensity per month within the last 3 months; and not less than 2 attacks per month. Exclusion: Patients with history of basilar migraine or hemiplegic migraine.		Fair

Notes. [a] All active treatment and placebos are monthly unless otherwise specified; [b] Patients in the 225-mg group received fremanezumab 675-mg at baseline and 225 mg of fremanezumab at weeks 4 and 8. Abbreviations. CGRP: calcitonin gene-related peptide; ICHD-3: International Classification of Headache Disorders, 3rd edition; IV: intravenous; NCT: U.S. National Clinical Trial; NR: not reported; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation.

Table B2. Efficacy of CGRP Inhibitors in Randomized Trials Evaluating Chronic Migraine

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Bigal et al., 2015[36]		Fremanezumab 225-mg[b]	Fremanezumab 900-mg
Migraine or Headache Events (N Analyzed)		Mean difference from placebo (95% CI; P value)	
Mean change in headache (any severity) hours per month from baseline (261) [Primary study endpoint]	Weeks 9 to 12	-22.7 (-44.3 to -1.2; *P* = .04)	-30.4 (-51.9 to -9.0; *P* = .006)
Mean change in headache (moderate to severe) days per month from baseline (261)	Weeks 9 to 12	-1.8 (-3.5 to -0.14; *P* = .03)	-2.0 (-3.7 to -0.26; *P* = .02)
Mean change in headache (moderate to severe) hours per month from baseline (261)	Weeks 9 to 12	-13.6 (-29.3 to 2.2; *P* = .09)	-11.3 (-26.9 to 4.4; *P* = .16)
Mean change in headache (any severity) days per month from baseline (261)	Weeks 9 to 12	-1.7 (-3.6 to 0.1; *P* = .07)	-2.7 (-4.6 to -0.9; *P* = .004)
Mean change in migraine days per month from baseline (261)	Weeks 9 to 12	-1.7 (-3.7 to 0.2; *P* = .08)	-2.0 (-3.9 to -0.1; *P* = .04)
Mean change in days of acute headache drug use (261)	Weeks 9 to 12	-2.2 (-4.0 to 0.3; *P* = .02)	-2.0 (-3.9 to -0.20; *P* = .03)
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (95% CI; P value)	
NR	NR	NR	NR
Detke et al., 2018[13] (REGAIN)		Galcanezumab 120-mg	Galcanezumab 240-mg
Migraine or Headache Events (N Analyzed)		Mean difference from placebo (95% CI; P value)	
Mean change in MHDs per month from baseline [Primary study endpoint] (1,085)	Weeks 4 to 12	-2.1 (-2.9 to -1.3; *P* < .001)	-1.9 (-2.7 to -1.1; *P* < .001)
Mean change in MHDs per month with acute medication use (1,085)	Weeks 4 to 12	-2.5 (-3.3 to -1.8; *P* < .001[c])	-2.0 (-2.8 to -1.3; *P* < .001)
Mean change in MHDs per month (1,085)	Weeks 4 to 12	-1.8 (-2.7 to -1.0; *P* < .001)	-1.6 (-2.4 to -0.8; *P* < .001)
Mean change in headache hours per month (1,085)	Weeks 4 to 12	-22.7 (-31.7 to -13.7;' *P* < .001)	-18.1 (-27.1 to -9.1; *P* < .001)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Mean change in migraine headache hours per month (1,085)	Weeks 4 to 12	-22.1 (-30.9 to -13.3; *P* < .001)	-18.0 (-26.8 to -9.3; *P* < .001)
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (1,085)	Weeks 4 to 12	% (SD %), OR (95% CI), P value	
		27.6 (2.7), 2.1 (1.6 to 2.8), *P* < .001	27.5 (2.6), 2.1 (1.6 to 2.8), *P* < .001
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (1,085)	Weeks 4 to 12	7.0 (1.4), 1.6 (1.0 to 2.5), *P* =.03[d]	8.8 (1.7), 2.0 (1.4 to 3.1), *P* < .001
Percentage of participants with 100% or greater reduction in the mean number of MHDs per month from baseline (1,085)	Weeks 4 to 12	0.7 (0.4), 1.4 (0.4 to 4.4), *P* = .597	1.3 (0.6), 2.6 (1.0 to 7.0), *P* =.058
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (95% CI; P value)	
Mean change in functioning at month 3 measured by the MSQL role function-restrictive score (1,085)	Weeks 4 to 12	5.1 (2.1 to 8.0; *P* < .001)[c]	6.3 (3.0 to 9.6; *P* < .001)
Mean change in functioning at month 3 measured by the MSQL emotional function score (1,085)	Weeks 4 to 12	7.0 (3.2 to 10.8; *P* < .001)	6.6 (2.8 to 10.4; *P* < .001)
Mean change in functioning at month 3 measured by the MSQL role function-preventive score (1,085)	Weeks 4 to 12	7.0 (4.2 to 9.8; *P* < .001)	5.1 (2.3 to 7.9; *P* < .001)
Mean change in functioning at month 3 measured by the MIDAS score (1,085)	Weeks 4 to 12	-8.7 (−16.4 to −1.1; *P* = .025)	−5.5 (−13.1 to 2.1; *P* = .157)
Mean change in PGI-S (1,085)	Weeks 4 to 12	-0.1 (-0.3 to 0.1; *P* = .181)	-0.3 (-0.5 to -0.1; *P* = .006)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]			
Dodick et al., 2019[11]		Eptinezumab 300-mg IV single dose	Eptinezumab 100-mg IV single dose	Eptinezumab 30-mg IV single dose	Eptinezumab 10-mg IV single dose
Migraine or Headache Events (N Analyzed)		N (%); P value			
Percentage of patients with a 75% or greater reduction in the mean number of MHDs per month from baseline (588) [Primary study end point]	Weeks 1 to 12	300-mg: *38* (33.3) Placebo: *24* (20.7) *P* = .033	100-mg: 37 (31.4) Placebo: *24* (20.7) *P* =.072	30-mg: *33* (28.2) Placebo: *24* (20.7) *P* = .201	10-mg: *33* (26.8) Placebo: *24* (20.7) *P* = .294
Percentage of patients with a 50% or greater reduction in the mean number of MHDs per month from baseline (588)	Weeks 1 to 12	300-mg: *65* (57.0) Placebo: *47* (40.5) *P* = .013	100-mg: *65* (55.1) Placebo: *47* (40.5) *P* =.029	30-mg: *65* (55.6) Placebo: *47* (40.5) *P* = .024	10-mg: *54* (43.9) Placebo: *47* (40.5) *P* = .621
Mean change in monthly MHDs from baseline (588)	Weeks 1 to 12	Mean difference from placebo (95% CI, P value)			
		-2.7 (-4.4 to -0.9), *P* = .003	-2.1 (-3.8 to -0.4), *P* = .018	-2.4 (-4.0 to -0.7), *P* = .005	-1.2 (-2.9 to 0.6), *P* = .180
Mean change in monthly headache days from baseline (588)	Weeks 1 to 12	-2.8 (-4.5 to -1.0), *P* = .002	-2.0 (-3.7 to -0.3), *P* = .022	-2.4 (-4.0 to -0.7), *P* = .006	-0.7 (-2.4 to 1.0), *P* = .44
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (95% CI), P value			
Mean change in HIT-6 score from baseline (588)	Week 12	-4.2 (-6.3 to -2.1), P < .001	-1.1 (-3.1 to 0.88), P = .27	-0.7 (-2.7 to 1.3), P = .49	-0.7 (-2.7 to 1.3), P = .50
Ferrari et al., 2019[12] (FOCUS)		Fremanezumab 675-mg quarterly		Fremanezumab 225-mg monthly[e]	
Migraine or Headache Events (N Analyzed)		Mean difference from placebo (95% CI); P value			
Mean change from baseline in the monthly average number of MHDs [Primary study endpoint] (837)	Weeks 1 to 12	−3.1 (−3.8 to −2.4; *P* <.0001)		−3.5 (−4.2 to −2.8; *P* <.0001)	
Mean change in MHDs of at least moderate severity per month (837)	Weeks 1 to 12	−3.2 (−3.9 to −2.5; *P* <.0001)		−3.6 (−4.3 to −2.9; *P* <.0001)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Mean change in number of days of use of any acute headache medication per month from baseline (837)	Weeks 1 to 12	−3.1 (−3.8 to −2.4; *P* <.0001)	−3.4 (−4.0 to −2.7; *P* <.0001)
Mean change in number of days with nausea or vomiting per month from baseline (837)	Weeks 1 to 12	-1.9 (-2.5 to -1.4); *P* < .001	-2.1 (-2.6 to -1.5); *P* < .001
Mean change in number of days with photophobia or phonophobia per month from baseline (837)	Weeks 1 to 12	-2.2 (-2.9 to -1.6); *P* < .001	-2.8 (-3.4 to -2.1); *P* < .001
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (837)	Weeks 1 to 12	N (%); OR (95% CI), P value	
		95 (34); 5.8 (3.6 to 9.6); *P* <.0001	97 (34); 5.8 (3.6 to 9.5); *P* <.0001
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (837)	Weeks 1 to 12	23 (8); 4.2 (1.7 to 10.6); *P*.0021	35 (12); 6.6 (2.7 to 16.1); *P* <.001
Percentage of participants with 100% in the mean number of MHDs per month from baseline (837)	Weeks 1 to 12	0 (0); 1.0 (0 to $6.9*10^{203}$); *P* =1.0	4 (1); 109.9 (0 to $5.6*10^{147}$); *P* = .95
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (95% CI); P value)	
Mean change in HIT-6 score from baseline (837)	Week 12	-3.0 (-4.1 to -1.8); *P* < .001	-3.8 (-5.0 to -2.7); *P* < .001
Mean change in MIDAS score from baseline (837)	Week 12	-12.7 (-19.5 to -6.0); *P* = .0002	-17.7 (-24.5 to -11.0); *P* < .0001
Mean change in MSQL score from baseline (837)	Week 12	8.8 (5.7 to 11.9); *P* < .0001	10.6 (7.5 to 13.7); *P* < .0001
Mean change in EQ-5D score from baseline (837)	Week 12	3.0 (0.1 to 5.9); *P* = .04	5.6 (2.7 to 8.5); *P* = .0002
Mean change in WPAI score from baseline (837)	Week 12	-4.3 (-8.7 to 0.2); *P* = .06	-4.9 (-9.3 to -0.5); *P* = .03
Silberstein et al., 2017[37] (HALO CM)		Fremanezumab 225-mg[b]	Fremanezumab 675-mg quarterly
Migraine or Headache Events (N Analyzed)		Mean difference from placebo (SE; P value)	
Mean change in MHDs per month from baseline (1,121) [Primary study endpoint]	Weeks 9 to 12	-2.1 (0.3; *P* < .001)	-1.8 (0.3; *P* < .001)
Mean change in MHDs per month from baseline (1,121)	Weeks 9 to 12	-1.8 (0.4; *P* < .001)	-1.7 (0.4; *P* < .001)
Mean change in days of acute headache medication use per month from baseline (1,121)	Weeks 9 to 12	-2.3 (0.3; *P* < .001)	-1.8 (0.3; *P* < .001)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Mean change in MHDs per month from baseline for those not receiving concomitant preventive medication (882)	Weeks 9 to 12	-2.2 (0.4; *P* < .001)	-1.9 (0.4; *P* < .001)
Patients with a reduction of ≥ 50% in mean number of MHDs per month (1,121)	Weeks 9 to 12	**N (%), RD and RR (95% CI)**	
		225-mg: 153 (41) Placebo: 67 (18); *P* < .001 *RD: 22.7 (16.4 to 29.1, P < .001)* RR: 2.3 (1.8 to 2.9, P < .001)	675-mg: 141 (38) Placebo: 67 (18); *P* < .001 *RD: 19.5 (13.3 to 25.8, P < .001)* RR: 2.1 (1.6 to 2.7, P < .001)
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (SE; P value)**	
Mean change in HIT-6 score[f] from baseline (1,121)	Week 12	-2.4 (0.5; *P* < .001)	-1.9 (0.5; *P* < .001)
Tepper et al., 2017[34]; Lipton et al. 2019[35]		**Erenumab 70-mg**	**Erenumab 140-mg**
Migraine or Headache Event (N analyzed)		**Mean difference from placebo (95% CI; P value)**	
Mean change in MHDs per month from baseline (656) [Primary study endpoint]	Weeks 9 to 12	-2.5 (-3.5 to -1.4; *P* < .0001)	-2.5 (-3.5 to -1.4; *P* < .0001)
Mean change in days of acute migraine medication use per month from baseline (656)	Weeks 9 to 12	-1.9 (-2.6 to -1.1; *P* < .0001)	-2.6 (-3.3 to -1.8; *P* < .0001)
Mean change in headache (of any severity) hours per month from baseline (656)	Weeks 9 to 12	-9.5 (-27.0 to 7.9; *P* = .28)	-19.3 (-36.7 to -1.9; *P* = .03)
Patients with a reduction of ≥ 50% in MHDs per month (656)	Weeks 9 to 12	**N (%), OR, RD, and RR (95% CI)**	
		70-mg: 75 (40) Placebo: 66 (23) OR 2.2 (1.5 to 3.3, *P* = .0001) RD 16.4 (7.8 to 25.0, *P* = .0002) RR 1.70 (1.29 to 2.23, *P* = .0002)	140-mg: 77 (41) Placebo: 66 (23) OR 2.3 (1.6 to 3.5, *P* < .0001) RD 17.7 (9.1 to 26.3, *P* < .0001) RR 1.75 (1.34 to 2.30, *P* < .0001)
Functioning and Quality of Life (N Analyzed)		**OR (95% CI; P value)**	
Change in MSQL role function-preventive domain score ≥ 5 from baseline (656)	Weeks 9 to 12	1.5 (0.9 to 2.6; *P* = .13)	1.6 (0.9 to 2.8; *P* = .085)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Change in MSQL role function-restrictive domain score ≥ 5 from baseline (656)	Weeks 9 to 12	1.9 (1.1 to 3.3; *P* = .031)	2.8 (1.6 to 4.9; *P* < .001)
Change in MSQL emotional-functioning domain score ≥ 8 from baseline (656)	Weeks 9 to 12	2.4 (1.4 to 4.3; *P* = .003)	2.4 (1.4 to 4.3; *P* = .003)
Change in HIT-6 score ≥ 5 from baseline (656)	Weeks 9 to 12	2.3 (1.5 to 3.4; *P* < .001)	2.3 (1.5 to 3.4; *P* < .001)
Proportion with MIDAS score ≥ 21 (severe or very severe; (656)	Weeks 9 to 12	0.4 (0.3 to 0.7; *P* <.001)	0.4 (0.2 to 0.6; *P* < .001)
Proportion with MIDAS score ≥ 41 (very severe; 656)	Weeks 9 to 12	0.5 (0.3 to 0.8; *P* = .002)	0.5 (0.3 to 0.7; *P* < .001)
PROMIS pain interference scale short form score ≥ 60 (656)	Weeks 9 to 12	0.3 (0.2 to 0.7; *P* = .003)	0.3 (0.1 to 0.6; *P* < .001)

Notes. Calculated values are indicated with italics. [a] All active treatments and placebos administered monthly unless otherwise specified. [b] Patients in the 225-mg group received fremanezumab 675-mg at baseline and 225 mg of fremanezumab at weeks 4 and 8. [c] Nominal significance without multiplicity testing; this outcome was not tested after multiplicity adjustment because all α was expended on previous items; thus, it is considered not significant regardless of nominal P value. [d] Not significant after multiplicity adjustment. [e] Participants with chronic migraine received an initial dose of 675-mg SC. [f] HIT-6 scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability. A minimally important difference is 1.5 points. Abbreviations. CGRP: calcitonin gene-related peptide; CI: confidence interval; EQ-5D: European Quality of Life 5-Dimension measure; HIT-6: 6-item Headache Impact Test; IV: intravenous; MHD: migraine headache day; MIDAS: Migraine Disability Assessment; MSQL: migraine-specific quality of life questionnaire; NR: not reported; OR: odds ratio; PGI-S: Patient Global Impression Survey; PROMIS: Patient-Reported Outcomes Measurement Information System; RD: risk difference; RR: risk ratio; SC: subcutaneous; SD: standard deviation; SE: standard error; WPAI: Work Productivity and Activity Impairment Questionnaire.

Table B3. Adverse Events From CGRP Inhibitors in Randomized Trials Evaluating Chronic Migraine

Outcome	Treatment Groups[a]				
Bigal et al., 2015[36]	Placebo	Fremanezumab 225-mg[b]	Fremanezumab 900-mg		
N (%) with at least 1 adverse event	NR	NR	NR		
N (%) with at least 1 treatment-emergent adverse event	36 (40)	47 (53)	41 (48)		
N (%) with at least 1 treatment-related adverse event	15 (17)	25 (29)	28 (32)		
N (%) with a nonfatal adverse event leading to discontinuation	1 (1)	4 (5)	3 (4)		
N (%) with at least 1 serious adverse event/N events	1 (1)/1 1 nephrolithiasis	1 (1)/1 1 pneumonia	2 (2)/3 1 irritable bowel syndrome 1 depression 1 suicide attempt		
N (%) with treatment-related liver injury	1 (1.1) with transient liver enzyme increase, none were considered treatment-related	3 (1.7) with transient liver enzyme increase, none were considered treatment-related			
Detke et al., 2018[13] (REGAIN)	Placebo	Galcanezumab 120-mg	Galcanezumab 240-mg		
N (%) with at least 1 adverse event	279 (50)	159 (58)	160 (57)		
N (%) with adverse event leading to discontinuation	6 (1.0)	1 (0.4)	4 (1.4)		
N (%) with serious adverse event/N events	4 (0.7)/4	1 (0.4)/1	4 (1.4)/5		
N (%) with treatment-related liver injury	0	0	1 (increased hepatic enzymes)		
Dodick et al., 2019[11]	Placebo	Eptinezumab 300-mg	Eptinezumab 100-mg	Eptinezumab 30-mg	Eptinezumab 10-mg
N (%) with treatment-emergent adverse event	68 (56.2)	77 (63.6)	70 (57.5)	56 (45.9)	74 (56.9)
N (%) with study drug-related treatment-emergent adverse event	17 (14.0)	21 (17.4)	24 (19.8)	18 (14.8)	21 (16.2)
N (%) with severe treatment-emergent adverse event/ N events	0/0	4 (3.3)/6	3 (2.5)/4	3 (2.5)/3	1 (0.8)/2

Outcome	Treatment Groups[a]				
N (%) with serious treatment-emergent adverse event/ N events	1 (0.8)/1	7 (5.8)/9	4 (3.3)/5	0/0	1 (0.8)/1
N (%) with treatment-emergent adverse event leading to infusion interruption	0	4 (3.3)	2 (1.6)	4 (3.3)	0
N (%) with treatment-related liver injury	"Laboratory tests including liver function were unremarkable and did not exhibit any dosage-related signals"				
Ferrari et al., 2019[12] (FOCUS)	**Placebo**	**Quarterly Fremanezumab**	**Monthly Fremanezumab**		
N (%) with at least 1 adverse event	134 (48%)	151 (55%)	129 (45%)		
N (%) with at least 1 serious adverse event	4 (1%)	2 (<1%)	4 (1%)		
N (%) with at least 1 treatment-related adverse event	55 (20%)	57 (21%)	55 (19%)		
N (%) with adverse events leading to discontinuation	3 (1%)	1 (<1%)	4 (1%)		
N (%) with liver injury	0	0	1 (< 1%) [cholelithiasis/ elevated liver function tests]		
Silberstein et al., 2017[37] (HALO CM)	**Placebo**	**Fremanezumab 225-mg[b]**	**Fremanezumab 675-mg quarterly**		
N (%) with at least 1 adverse event	240 (64)	270 (71)	265 (70)		
N (%) with at least 1 treatment-related adverse event	159 (42)	194 (51)	186 (49)		
N (%) with adverse event leading to discontinuation	8 (2)	7 (2)	5 (1)		
N (%) with at least 1 serious adverse event/N events	6 (2)/10 1 accident 1 clavicle fracture 1 nephrolithiasis 1 asthma 1 dyspnea 1 diplopia 1 peripheral edema	5 (1)/7 1 fall 1 radius fracture 1 ulna fracture 1 back pain 1 suicidal ideation 1 urinary calculus 1 hypertensive crisis	3 (< 1)/4 1 road traffic accident 1 wrist fracture 1 pneumonia 1 death attributed to chronic obstructive pulmonary disease		

Outcome	Treatment Groups[a]		
	1 drug hypersensitivity 1 uterine leiomyoma 1 migraine		
N (%) with treatment-related liver injury (defined as increased liver enzymes, total bilirubin or international normalized ratio > 1.5)	3 (< 1)	5 (1)	5 (1)
Tepper et al., 2017[34], Lipton et al., 2019[35]	**Placebo**	**Erenumab 70-mg**	**Erenumab 140-mg**
N (%) with at least 1 adverse event	110 (39)	83 (44)	88 (47)
N (%) with adverse event leading to discontinuation	2 (< 1)	0 (0)	2 (1)
N (%) with at least 1 serious adverse event/N events	7 (2)/7 1 intervertebral disc protrusion 1 cholecystitis 1 migraine 1 pancreatitis 1 parotitis 1 urinary tract infection 1 vomiting	6 (3)/6 1 intervertebral disc protrusion 1 appendicitis 1 costochondritis 1 fibroma 1 noncardiac chest pain 1 radius fracture	2 (1)/3 1 abdominal adhesions 1 abdominal pain 1 cartilage injury
N (%) with treatment-related liver injury	0 (0)	0 (0)	1 (< 1) abnormal increases in alanine and aspartate aminotransferases

Notes. Calculated values are indicated with italics. [a] All treatments and placebos administered monthly unless otherwise specified. [b] Patients in the 225-mg group received fremanezumab 675-mg at baseline and 225 mg of fremanezumab at weeks 4 and 8. Abbreviations. CGRP: calcitonin gene-related peptide; NR: not reported.

Table B4. Characteristics of Studies Evaluating CGRP Inhibitors for Episodic Migraine

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Ashina et al., 2020[38] PROMISE-1 NCT02559895	Phase 3, double-blind, parallel assignment RCT Eptinezumab 30-mg IV = 224 100-mg IV = 225 300-mg IV = 224 Placebo IV = 225 Total IV = 898	Age: 39.8 (11.4) Female: 749 (84.3) Baseline migraine headache days (MHDs) per month by group: 30-mg: 10.2 (3.4) 100-mg: 10.0 (3.0) 300-mg: 10.1 (3.1) Placebo: 9.9 (2.8) Inclusion: Men and women ages 18 to 75 years, diagnosed with migraine according to ICHD criteria at or before 50 years, history of migraine for ≥ 12 months with ≤ 14 headache days per month, including ≥ 4 migraine days per month in the 3 months prior to screening. Exclusion: Those with confounding pain syndromes, uncontrolled or untreated psychiatric conditions, temporal mandibular disorders, present or prior malignancies, headache or migraine disorders that did not meet the ICHD criteria, or unable to distinguish migraine from other headaches.	4 weeks 12 weeks 12 weeks Use of prophylactic treatment for menstrual migraine, migraine medications, barbiturates or prescription opiates, non-prescription codeine, hormone therapies, were permitted if dosages were stable and did not exceed thresholds.	84 sites in U.S. and Republic of Georgia H. Lundbeck A/S, Copenhagen, Denmark Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Bigal et al., 2015[26] NCT02025556 NR	Phase 2b, double-blind, parallel-assignment RCT Fremanezumab 225-mg SC = 96 675-mg SC = 97 Placebo SC =104 Total N = 297[b]	Age, by group: 225-mg: 40.8 (12.4) 675-mg: 40.7 (12.6) Placebo: 42.0(11.6) Female, by group: 225-mg: 87 (91%) 675-mg: 82 (85%) Placebo: 92 (88%) Baseline MHDs per month, by group: 225-mg: 11.5 (1.9) 675-mg: 11.3 (2.2) Placebo: 11.5 (2.24) Inclusion: Ages 18 to 65, diagnosed with migraine according to ICHD-3 with 8 to 14 days MHDs per month with at least 8 of these fulfilling migraine criteria, compliance with electronic headache diary of at least 80% during run-in phase. Exclusion: Chronic migraine, used opioids or barbiturates for more than 4 days during run-in, onabotulinumtoxinA use within 6 months, used 3 or more preventive medications without efficacy, clinically significant medical or psychiatric conditions.	4 weeks 12 weeks 12 weeks Use of no more than 1 preventive medication or device if use was stable for 2 months prior to run-in.	62 U.S. sites, including headache centers, neurology clinics, and primary care sites Teva Pharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Dodick et al., 2018[22] NCT02483585 ARISE	Phase 3 double-blind, parallel-assignment RCT Erenumab 70-mg SC =286 Placebo SC = 291 Total N = 577	Age: 42 (11) Female: 492 (85.3) Baseline MHDs per month: 8.3 (2.6) Inclusion: Men and women ages 18 to 65 with a history of episodic migraine (with or without aura) defined as 4 to 15 MHDs per month and < 15 MHDs per month for ≥ 12 months. Exclusion: Migraine onset occurred after age 50, history of cluster headache or hemiplegic migraine, used > 2 preventive medication classes without efficacy, had medical conditions that could interfere with treatment.	4 weeks 12 weeks 28 weeks (14 weeks of which was open-label) Use of 1 preventive medication allowed if use was stable ≥ 2 months (≥ 4 months for botulinum toxin) prior to run-in.	69 sites in North America and Europe, including headache centers, neurology clinics, and clinical research sites Amgen Fair
Dodick et al., 2018[27] Brandes et al., 2019[39] NCT02629861 HALO EM	Phase 3 double-blind, randomized, parallel-assignment RCT Fremanezumab 225-mg SC = 290 675-mg SC quarterly = 291 Placebo SC = 294 Total N = 875	Age, by group: 225-mg: 42.9 (12.7) 675-mg: 41.1 (11.4) Placebo: 41.3 (12.0) Female, by group: 225-mg: 244 (84.1) 675-mg: 251 (86.3) Placebo: 247 (84.0) Baseline MHDs per month: 9.1 (2.6)	4 weeks 12 weeks 12 weeks Use of 1 preventive medication if use was stable for 2 months prior to run-in permitted for up to 30% of enrolled participants.	123 sites in 9 countries Teva Pharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		Inclusion: Men and women ages 18 to 70 with a history of migraine according to ICHD-3 criteria for ≥ 12 months and onset prior to age 50; with episodic migraine during the run-in phase defined as having a headache on 6 to 14 days of which ≥ 4 fulfill criteria for migraine (with or without aura), probable migraine, or use of triptans or ergot derivatives. Exclusion: Used onabotulinumtoxinA within 4 months, used opioid or barbiturates for > 4 days during run-in, used ≥ 2 of 4 clusters of preventive medications without efficacy, used interventions or devices such as nerve blocks and transcranial magnetic stimulation for migraine within 2 months.		
Dodick et al., 2014[28] NCT01625988 NR	Phase 2, double-blind, parallel-assignment RCT Galcanezumab every 2 weeks 150-mg SC = 108 Placebo SC = 110 Total N = 218	Age, by group: 150-mg: 40.9 (11.4) Placebo: 41.9 (11.7) Female, by group: 150-mg: 88 (82) Placebo: 96 (87) Baseline MHDs per month, by group: 150-mg: 6.7 (2.4) Placebo: 7.0 (2.5)	4 weeks 12 weeks 12 weeks No ongoing preventive therapy allowed	35 U.S. sites Arteaus Therapeutics Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		Inclusion: Ages 18 to 65 with at least a 1-year history of migraine according to ICHD-2, migraine onset prior to age 50, between 4 and 14 MHDs per month, at least 80% compliance of daily electronic headache entries during run-in phase. Exclusion: History of chronic migraine or migraine subtypes, history of headache other than migraine or tension-type headache within 12 months, failure to respond to more than 2 prevention treatments, prevention treatment within 30 days (120 days for onabotulinumtoxinA), and clinically significant medical or psychiatric conditions.		
Dodick et al., 2014[21] NCT01772524 NR	Phase 2, double-blind, parallel-assignment RCT Eptinezumab 1,000-mg IV single dose = 86 Placebo IV = 88 Total N = 174	Age, by group: 1,000-mg: 38.6 (10.8) Placebo: 39.0 (9.6) Female, by group: 1,000-mg: 67 (83) Placebo: 66 (80) Baseline MHDs per month, by group: 1,000-mg: 8.4 (2.1) Placebo: 8.8 (2.7) Inclusion: Ages 18 to 55 with at least a 1-year history of migraine according to ICHD-2, migraine onset prior to	4 weeks 12 weeks 24 weeks Ongoing preventive therapy not allowed	26 U.S. sites Alder Biopharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		age 50, between 5 and 14 MHDs in each of the prior 3 months; and between 5 and 14 MHDs and compliance with daily electronic headache entries on at least 25 of 28 days during run-in phase. Exclusion: Regular use of preventive headache drug with efficacy, botulinum toxin use within 6 months, other headache types, confounding pain syndromes, hypertension, and clinically significant medical or psychiatric conditions.		
Goadsby et al., 2017[23] Buse et al., 2018[24] NCT02456740 STRIVE	Phase 3 double-blind, parallel-assignment RCT Erenumab 70-mg SC = 317 140-mg SC = 319 Placebo = 319 Total N = 955	Age, by group: 70-mg: 41.1 (11.3) 140-mg: 40.4 (11.3) Placebo: 41.3 (11.2) Female, by group: 70-mg: 268 (84.5) 140-mg: 272 (85.3) Placebo: 274 (85.9) Baseline MHDs per month, by group: 70-mg: 8.3 (2.5) 140-mg: 8.3 (2.5) Placebo: 8.2 (2.5) Inclusion: Ages 18 to 65 with at least a 1-year history of migraine according to ICHD-3 with or without aura,	4 weeks 24 weeks 24 weeks[c] Use of 1 medication was permitted if the dosage was stable within 2 months before the start of the baseline phase and throughout the study.	121 sites across North America and Europe and Turkey Amgen and Novartis Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		migraine onset prior to age 50, and between 4 and 15 MHDs and fewer than 15 MHDs per month and at least 80% compliance of daily electronic headache entries during run-in phase. Exclusion: History of hemiplegic migraine or cluster headache; received botulinum toxin within 4 months; received procedures for migraine prevention, ergotamine derivatives, steroids, or triptans within 2 months; received investigational medication or device within 90 days; and had no therapeutic response to more than 2 prevention treatment categories.		
Reuter et al., 2018[9] NCT03096834 LIBERTY	Phase 3b double-blind, parallel-assignment RCT Erenumab 140-mg SC monthly= 121 Placebo monthly SC =125 Total N = 246	Age, by group: 140-mg: 44.6 (10.5) Placebo: 44.2 (10.6) Female, by group: 140-mg: 97 (80) Placebo: 103 (82) Baseline mean MHDs per month, by group: 140-mg: 9.2 (2.6) Placebo: 9.3 (2.7) Inclusion: Men and women 18–65 years with episodic migraine for at least 12 months, with migraine on an	4 weeks 12 weeks 12 weeks	59 sites in 16 countries across Europe and Australia Novartis Pharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		average of 4 to 14 days per month during the 3 months before screening and had been treated unsuccessfully with between two and four preventive treatments. Exclusion: Older than 50 years at migraine onset; pregnant or nursing; history of cluster headache, hemiplegic migraine headache, seizure, or psychiatric disorder; active chronic pain syndrome, hepatic disease, malignancy of any organ; used a preventive migraine medication within 5 times the drug's half-life before baseline or a device or procedure within the month before the baseline; received botulinum toxin A treatment in the head or neck region within the 4 months before baseline phase; preexisting myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery or other revascularization procedures within the 12 months before screening, medication overuse for any indication in the month before the baseline phase or during the baseline phase.		

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Sakai et al., 2019[8] NCT01081795 NR	Phase 2, double-blind, placebo-controlled RCT Erenumab 28-mg SC = 67[d] 70-mg SC = 135 140-mg SC = 137 Placebo SC = 136 Total N = 475	Age, by group (median, range): 70-mg: 44 (20 to 64) 140-mg: 45 (23 to 64) Placebo: 45 (21 to 61) Female, by group: 70-mg: 115 (85.2) 140-mg: 112 (81.8) Placebo: 118 (86.8) Baseline MHDs per month, by group: 70-mg: 7.8 (2.3) 140-mg: 8.1 (2.4) Placebo: 7.7 (2.3) Inclusion: Patients aged 20 to 65 with history of migraine (with or without aura) for ≥12 months (ICHD-3 beta); migraine frequency of 4 to 15 days per month on average across the 3 months prior to screening. Exclusion: Age > 50 at migraine onset; history of cluster headache or hemiplegic migraine; no therapeutic response to >2 migraine-preventive treatment categories; use of botulinum toxin within 4 months before baseline phase; use of devices or procedures for migraine prevention within 2 months before baseline;	4 weeks 24 weeks 24 weeks One migraine preventive medication was allowed with no changes to the dosage within 2 months before the start of the baseline phase and throughout the study.	43 centers in Japan Amgen Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		taking >1 migraine-preventive medication.		
Skljarevski et al., 2018[29] NCT02614196 EVOLVE-2	Phase 3, multicenter, double-blind RCT Galcanezumab 120-mg SC[e] = 231 240-mg SC = 223 Placebo = 461 Total N = 915	Age, by group: 120-mg: 40.9 (11.2) 240-mg: 41.9 (10.8) Placebo: 42.3 (11.3) Female, by group: 120-mg: 85.3 240-mg: 85.7 Placebo: 85.3 Baseline MHDs per month, by group: 120-mg: 9.07 (2.9) 240-mg: 9.06 (2.9) Placebo: 9.2 (3.0) Inclusion: Ages 18 to 65 with at least a 1-year history of migraine according to ICHD-3 with or without aura, migraine onset prior to age 50, and between 4 and 14 monthly MHDs, at least 2 migraine attacks during the baseline period, and at least 80% compliance using the electronic diary during run-in phase. Exclusion: Failed treatment with 3 or more migraine prevention drugs, using opioids or barbiturates more than twice in a month, participation in	30 to 40 days 6 months 4 months Ongoing preventive therapy not allowed (washout phase of 3 to 45 days prior to run-in phase).	109 study sites across the North America, Europe, South America, and Asia Eli Lilly and Company

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		another clinical trial within the last 30 days, prior exposure to CGRPs , taking any therapeutic antibody in the past 12 months, known drug hypersensitivity, medical/psychiatric illness precluding participation.		
Skljarevski et al., 2018[30]; Oakes et al., 2018[31]; Ayer et al., 2018[32] NCT02163993 NR	Phase 2b double-blind, parallel-assignment RCT Galcanezumab[f] 5-mg SC = 68 50-mg SC = 68 120-mg SC = 70 300-mg SC = 67 Placebo = 137 Total N = 410	Age, by group: Galcanezumab groups: 40.6 (11.9) Placebo: 39.5 (12.1) Female, by group: Galcanezumab groups: 231 (84.6) Placebo: 109 (79.6) Baseline MHDs per month, by group: Galcanezumab groups: 6.7 (2.6) Placebo: 6.6 (2.7) Inclusion: Ages 18 to 65 with at least a 1-year history of migraine according to ICHD-3 with or without aura, migraine onset prior to age 50, and between 4 and 14 MHDs and 2 migraine attacks per month and at least 80% compliance of daily electronic headache entries during run-in phase. Exclusion: History of hemiplegic, ophthalmoplegic, or basilar-type migraine; history of headache other than migraine or tension-type	28 to 38 days 12 weeks 12 weeks No ongoing preventive therapy allowed.	Offices of 37 licensed physicians in the U.S. Eli Lilly and Company Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		headache within 3 months; received prevention treatment within 30 days (4 months for botulinum toxin-A or toxin-B); received therapeutic antibodies; failure to respond to more than 2 prevention treatments; and clinically significant medical or psychiatric conditions.		
Stauffer et al., 2018[33] NCT02614183 EVOLVE-1	Phase 3, double-blind, parallel-assignment RCT Galcanezumab 120-mg SC = 213 240-mg SC = 212 Placebo = 433 Total N = 862	Age, by group: 120-mg: 40.9 (11.9) 240-mg: 39.1 (11.5) Placebo: 41.3 (11.4) Female, by group: 120-mg: 181 (85.0) 240-mg: 175 (82.6) Placebo: 362 (83.6) Baseline MHDs per month, by group: 120-mg: 9.2 (3.1) 240-mg: 9.1 (2.9) Placebo: 9.1 (3.0) Inclusion: Ages 18 to 65 with at least a 1-year history of migraine according to ICHD-3, migraine onset prior to age 50, and between 4 and 14 MHDs and 2 migraine attacks per month and at least 80% compliance of daily electronic headache entries during run-in phase.	30 to 40 days 6 months 10 months (includes 4 months of posttreatment observation) No ongoing preventive therapy allowed	90 sites in North America Eli Lilly and Company Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		Exclusion: Received botulinum toxin-A or toxin-B within 4 months, received preventive medication within 30 days, failure to respond to 3 or more classes of preventive treatments, and clinically significant medical or psychiatric conditions.		
Sun et al., 2016[25] NCT01952574 NR	Phase 2 double-blind, parallel-assignment RCT Erenumab[g] 7-mg SC = 108 21-mg SC = 108 70-mg SC = 107 Placebo = 160 Total N = 483	Age, by group: 70-mg: 42.6 (9.9) Placebo: 41.4 (10.0) Female, by group: 70-mg: 82 (77) Placebo: 132 (83) Baseline MHDs per month, by group: 70-mg: 8.6 (2.5) Placebo: 8.8 (2.7) Inclusion: Ages 18 to 60 with at least a 1-year history of migraine according to ICHD-2 with or without aura, migraine onset prior to age 50, between 4 and 14 MHDs and fewer than 15 MHDs (> 50% of headache days being MHDs) per month, and at least 80% compliance of daily electronic headache entries during run-in phase Exclusion: History of hemiplegic migraine or cluster headache, overuse	4 weeks 12 weeks 12 weeks No ongoing preventive therapy allowed	59 headache and clinical research sites in North America and Europe Amgen Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator[a] (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		of acute treatment for headaches, received botulinum toxin within 6 months, more than 1 migraine lasting longer than 72 hours within 3 months, received preventive medication within 2 months, had no therapeutic response to more than 2 prevention treatment categories, and clinically significant medical or psychiatric conditions.		

Notes. [a] All active treatment and placebos are monthly unless otherwise specified. [b] Trial registration on clinicaltrials.gov indicates 319 enrolled participants. [c] This study also included repeat randomization at 24 weeks to either 70-mg or 140-mg (dose-blinded) and follow-up for an additional 24 weeks (48 weeks total), but findings from the additional 24 weeks of follow-up are not yet reported. [d] We did not extract data for this dosage since the FDA-approved dosages are 70-mg and 140-mg. [e] A loading dose of 240-mg was used for the first dose. [f] Outcomes from the 5-mg and 50-mg dosages are not included this review because they are outside of the dosing range that is being considered for FDA approval based on phase 3 studies. [g] Outcomes from the 7-mg and 21-mg dosages are not included in this review because they are outside of the FDA-approved dosage range for this agent. Abbreviations. CGRP: calcitonin gene-related peptide; ICHD-2 or -3: International Classification of Headache Disorders, 2nd or 3rd revision; IV: intravenous; MHD: migraine headache day; NCT: U.S. National Clinical Trial; NR: not reported; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation.

Table B5. Efficacy of CGRP Inhibitors in Randomized Trials Evaluating Episodic Migraine

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]		
Ashina et al., 2020,[38] PROMISE-1		Eptinezumab 30-mg	Eptinezumab 100-mg	Eptinezumab 300-mg
Migraine or Headache Event (N analyzed)		**Mean difference from placebo (95% CI)**		
Mean change in migraine days per month from baseline [Primary study endpoint] (888)	Weeks 0 to 12	-0.82 (-1.39 to -0.25; *P* = .0046)	-0.69 (-1.25 to -0.12; *P* = .02)	-1.11 (-1.68 to -0.54; *P* = .0001)
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (888)	Weeks 1 to 12	8.4% (1.0% to 15.9%; *P* = .03)	6.0% (-1.4% to 13.3%; *P* = .11)	13.5% (5.8% to 21.2%; *P* = .0007)
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (888)	Weeks 1 to 12	12.8% (3.7% to 21.5%; *P* = .006)	12.4% (3.2% to 21.5%; *P* = .009)	18.9% (9.8% to 28.0%; *P* = .0001)
Functioning and Quality of Life (N analyzed)				
None reported				
Bigal et al., 2015[26]		**Fremanezumab 225-mg**	**Fremanezumab 675-mg**	
Migraine or Headache Event (N analyzed)		**Mean difference from placebo (95% CI)**		
Mean change in MHDs per month from baseline (295) [Primary study endpoint]	Weeks 9 to 12	-2.8 (-4.1 to -1.6)	-2.6 (-3.9 to -1.4)	
Mean change in MHDs (of any severity) per month from baseline (295)	Weeks 9 to 12	-2.6 (-3.9 to -1.3)	-2.6 (-3.9 to -1.3)	
Mean change in days of acute headache medication use (295)	Weeks 9 to 12	-1.8 (-2.9 to -0.66)	-1.7 (-2.8 to -0.60)	
Mean change in MHDs (moderate to severe) per month from baseline (295)	Weeks 9 to 12	-1.8 (-2.9 to -0.78)	-2.0 (-3.0 to -0.90)	
Mean change in headache (moderate to severe) hours per month from baseline (295)	Weeks 9 to 12	-12.7 (-21.0 to -4.3)	-10.8 (-19.1 to -2.5)	
Mean change in headache (of any severity) hours per month from baseline (295)	Weeks 9 to 12	-22.2 (-34.9 to -9.4)	-21.8 (-34.5 to -9.1)	
Mean change in days with nausea and vomiting per month from baseline (295)	Weeks 9 to 12	-1.5 (-2.3 to -0.63)	-0.78 (-1.6 to 0.06)	

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Mean change in days with photophobia or phonophobia per month from baseline (295)	Weeks 9 to 12	-1.4 (-2.5 to -0.35)	-1.2 (-2.3 to -0.14)
Patients with a 50% or greater reduction in MHDs per month from baseline (295)	Weeks 9 to 12	N (%), RD and RR (95% CI)	
		225-mg: 53 (56) Placebo: 36 (35); *P* = .003 *RD 21.2 (7.6 to 34.7, P = .003)* *RR 1.61 (1.17 to 2.22, P = .003)*	675-mg: 55 (57) Placebo: 36 (35); *P* = .001 *RD 22.7 (9.2 to 36.1, P = .002)* *RR 1.66 (1.21 to 2.27, P = .002)*
Patients with a 50% or greater reduction in MHDs per month from baseline among participants not taking concomitant preventive therapy (211)	Weeks 9 to 12	N (%); P value	
		225-mg: 19 (66) Placebo: 8 (22); *P* = .0004	675-mg: 22 (67) Placebo: 8 (22); *P* = .0002
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (95% CI)	
Mean change in MIDAS score[b] from baseline (295)	Weeks 9 to 12	-14.5 (-26.8 to -2.2)	-15.2 (-27.6 to -2.8)
Dodick et al., 2018,[22] ARISE		Erenumab 70-mg	
Migraine or Headache Events (N analyzed)		Mean difference from placebo (95% CI; P value)	
Mean change in MHDs per month from baseline (570) [Primary study endpoint]	Weeks 9 to 12	-1.0 (-1.6 to -0.5; *P* < .001)	
Mean change in days of acute migraine medication use per month from baseline (570)	Weeks 9 to 12	-0.6 (-1.0 to -0.2; *P* = .002)	
Patients with a 50% or greater reduction in MHDs per month from baseline (570)	Weeks 9 to 12	N (%), OR, RD, and RR (95% CI)	
		70-mg: 112 (39.7) Placebo: 85 (29.5) OR 1.59 (1.12 to 2.27, *P* = .01) RD 10.2 (2.4 to 18.0, *P* = .01) RR 1.35 (1.07 to 1.69, *P* = .01)	
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (95% CI; P value)	

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Mean change in MPFID overall impact on everyday activities score[c] from baseline (570)	Weeks 9 to 12	-1.4 (-2.6 to -0.2; *P* = .03)
Mean change in MPFID physical impairment domain score[c] from baseline (570)	Weeks 9 to 12	-1.3 (-2.4 to -0.2; *P* = .02)
Mean change in MPFID everyday activities domain score[c] from baseline (570)	Weeks 9 to 12	-1.1 (-2.3 to 0.1; *P* = .06)
Mean change in HIT-6 score[d] from baseline (570)	Weeks 9 to 12	-2.3 (-3.3 to -1.3; *P* < .001)
Mean change in MIDAS score[b] from baseline (570)	Weeks 9 to 12	-1.7 (-3.1 to -0.3; *P* = .02)
Mean change in modified MIDAS absenteeism domain score[b] from baseline (570)	Weeks 9 to 12	-0.8 (-1.7 to 0.0; *P* = .06)
Mean change in MIDAS presenteeism domain score[b] from baseline (570)	Weeks 9 to 12	-0.8 (-1.6 to 0.1; *P* = .027) (as reported in study publication)
Mean change in MSQL role functioning-restrictive domain score[e] from baseline (570)	Weeks 9 to 12	5.5 (2.8 to 8.2; *P* < .001)
Mean change in MSQL role functioning-preventive domain score[e] from baseline (570)	Weeks 9 to 12	3.6 (1.1 to 6.0; *P* = .005)
Mean change in MSQL emotional functioning domain score[e] from baseline (570)	Weeks 9 to 12	4.5 (1.6 to 7.4; *P* = .002)
Patients with a reduction of ≥ 5 points in MPFID physical impairment domain score[c] (570)	Weeks 9 to 12	*N (%), OR (95% CI)*
		70-mg: 93 (33.0) Placebo: 78 (27.1) 1.33 (0.92 to 1.90, *P* = .13)
Patients with a reduction of ≥ 5 points in MPFID everyday activities domain score[c] (570)	Weeks 9 to 12	70-mg: 114 (40.4) Placebo: 103 (35.8) 1.22 (0.87 to 1.71, *P* = .26)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Dodick et al., 2018[27] (HALO EM), Brandes et al., 2019[39]		Fremanezumab 225-mg monthly	Fremanezumab 675-mg quarterly
Migraine or Headache Events (N analyzed)		Mean difference from placebo (95% CI; P value)	
Mean change in MHDs per month from baseline (865) [Primary study endpoint]	Weeks 9 to 12	-1.5 (-2.0 to -0.93; *P* < .001)	-1.3 (-1.8 to -0.72; *P* < .001)
Mean change in days of acute headache medication use per month from baseline (865)	Weeks 9 to 12	-1.4 (-1.8 to -0.89; *P* < .001)	-1.3 (-1.8 to -0.82; *P* < .001)
Mean change in MHDs per month from baseline for those not receiving concomitant preventive medication (865)	Weeks 9 to 12	-1.3 (-1.9 to -0.70; *P* < .001)	-1.1 (-1.8 to -0.54; *P* < .001)
Mean change in days with nausea or vomiting from baseline (865)	Weeks 0 to 12	-0,7 (-1.1 to -0.3; *P* < .001)	-0.5 (-0.9 to -0.04; *P* = .031)
Mean change in days with photophobia from baseline (865)	Weeks 0 to 12	-0.9 (-1.4 to -0.5; *P* < .001)	-0.8 (-1.3 to -0.3; *P* = .002)
Mean change in days with phonophobia from baseline (865)	Weeks 0 to 12	-1.0 (-1.5 to -.5; *P* < .001)	-0.6 (-1.1 to -0.2, *P* = .009; *P* = .009)
Percentage of participants with 50% or greater reduction in MHDs per month from baseline (865)	Weeks 9 to 12	N (%), RD (95% CI; P value), RR (95% CI)	
		225-mg: 137 (47.7) Placebo: 81 (27.9) RD: 19.8 (12.0 to 27.6, *P* < .001) *RR: 1.71 (1.37 to 2.13, P < .001)*	675-mg: 128 (44.4) Placebo: 81 (27.9) RD: 16.5 (8.9 to 24.1, *P* < .001) *RR: 1.59 (1.27 to 1.99, P < .001)*
Functioning and Quality of Life		Mean difference from placebo (95% CI; P value)	
Mean change in MIDAS score[b] from baseline (865)	Weeks 9 to 12	-7.0 (-10.5 to -3.5; *P* < .001)	-5.4 (-8.9 to -1.9; *P* = .002)
Dodick et al., 2014[28]		Galcanezumab 150-mg every 2 weeks	
Migraine or Headache Events (N analyzed)		Mean difference from placebo (90% CI; P value)	
Mean change in MHDs per month from baseline (217) [Primary study endpoint]	Weeks 9 to 12	-1.2 (-1.9 to -0.6; *P* = .003)	

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Mean change in MHDs per month from baseline (217)	Weeks 9 to 12	-1.3 (-2.1 to -0.5; *P* = .01)
Mean change in migraine or probably MHDs per month from baseline (217)	Weeks 9 to 12	-1.3 (-2.2 to -0.5; *P* = .01)
Mean change in migraine attack days per month from baseline (217)	Weeks 9 to 12	-0.8 (-1.3 to -0.3; *P* = .005)
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (217)	Weeks 9 to 12	**N (%), OR (90% CI), RD and RR (95% CI)** 150-mg: 48 (49.0%) Placebo: 28 (26.9%) OR 2.54 (1.56 to 4.13)
Percentage of participants with 100% reduction in the mean number of MHDs per month from baseline (217)	Weeks 9 to 12	150-mg: 31 (31.6%) Placebo: 18 (17.3%) OR 2.16 (1.24 to 3.75)
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (217)	Weeks 9 to 12	150-mg: 69 (70.4%) Placebo: 47 (45.2%) OR 2.88 (90% CI, 1.78 to 4.69); 95% CI, 1.61 to 5.18 RD 25.2 (95% CI, 12.1 to 38.4, *P* < .001) RR 1.56 (95% CI, 1.22 to 2.00, *P* < .001)
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (study authors did not perform statistical test and data not available to calculate confidence intervals)**
Mean change in MSQL role function-restrictive domain score[e] from baseline (217)	Weeks 9 to 12	*7.1*
Mean change in MSQL role function-preventive domain score[e] from baseline (217)	Weeks 9 to 12	*1.8*
Mean change in MSQL emotional-function domain score[e] from baseline (217)	Weeks 9 to 12	*1.6*
Mean change in HIT-6 score[d] from baseline (217)	Weeks 9 to 12	-2.2

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2014[21]		Eptinezumab 1,000-mg
Migraine or Headache Events (N analyzed)		Mean difference from placebo (95% CI)
Mean change in MHDs per month from baseline (158) [Primary study endpoint][e]	Weeks 5 to 8	-1.0 (-2.0 to 0.1)[f]
Mean change in MHDs per month from baseline (151)	Weeks 9 to 12	-1.0 (-2.1 to 0.2)[g]
Mean change in migraine episodes per month from baseline (151)	Weeks 9 to 12	-0.3 (-1.1 to 0.6)
Mean change in migraine hours per month from baseline (151)	Weeks 9 to 12	-17.5 (-34.2 to -0.9)
Mean change in MHDs per month from baseline (151)	Weeks 9 to 12	-0.7 (-2.0 to 0.5)
Change in percentage of migraines with acute migraine treatment from baseline (151)	Weeks 9 to 12	-10.4 (-20.5 to -0.2)
Mean change in migraine severity (measured on 4-point scale [1 = mild, 4 = severe]) from baseline (151)	Weeks 9 to 12	-0.03 (-0.22 to 0.16)
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (143)	Weeks 9 to 12	N (%), RD, RR, OR (95% CI)
		1,000-mg: 56 (73) Placebo: 52 (67) RD: 10 (-4 to 24) *RR: 1.15 (0.94 to 1.41, P =0.21)*
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (143)	Weeks 9 to 12	1,000-mg: 22 (33) Placebo: 7 (9) RD: 24 (10 to 36) RR: 3.57 (1.63 to 7.81, *P* < .001)
Migraine or Headache Events (N analyzed) (continued)		Mean difference from placebo (95% CI)
Percentage of participants with 100% or greater reduction in the mean number of MHDs per month from baseline (143)	Weeks 9 to 12	1,000-mg: 11 (16) Placebo: 0 (0) RD 16% (8% to 27%)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
		RR: not calculable due to 0 events in placebo group OR: not calculable due to 0 events in placebo group	
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in HIT-6 score[d] from baseline (151)	Weeks 9 to 12	-2.4 (-5.5 to 0.7)	
Mean change in MSQL role function-preventive domain score[h] from baseline (151)	Weeks 9 to 12	6.3 (-1.2 to 13.9)	
Mean change in MSQL role function-restrictive domain score[h] from baseline (151)	Weeks 9 to 12	3.4 (-3.6 to 10.3)	
Mean change in MSQL emotional-function domain score[h] from baseline (151)	Weeks 9 to 12	2.0 (-6.3 to 10.3)	
Goadsby et al., 2017[23]; Buse et al., 2018[24] (STRIVE)		**Erenumab 70-mg**	**Erenumab 140-mg**
Migraine or Headache Events (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in MHDs per month from baseline (946) [Primary study endpoint]	Months 4 to 6	-1.4 (-1.9 to -0.9; *P* < .001)	-1.9 (-2.3 to -1.4; *P* < .001)
Mean change in number of days of use of acute migraine–specific medication (including triptans or ergotamine derivatives) per month from baseline (946)	Months 4 to 6	-0.9 (-1.2 to -0.6; *P* < .001)	-1.4 (-1.7 to -1.1; *P* < .001)
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (946)	Months 4 to 6	**N (%), OR, RD, and RR (95% CI)**	
		70-mg: 135 (43.3%) Placebo: 84 (26.6%) OR 2.13 (1.52 to 2.98, *P* < .001) RD 16.7 (9.3 to 24.0, *P* < .001) RR 1.63 (1.30 to 2.03, *P* < .001)	140-mg: 159 (50.0%) Placebo: 84 (26.6%) OR 2.81 (2.01 to 3.94, *P* < .001) RD 23.4 (16.1 to 30.8, *P* < .001) RR 1.89 (1.52 to 2.33, *P* < .001)
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in the MPFID physical impairment domain score[c] from baseline (946)	Months 4 to 6	-2.2 (-3.3 to -1.2, *P* < .001)	-2.6 (-3.6 to -1.5, *P* < .001)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Mean change in the MPFID everyday activities domain score[c] from baseline (946)	Months 4 to 6	-1.9 (-3.0 to -0.8, *P* < .001)	-2.4 (-3.5 to -1.4, *P* < .001)
Mean change in monthly MIDAS score from baseline (946)	Months 4 to 6	-2.1 (-3.3 to -0.9; *P* < .001)	-2.8 (-4.0 to -1.7; *P* < .001)
Mean change in monthly MIDAS absenteeism domain score from baseline (946)	Months 4 to 6	-1.0 (-1.7 to - 0.3; *P* = .003)	-1.6 (-2.2 to -0.9; *P* < .001)
Mean change in monthly MIDAS presenteeism domain score from baseline (946)	Months 4 to 6	-1.1 (-1.7 to -0.5; *P* < .001)	-1.3 (-1.9, to -0.7; *P* < .001)
Mean change in HIT-6 score from baseline (946)	Months 4 to 6	-2.1 (-3.0 to -1.1; *P* < .001)	-2.3 (-3.2 to -1.3; *P* < .001)
Mean change in MSQL role function-restrictive domain score from baseline (946)	Months 4 to 6	5.1 (2.8 to 7.4; *P* < .001)	6.5 (4.2 to 8.8; *P* < .001)
Mean change in MSQL role function-preventive domain score from baseline (946)	Months 4 to 6	4.2 (2.2 to 6.3; *P* < .001)	5.4 (3.4 to 7.5; *P* < .001)
Mean change in MSQL emotional-functioning domain score from baseline (946)	Months 4 to 6	5.2 (2.8 to 7.6; *P* < .001)	6.7 (4.4 to 9.1; *P* < .001)
Patients with an increase of ≥ 5 points in MSQL role function-restrictive domain score from baseline (946)	Months 4 to 6	N (%), OR (95% CI); P value	
		226 (72.4), 2.2 (1.5 to 3.0; *P* < .001)	214 (67.3), 1.7 (1.2 to 2.3; *P* = .002)
Patients with an increase of ≥ 5 points in MSQL role function-preventive domain score from baseline (946)	Months 4 to 6	197 (63.1), 1.6 (1.2 to 2.2; *P* = .003)	203 (63.8),1.7 (1.2 to 2.3; *P* = .002)
Patients with an increase of ≥ 8 points in MSQL emotional functioning domain score from baseline (946)	Months 4 to 6	163 (52.2), 1.7 (1.2 to 2.4; *P* < .001)	158 (49.7),1.6 (1.1 to 2.1; *P* = .007)
Patients with severe or very severe monthly MIDAS score (≥21; 946)	Months 4 to 6	120 (38.5)), 0.58 (0.42 to 0.80); *P* < .001	99 (31.1), 0.42 (0.30 to 0.58); *P* < 0.001
Patients with very severe monthly MIDAS score (≥41; 946)	Months 4 to 6	63 (20.2), 0.69 (0.47 to 1.0); *P* = .048	38 (11.9), 0.37 (0.24 to 0.56); *P* < .001
Reuter et al., 2018[9] (LIBERTY)		Erenumab 140-mg SC	
Migraine or Headache Events (N analyzed)		N (%), OR (95% CI); P value	

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (243) [Primary study endpoint]	Weeks 9-12	36 (30); 2.7 (1.4 to 5.2); *P* = .002	
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (243)	Weeks 9-12	14 (12); 3.2 (1.1 to 9.0); *P* = .025	
Percentage of participants with 100% reduction in the mean number of MHDs per month from baseline (243)	Weeks 9-12	7 (6); OR not calculable[i]	
Mean change in MHDs per month from baseline (243)	Weeks 9-12	**Mean difference from placebo (95% CI); P value**	
		-1.6 (−2.7 to −0.5); *P* = .004	
Mean change in acute migraine-specific medication days per month from baseline ((243)	Weeks 9-12	-1.7 (−2.4 to −1.0); *P* <.001	
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in MPFID physical impairment score from baseline (243)	Weeks 9-12	−3.5 (−5.7 to −1.2); *P* = .003	
Mean change in MPFID everyday activities score from baseline (243)	Weeks 9-12	−3.9 (−6.1 to −1.7); *P* <.001	
Sakai et al., 2019[8]		**Erenumab 70-mg**	**Erenumab 140-mg**
Migraine or Headache Events (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in MHDs per month from baseline (407) [Primary study endpoint]	Months 4-6	−2.3 (−3.0 to −1.6; *P* < .001)	−1.9 (−2.6 to −1.2; *P* < .001)
Mean change in number of days of use of acute migraine–specific medication per month from baseline (407)	Months 4-6	−2.1 (−2.7 to −1.5); *P* < .001	−2.0 (−2.6 to−1.5); *P* < .001
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (407)	Months 4-6	**N (%); OR (95% CI), P value**	
		39 (28.9); 5.6 (2.6 to 12.1); *P* < .001	37 (27.2); 4.7 (2.2 to 10.0); *P* < .001
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in HIT-6 score from baseline (407)	Months 4-6	−2.1 (−3.3 to −0.9); *P* < .001	−2.0 (−3.2 to −0.8); *P* = .001

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Mean change in average migraine symptoms interference per month from baseline (407)	Months 4-6	−0.32 (−0.45 to −0.19); *P* < .001	−0.30 (−0.43 to −0.17); *P* < .001
Mean change in MPFID everyday activities score from baseline (407)	Months 4-6	−2.5 (−3.7 to −1.3); *P* < .001	−2.3 (−3.5 to −1.1); *P* < .001
Achievement of ≥5-point reduction from baseline in HIT-6 (407)	Months 4-6	**N (%); OR (95% CI), P value**	
		56 (41.5); 1.5 (0.9 to 2.5); *P* = .092	61 (44.9); 1.8 (1.1 to 2.9); *P* = .024
Skljarevski et al., 2018,[29] (EVOLVE-2)		**Galcanezumab 120-mg**	**Galcanezumab 240-mg**
Migraine or Headache Event (N analyzed)		**Mean difference from placebo**	
Mean change in MHDs per month from baseline (896) [Primary study endpoint]	Months 1 to 6	-2.0 (-2.6 to -1.5; adjusted *P* = .026)	-1.9 (-2.4 to -1.4; adjusted *P* = .026)
Mean change in number of days with acute migraine medication use from baseline (896)	Months 1 to 6	-1.8 (-2.6 to -0.98; adjusted *P* = .0125)	-1.7 (-2.2 to -1.2; adjusted *P* = .0125)
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (896)	Months 1 to 6	**N (%), RD, and RR (95% CI)**	
		120-mg: 137 (59.3%) Placebo: 233 (36.0%) adjusted *P* = .025 RD 23.3% (15.6% to 31.0%) RR 1.65 (1.40 to 1.94)	240-mg: 126 (56.5%) Placebo: 233 (36.0%) adjusted *P* = .025 RD 20.5% (12.7% to 28.3%) RR 1.57 (1.33 to 1.86)
Percentage of participants with 75% or greater reduction in the mean number of MHDs per month from baseline (896)	Months 1 to 6	120-mg: 77 (33.5%) Placebo: 82 (17.8%) adjusted *P* = .025 RD 15.6% (8.5% to 22.6%) *RR 1.87 (1.43 to 2.45)*	240-mg: 76 (34.3%) Placebo: 82 (17.8%) adjusted *P* = .025 RD 16.3% (9.2% to 23.4%) RR 1.92 (1.47 to 2.51)
Percentage of participants with 100% reduction in the mean number of MHDs per month from baseline (896)	Months 1 to 6	120-mg: 27 (11.5%) Placebo: 26 (5.7%) adjusted *P* = .025 RD 6.0% (1.4% to 10.7%) RR 2.07 (1.24 to 3.47)	240-mg: 64 (13.8%) Placebo: 26 (5.7%) adjusted *P* = .025 RD 8.3% (3.3% to 13.3%) RR 2.47 (1.50 to 4.05)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Functioning and Quality of Life (N analyzed)		**Mean difference (95% CI) from placebo, P value**	
Mean change from baseline in the R-FR domain score of the MSQL (819)	Months 4 to 6	8.8 (6.3 to 11.3; adjusted *P* = .025)	7.3 (5.2 to 9.4; adjusted *P* = .025)
Mean change from baseline in the Patient Global Impression of Severity rating (819)	Months 4 to 6	-0.3 (-0.39 to -0.21; adjusted *P* = .025)	-0.3 (-0.41 to -0.19; adjusted *P* = .025)
Mean change from baseline in the MIDAS score (770)	Months 4 to 6	-9.2 (-11.8 to-6.6; *P* < .001)	-8.2 (-10.5 to -5.9; *P* < .001)
Skljarevski et al., 2018,[30] Oakes et al., 2018,[31] Ayer et al., 2018[32]		**Galcanezumab 120-mg**	**Galcanezumab 300-mg**
Migraine or Headache Event (N analyzed)		**Change in migraine headache days (90% Bayesian credible interval); probability of greater improvement compared to placebo**	
Posterior probability of greater improvement in MHDs compared to placebo[j] [Primary study endpoint] (258)	Weeks 9 to 12	-4.8[k] (-5.4 to 4.2); 99.6%	NR
Mean change in MHDs per month from baseline (258)	Repeated measures across weeks 1 to 12	**Mean difference from placebo**	
		-0.9 (P = .02)	*-0.9 (P = .02)*
Mean change in migraine and probable MHDs per month from baseline (196)	Weeks 9 to 12	*-1.9 (P < .001)*	NR
Mean change in probable MHDs per month from baseline (196)	Weeks 9 to 12	*-0.4 (P = .049)*	NR
Mean change in MHDs per month from baseline (196)	Weeks 9 to 12	NR (difference reported as not significant)	NR
Mean change in migraine attacks per month from baseline (196)	Weeks 9 to 12	*-0.8 (P = .003)*	NR
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (196)	Weeks 9 to 12	**N (%), OR, RD, and RR (95% CI)**	
		120-mg: 47 (75.8) Placebo: 78 (61.9); *P* = .03 RD: 13.9 (0.3 to 27.5, *P* = .07)	NR

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
		RR: 1.22 (1.01 to 1.49, *P* = .07)	
Percentage of participants with greater than 100% reduction in the mean number of MHDs per month from baseline (196)	Weeks 9 to 12	120-mg: 22 (35.5) Placebo: 29 (23.0); *P* = .04 RD: 12.5 (-1.5 to 26.5, *P* = .08) RR: 1.5 (0.97 to 2.5, *P* = .08)	NR
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in MSQL score[e] from baseline (NR)	Weeks 9 to 12	NR (mean difference reported as not significant)	NR (mean difference reported as not significant)
Mean change in HIT-6 score[d] from baseline (NR)	Weeks 9 to 12	*-2.7 (P = .04)*	NR (mean difference reported as not significant)
		Galcanezumab 120-mg[l]	
Mean change in total MSQL score from baseline (187)	Weeks 1 to 12	8.7 (2.45 to 15.0; *P* = .0067)	
Mean change in MSQL role function-restrictive domain score from baseline (187)	Weeks 1 to 12	9.6 (2.6 to 16.5; *P* = .0071)	
Mean change in MSQL role function-preventive domain score from baseline (187)	Weeks 1 to 12	6.3 (0.48 to 12.2; *P* = .0342)	
Mean change in MSQL emotional-functioning domain score from baseline (187)	Weeks 1 to 12	9.7 (2.8 to 16.7; *P* = .0063)	
Mean change in HIT-6 score from baseline (187)	Weeks 1 to 12	-2.5 (-5.1 to 0.14; *P* = .0638)	
Stauffer et al., 2018[33] (EVOLVE-1)		**Galcanezumab 120-mg**	**Galcanezumab 240-mg**
Migraine or Headache Events (N analyzed)		**Mean difference from placebo (95% CI)**	
Mean change in MHDs per month from baseline (843) [Primary study endpoint]	Months 1 to 6	-1.9 (-2.5 to -1.4, *P* < .001)	-1.8 (-2.3 to -1.2, *P* < .001)
Mean change in MHDs with acute medication use per month from baseline (843)	Months 1 to 6	-1.8 (-2.3 to -1.3, *P* < .001)	-1.6 (-2.1 to -1.1, *P* < .001)
Mean change in headache hours per month from baseline (843)	Months 1 to 6	*-14.0 (P < .001)*	*-13.6 (P < .001)*

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Percentage of participants with 50% or greater reduction in the mean number of MHDs per month from baseline (843)	Month 6	N (%), OR, RD, and RR (95% CI)	
		120-mg: 131 (62.3) Placebo: 164 (38.6) OR 2.6 (2.0 to 3.4, *P* < .001) RD 23.8 (15.8 to 31.8, *P* < .0001) RR 1.62 (1.38 to 1.90, *P* < .0001)	240-mg: 127 (60.9) Placebo: 164 (38.6) OR 2.5 (1.9 to 3.2, *P* < .001) RD 22.5 (14.4 to 30.6, *P* < .0001) RR 1.58 (1.35 to 1.86, *P* < .0001)
Percentage of participants with greater than 75% reduction in the mean number of MHDs per month from baseline (843)	Month 6	120-mg: 81 (38.8) Placebo: 82 (19.3) OR 2.7 (2.0 to 3.5, *P* < .001)	240-mg: 80 (38.5) Placebo: 82 (19.3) OR 2.6 (2.0 to 3.4, *P* < .001)
Percentage of participants with greater than 100% reduction in the mean number of MHDs per month from baseline (843)	Month 6	120-mg: 33 (15.6) Placebo: 26 (6.2) OR 2.8 (2.0 to 4.0, *P* < .001)	240-mg: 30 (14.6) Placebo: 26 (6.2) OR 2.6 (1.8 to 3.7, *P* < .001)
Percentage of participants who maintained greater than 50% reduction in the mean number of MHDs per month for 6 consecutive months (843)	Month 6	120-mg: NR (20.5%) Placebo: NR (8.9%); *P* < .001	240-mg: NR (19.2%) Placebo: NR (8.9%); *P* < .001
Functioning and Quality of Life (N analyzed)		Mean difference from placebo (SE)	
Mean change in MSQL score[h] from baseline (NR)	Months 4 to 6	7.3 (1.2, *P* < .001)	6.7 (1.3, *P* < .001)
Mean change in MSQL role function-restrictive domain score[h] from baseline (750)	Months 4 to 6	7.7 (1.3, *P* < .001)	7.4 (1.3, *P* < .001)
Mean change in MSQL role function-preventive domain score[h] from baseline (NR)	Months 4 to 6	5.6 (1.1, *P* < .001)	4.7 (1.2, *P* < .001)
Mean change in MSQL emotional-function domain score[h] from baseline (NR)	Months 4 to 6	8.3 (1.5, *P* < .001)	7.2 (1.5, *P* < .001)
Mean change in MIDAS score[b] from baseline (NR)	Months 4 to 6	*-6.3 (NR, P < .001)*	*-5.2 (NR, P < .002)*
Mean change in PGI-S score[m] from baseline (750)	Months 4 to 6	-0.3 (0.1, *P* = .002)	-0.3 (0.1), *P* = .008)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Sun et al., 2016[25]		Erenumab 70-mg
Migraine or Headache Events (N analyzed)		Mean difference from placebo (95% CI)
Mean change in MHDs (including probable migraine) per month from baseline (257) [Primary study endpoint]	Weeks 9 to 12	−1.1 (−2.1 to −0.2; *P* = .02)
Mean change in migraine attacks per month from baseline (257)	Weeks 9 to 12	−0.4 (−0.9 to 0.1; *P* = .13)
Mean change in MHDs (including migraine, probable migraine, and non-migraine headache) per month from baseline (257)	Weeks 9 to 12	-1.2 (-2.1 to -0.2; *P* = .02)
Mean change in migraine (including probable migraine) severity from baseline (257)	Weeks 9 to 12	0.1 (-0.04 to 0.2; *P* = .20)
Mean change in average severity of nausea from baseline (257)	Weeks 9 to 12	-0.1 (-0.2 to 0.1; *P* = .46)
Mean change in average severity of vomiting from baseline (257)	Weeks 9 to 12	0.02 (-0.1 to 0.1; *P* = .64)
Mean change in average severity of aura from baseline (257)	Weeks 9 to 12	0.1 (-0.1 to 0.2; *P* = .40)
Mean change in average severity of photophobia from baseline (257)	Weeks 9 to 12	0.04 (-0.1 to 0.2; *P* =. 65)
Mean change in average severity of phonophobia from baseline (257)	Weeks 9 to 12	0.1 (-0.1 to 0.2; *P* = .35)
Mean change in migraine-specific medication use days per month from baseline (257)	Weeks 9 to 12	-1.0 (-1.6 to -0.3; *P* = .004)
Mean change in acute medication use days per month from baseline (257)	Weeks 9 to 12	-1.2 (-2.0 to -0.3; *P* = .006)
Mean change in hours of migraine (including probably migraine) pain per month from baseline (257)	Weeks 9 to 12	-11.3 (-23.7 to 1.1; *P* = .07)
Mean change in cumulative hours of headache per month from baseline (257)	Weeks 9 to 12	-13.1 (-26.2 to 0.1; *P* = .05)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Monthly incidence of MHDs (including probably migraine) per month (257)	Weeks 9 to 12	**Incidence rate ratio (95% CI)**
		0.8 (0.7 to 1.0; *P* = .01)
Percentage of participants with 50% or greater reduction in the mean number of MHDs (including probable migraine) per month from baseline (243)	Weeks 9 to 12	**N (%), OR, RD, and RR (95% CI)**
		70-mg: 46 (46%) Placebo: 43 (30%) OR 2.0 (1.2 to 3.4, *P* = .01) RD 16.6 (4.3 to 29.0, *P* = .008) RR 1.56 (1.12 to 2.16, *P* = .008)
Functioning and Quality of Life (N analyzed)		**Mean difference from placebo (95% CI)**
Mean change in MIDAS score[b] from baseline (227)	Week 12	-5.3 (-10.9 to 0.3; *P* = .06)
Mean change in HIT-6 score[d] from baseline (255)	Week 12	-1.0 (-2.5 to 0.6; *P* = .22)
Mean change in PROMIS pain interference scale short form[n] from baseline (244)	Week 12	-1.4 (-3.0 to 0.2; *P* = .08)
Mean change in MSQL role function-restrictive domain score[h] from baseline (255)	Week 12	1.8 (-2.5 to 6.1; *P* = .41)
Mean change in MSQL role function-preventive domain score[h] from baseline (255)	Week 12	0.5 (-3.3 to 4.3; *P* = .79)
Mean change in MSQL emotional-function domain score[h] from baseline (255)	Week 12	1.9 (-2.6 to 6.3; *P* = .41)
Mean change in MIDAS question A response[o] from baseline (227)	Week 12	-2.2 (-5.0 to 0.7; *P* = .13)
Mean change in MIDAS question B response[p] from baseline (227)	Week 12	-0.3 (-0.8 to 0.1; *P* = .18)

Notes. Calculated values are indicated with italics. [a]All active treatments and placebos administered monthly unless otherwise specified. [b]MIDAS scores range from 0 to 270, with higher scores indicating a greater degree of headache-related disability. [c]MPFID scores range from 0 to 100, with higher scores indicating a greater degree of migraine-related disability. [d]HIT-6 scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability. [e]Study publication lists this as the primary study endpoint; however, the clinicaltrials.gov registry entry lists safety outcomes a primary outcomes and efficacy outcomes as secondary outcomes. [f]P reported as .0306. [g]P reported as .065. [h]MSQL scores range from 0 to 100, with lower scores indicating a greater degree of migraine-related disability. [i]Because there were no participants that achieved a 100% reduction in monthly migraine days in the placebo group, the OR could not be calculated. [j]Study authors performed this analysis using a Bayesian dose-response model; 90% Bayesian credible

intervals were calculated for the posterior mean change from baseline in migraine headache days. [k]The corresponding change in migraine headache days in the placebo group was -3.7 (90% Bayesian credible interval -4.1 to -3.2). [l]Results for the 300-mg dosage were not included in this analysis because 120-mg was determined to be the least efficacious dosage and higher dosages were not going to be carried forward into phase 3 trials. [m]PGI-S scores range from 1 to 7, with higher scores indicating a greater severity of illness. [n]PROMIS pain interference scores range from 41.0 to 78.3, with higher scores indicating a greater degree of interference. [o]Responses to MIDAS question A range from 0 to 90, with higher responses indicating a higher frequency of headaches. [p]Responses to MIDAS question B range from 0 to 10, with higher responses indicating a greater degree of headache-related disability. Abbreviations. CGRP: calcitonin gene-related peptide; CI: confidence interval; HIT-6: 6-item Headache Impact Test; MHD: migraine headache day; MIDAS: Migraine Disability Assessment; MPFID: Migraine Physical Function Impact Diary; MSQL: Migraine-specific Quality of Life Questionnaire; NR: not reported; OR: odds ratio; PGI-S: Patient Global Impression Survey; PROMIS: Patient-Reported Outcomes Measurement Information System; RD: risk difference; R-FR: Role Function-Restrictive; RR: risk ratio.

Table B6. Adverse Events From CGRP Inhibitors in Randomized Trials Evaluating Episodic Migraine

Outcomes	Treatment Groups			
Ashina et al., 2020 [38] PROMISE-1	Placebo	Eptinezumab 30-mg	Eptinezumab 100-mg	Eptinezumab 300-mg
N (%) Any adverse event	132 (59.5)	128 (58.4)	141 (63.2)	129 (57.6)
N (%) with a serious treatment-emergent adverse event	6 (2.7)	11 (1.7)		
N (%) with adverse event leading to discontinuation	6 (2.7)	12 (5.5)	6 (2.7)	5 (2.2)
Bigal et al., 2015[26]	**Placebo**	**Fremanezumab 225-mg**	**Fremanezumab 675-mg**	
N (%) with at least 1 adverse event	NR	NR	NR	
N (%) with at least 1 treatment-emergent adverse event	58 (56)	44 (46)	57 (59)	
N (%) with at least 1 treatment-related adverse event	24 (23)	26 (27)	24 (25)	
N (%) with adverse event leading to discontinuation	*0 (0)*	*4 (4.2)*	*2 (2.1)*	
N (%) with at least 1 serious adverse event/N events	0 (0)/0	2 (2)/2 1 fibula fracture 1 migraine associated with hypertensive crisis	2 (2)/2 1 antiphospholipid syndrome 1 tremor	
N (%) with treatment-related liver injury	Liver enzymes were reported to be stable through active treatment in all groups.			
Dodick et al., 2018[22] (ARISE)	**Placebo**	**Erenumab 70-mg**		
N (%) with at least 1 adverse event	158 (54.7)	136 (48.1)		
N (%) with adverse event leading to discontinuation	1 (0.3)	5 (1.8)		
N (%) with at least 1 serious adverse event/N events	5 (1.7)/6 1 migraine 1 acute cholecystitis 1 flank pain 1 hypersensitivity 1 hyponatremia	3 (1.1)/3 1 migraine 1 intervertebral disc protrusion 1 urinary tract infection		

Outcomes	Treatment Groups		
	1 uterine leiomyoma		
N (%) with treatment-related liver injury	Treatment did not result in any observable effect on liver enzymes.		
Dodick et al., 2018[27] (HALO EM); Brandes et al., 2019[39]	Placebo	Fremanezumab 225-mg	Fremanezumab 675-mg quarterly
N (%) with at least 1 adverse event	171 (58.4)	192 (66.2)	193 (66.3)
N (%) with at least 1 treatment-related adverse event	109 (37.2)	138 (47.6)	137 (47.1)
N (%) with adverse event leading to discontinuation	5 (1.7)	5 (1.7)	5 (1.7)
N (%) with at least 1 serious adverse event	7 (2.4) Specific events NR	3 (1.0) Specific events NR	3 (1.0) Specific events NR except for 1 death from suicide
N (%) with treatment-related liver injury	1 (0.3) total bilirubin increase	2 (0.7) increase liver enzymes 1 (0.3) total bilirubin increase	1 (0.3) increase in liver enzymes
Dodick et al., 2014[28]	Placebo	Galcanezumab 150-mg every 2 weeks	
N (%) with at least 1 adverse event	74 (67)	77 (72)	
N (%) with adverse event leading to discontinuation	1 (0.9)	0 (0)	
N (%) with at least 1 serious adverse event / N events	4 (3.6) / 4 1 menorrhagia 1 cholelithiasis 1 diverticulitis 1 common bile duct stone	2 (1.9) / 2 1 pregnancy 1 peripheral vascular disease	
N (%) with treatment-related liver injury	There were no clinically important changes in laboratory parameters, including liver function tests.		
Dodick et al., 2014[21]	Placebo	Eptinezumab 1,000-mg IV single dose	
N (%) with at least 1 adverse event	43 (52)	46 (57)	

Outcomes	Treatment Groups		
N (%) with adverse event leading to discontinuation	0 (0)	0 (0)	
N (%) with at least 1 serious adverse event / N events	1 (1.2)/1 1 fibula fracture requiring hospitalization	2 (2.5)/5 1 pyelonephritis 1 chest pain 1 transient ischemic event 1 conversion disorder 1 dyspnea	
N (%) with treatment-related liver injury	No clinically significant differences in laboratory safety data (hematology and clinical chemistry) between patients treated with eptinezumab or placebo at any time during the study.		
Goadsby et al., 2017,[23] Buse et al., 2018[24] (STRIVE)	Placebo	Erenumab 70-mg	Erenumab 140-mg
N (%) with at least 1 adverse event	201 (63.0)	180 (57.3)	177 (55.5)
N (%) with adverse event leading to discontinuation	8 (2.5)	7 (2.2)	7 (2.2)
N (%) with at least 1 serious adverse event/N events	7 (2.2)/7 1 noncardiac chest pain 1 arthralgia 1 endometriosis 1 fall 1 hypersensitivity 1 intentional overdose 1 osteoarthritis	8 (2.5)/8 1 noncardiac chest pain 2 cholelithiasis 1 back pain 1 migraine 1 ovarian cyst 1 posttraumatic neck syndrome 1 acute pyelonephritis	6 (1.9)/10 1 noncardiac chest pain 1 ankle fracture 1 cerebral venous thrombosis 1 Clostridium difficile colitis 1 viral gastroenteritis 1 kidney infection 1 pyelonephritis 1 sepsis 1 spinal pain 1 vestibular neuronitis
N (%) with treatment-related liver injury	No clinically meaningful differences between the erenumab groups and the placebo group were observed regarding the results of hepatic-function testing.		
Reuter et al., 2018,[9] (LIBERTY)	Placebo	Erenumab 140-mg SC	
N (%) with at least 1 adverse event	67 (54)	65 (55)	
N (%) with serious adverse event	1 (1)	2 (2)	

Outcomes	Treatment Groups		
N (%) with adverse event leading to treatment discontinuation	1 (1)	0	
N (%) with liver injury	"No clinically meaningful differences were noted between groups with regards to results of hepatic-function testing,.."		
Sakai et al., 2018[8]	Placebo	Erenumab 70-mg SC	Erenumab 140-mg SC
N (%) with at least 1 adverse event	92 (67.6)	95 (70.4)	95 (69.3)
N (%) with serious adverse event	4 (2.9)	1 (0.7) [systemic lupus erythematosus thought to be related to study drug]	1 (0.7) [Unclear from article, either hand fracture or gastroenteritis/intestinal tuberculosis]
N (%) with adverse event leading to discontinuation	1 (0.7)	2 (1.5)	0 (0.0)
Skljarevski et al., 2018,[29] (EVOLVE-2)	Placebo	Galcanezumab 120-mg	Galcanezumab 240-mg
N (%) with at least 1 treatment-emergent adverse event	287 (62.3)	147 (65.0)	163 (71.5)
N (%) with adverse event leading to discontinuation	8 (1.7)	5 (2.2)	9 (4.0)
N (%) with at least 1 serious adverse event/N events	5 (1.1)/7 1 Gallbladder polyp 1 Hemorrhoids 1 Migraine 1 Suicide attempt 1 Foot fracture 1 Rib fracture 1 Road traffic accident	5 (2.2)/5 1 Adenocarcinoma of the cervix 1 Bladder dysfunction 1 Gastritis 1 Bacterial pharyngitis 1 Rectal polyp	7 (3.1)/8 1 myocardial infarction 1 cholelithiasis 1 generalized tonic-clonic seizure 1 influenza 1 meniscus injury 1 transient ischemic heart attack 1 disorientation 1 pyrexia
Skljarevski et al., 2018,[30] Oakes et al., 2018,[31] Ayer et al., 2018[32]	Placebo	Galcanezumab 120-mg	Galcanezumab 300-mg
N (%) with at least 1 adverse event during posttreatment follow-up period	35 (28.0)	17 (27.0)	21 (32.3)

Outcomes	Treatment Groups		
N (%) with at least 1 treatment-emergent adverse event	70 (51.1)	36 (51.4)	32 (47.8)
N (%) with adverse event leading to discontinuation	0 (0)	0 (0)	1 (1.5)
N (%) with at least 1 serious adverse event/N events	0 (0)/0	1 (1.4)/1 1 appendicitis	0 (0)/0 during active treatment 2 (3.0)/2 during posttreatment follow-up or after database lock 1 suicidal ideation 1 congenital ankyloglossia in male infant
N (%) with treatment-related liver injury	Among patients with normal hepatic laboratory values at baseline, no patient showed abnormal hepatic laboratory values during the treatment.		
Stauffer et al., 2018,[33] (EVOLVE-1)	**Placebo**	**Galcanezumab 120-mg**	**Galcanezumab 240-mg**
N (%) with at least 1 treatment-emergent adverse event	261 (60.4)	135 (65.5)	149 (67.7)
N (%) with serious adverse event leading to discontinuation	2 (0.5)	2 (1.0)	0 (0)
N (%) with at least 1 serious adverse event/N events	5 (1.2)/5 2 cholelithiasis 1 deep vein thrombosis 2 other events were not specified	6 (2.9)/7 1 incarcerated incisional hernia 1 seroma 1 tubular breast carcinoma 1 vertebral osteophyte 1 acute pancreatitis 2 other events were not specified	0 (0)/0
N (%) with treatment-related liver injury	NR		
Sun et al., 2016[25]	**Placebo**	**Erenumab 70-mg**	
N (%) with at least 1 adverse event	82 (54)	57 (54)	
N (%) with adverse event leading to discontinuation	2 (1)	3 (3)	

Outcomes	Treatment Groups	
N (%) with at least 1 serious adverse event	0 (0)	1 (1) 1 vertigo and migraine
N (%) with treatment-related liver injury	No clinically significant findings in laboratory values (includes liver enzyme)	

Abbreviations. CGRP: calcitonin gene-related peptide; NR: not reported.

Table B7. Characteristics of Studies Evaluating CGRP Inhibitors for Acute Migraine Treatment

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Ailani et al., 2020[20] NCT02873221 Open-label extension to ACHIEVE-I & II	Phase 3, double-blind, open-label, extension RCT Ubrogepant 50-mg = 404 100-mg = 409 Placebo = 417 Total = 1,230	Age: 41.8 (11.7) Female: 1,106 (90) Baseline MHDs per month: NR Use of preventive medication at baseline: 306 (25) Inclusion: Men and women ages 18 years and older, completed ACHIEVE-I or ACHIEVE-II Exclusion: ALT or AST ≥ 1.5-mg/dL, abnormal ECG, physical exam, or laboratory result, uncontrolled hypertension, significant cardiovascular or cerebrovascular disease, use of moderate to strong CYP3A4 inhibitors and inducers.	52 weeks 4 weeks Ongoing preventive therapy allowed, if dosage stable	161 U.S. sites Allergan plc. Poor
Croop et al., 2019[15] NCT03461757 NR	Phase 3, double-blind, RCT Rimegepant 75-mg ODT = 732 Placebo ODT = 734 Total N = 1,466	Age: 40.2 (12.0) Female: 1,147 (85) Moderate-to-severe attacks per month: 4.6 (1.8) Inclusion: Men and women ages 18 and older, at least a 1-year history of migraine, migraine onset before age 50 years, 2 to 8 attacks of moderate or severe intensity per month, 15 days per month with migraine or non-migraine headache in the past 3	45 days 7 days after initial dose Ongoing preventive therapy allowed, if dosage stable for 3 months	69 U.S. sites Biohaven Pharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		months, able to distinguish migraine from tension or cluster headache. Exclusion: A medical condition that might interfere with assessments or present risk of SAE, alcohol or drug problem or treatment in the last 12 months, history of drug allergies, concerning ECG or lab finding.		
Dodick et al., 2019[18] NCT02828020 ACHIEVE-I	Phase 3, Double-blind, RCT Ubrogepant 50-mg = 556 100-mg = 557 Placebo = 559 Total = 1,672 Participants allowed to take an optional second dose or their own rescue medication 2 to 48 hours after initial dose for persistent or recurring moderate-to-severe headache.	Age: 40.5 (11.8) Female: 1,266 (88.2) Baseline MHDs per month: NR Use of preventive medication at baseline: 302 (22.8) Inclusion: Men and women ages 18 to 75 years, 1-year history of migraine, onset before age 50 years, migraines last 4 to 72 hours, attacks separated by at least 48 hours, 2 to 8 moderate-to-severe migraines per month in 3 months before screening. Exclusion: pregnant, 15 or more MHDs per month in 6 months before screening, chronic migraine (unless controlled with preventive treatment to less than 15 MHDs per month), difficulty distinguishing migraine from tension headache, acute migraine treatment on ≥ 10 days in 3 months before study, participated in injectable CGRP trial, clinically	60 days 2 to 7 days after taking initial dose, safety visit at 4 weeks from initial dose Ongoing preventive therapy allowed	89 U.S. sites Allergan Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		significant cardiovascular or cerebrovascular disease, liver enzymes more than 1.5 times the upper limit of the normal , bilirubin level of more than 1.5-mg per deciliter, or a serum albumin less than 2.8 g per deciliter at screening.		
Lipton et al. 2019[19] NCT02867709 ACHIEVE-II	Phase 3, double-blind, RCT Ubrogepant 50-mg = 562 Placebo = 563 Total = 1,686 (including the 25-mg dosage group)>	Age, by group: 50-mg: 41.2 (12.5) Placebo: 41.7 (12.1) Female, by group: 50-mg: 444 (91.0) Placebo: 442 (88.6) Moderate-to-severe migraines per month, by group: 55-mg: 4.4 (1.8) Placebo: 4.6 (1.8) Inclusion: 18 to 75 years of age, history of migraine with or without aura for at least 1 year, 2 to 8 migraine attacks with moderate-to-severe headache pain in each of the 3 months before screening, migraine onset before age 50, history of migraine typically lasting 4 to 72 hours if untreated or treated unsuccessfully, and migraine	NR 30 days after initial event Ongoing preventive therapy allowed	99 U.S. sites including primary care and research clinics Allergan Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		episodes separated by at least 48 hours of headache pain freedom. Exclusion: difficulty distinguishing migraine from tension-type or other headaches, current diagnosis of chronic migraines, taking medication for treatment of migraine attacks on 10 or more days per month in any of the previous 3 months, clinically significant hematologic, endocrine, cardiovascular, cerebrovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease, and history of 15 or more MHDs per month on average in the previous 6 months.		
Lipton et al., 2019[16] NCT03237845 NR	Phase 3, double-blind, parallel-assignment RCT Rimegepant 75-mg = 594 Placebo = 592 Total = 1,186	Age: 40.6 (12.0) Female: 951 (88.7) Baseline migraine attacks per month: 4.6 (1.8) Inclusion: Men and women ages 18 years or older, 1-year history of migraine, onset before age 50 years, 2 to 8 moderate-to-severe migraines per month, fewer than 15 MHDs per month in last 3 months. Exclusion: clinically significant or unstable medical condition, including substance use disorders, received	45 days 7 days after initial dose Ongoing preventive therapy allowed, if dosage stable for 3 months prior to study	50 U.S. sites including clinics, institutions, and private office practices Biohaven Pharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		biological investigational agent within 90 days of baseline visit, basilar or hemiplegic migraine, significant lab or ECG findings during screening, pregnant or breastfeeding women, or women of reproductive age not on acceptable contraceptive.		
Marcus et al., 2014[14] NCT01430442 NR	Double-blind, parallel-assignment RCT Rimegepant (BMS-927711) 75-mg = 91 Sumatriptan 100-mg= 109 Placebo = 229 Total = 429[a]	Age, by group: Rimegepant: 38.5 (11.9) Sumatriptan: 40.6 (10.5) Placebo: 37.9 (11.4) Female, by group: Rimegepant: 81 (89) Sumatriptan: 91 (84) Placebo: 196 (84) Baseline MHDs per month: Rimegepant: 3.9 (1.7) Sumatriptan: 4.1 (1.8) Placebo: 4.0 (1.8) Inclusion: Men and women ages 18 to 65 years, at least 1-year history of migraine, onset before age 50 years, average duration of 4 to 72 hours, 2 to 7 moderate-to-severe attacks in last 3 months, less than 15 MHDs in the past month, able to distinguish migraine from tension headache, 14-	45 days 7 days after initial dose Ongoing preventive therapy allowed, if dosage stable for 3 months	41 U.S. sites Biohaven Pharmaceuticals Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		day washout period for SSRIs, SNRIs, and MAOIs. Exclusion: History of basilar-type or hemiplegic migraine, no relief from triptans, history of cardiovascular disease, uncontrolled diabetes, HIV, pain syndromes, psychiatric conditions, neurological disorders, history of substance use disorders, on medications metabolized by CYP3A or that may alter stomach pH, pregnant or breastfeeding women, women of childbearing potential not using acceptable contraceptive.		
Voss et al., 2016[17] NCT01613248 NR	Phase 2b, double-blind, parallel-assignment RCT Ubrogepant 50-mg = 139 100-mg = 140 Placebo = 139 Total = 418[b]	Age: 40.8 (11.4) Female: 559 (87.3) Baseline MHDs per month: NR Inclusion: Men and women ages 18 to 65 years, at least 1-year history of migraine, onset before age 50 years, 2 to 8 moderate-to-severe migraines a month for 2 months prior to screening, ability to distinguish migraine from tension headache. Exclusion: History of basilar-type or hemiplegic migraine, more than 15 MHDs per month or taken medication for acute headache on	Up to 2 months 4 days (± 2 days) after initial dose Ongoing preventive therapy allowed, if dose was not recently changed	NR Merck Fair

Author, Year Registry Number Trial Name	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Treatment Window Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		more than 10 days per month in prior 3 months, acute attack requiring inpatient or emergency department treatment in the prior 2 months, used opioid or barbiturate for migraine in prior 2 months, recently changed dosage of migraine prevention treatment.		

Notes. [a] Other doses of rimegepant were also evaluated in this study but were not included here because those dosages did not move forward to the phase 3 trials for the agent. [b] Additional dosages of ubrogepant were evaluated in this study but are not included here as they did not move forward to phase 3 trials. Abbreviations. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CGRP: calcitonin gene-related peptide; ECG: electrocardiogram; HIV: human immunodeficiency virus; MAOI: monoamine oxidase inhibitors; MHD: migraine headache day; NCT: U.S. National Clinical Trial; NR: not reported; ODT: orally dissolving tablet; RCT: randomized controlled trial; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

Table B8. Efficacy of CGRP Inhibitors in Randomized Trials Evaluating Acute Migraine Treatment

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Ailani et al., 2020[20] (open-label extension to ACHIEVE-I & II)		Ubrogepant 50-mg	Ubrogepant 100-mg
Migraine or Headache Events (N analyzed)			
None			
Functioning and Quality of Life (N analyzed)			
None			
Croop et al., 2019[15]		Rimegepant 75-mg	
Migraine or Headache Events (N analyzed)		Risk difference from placebo (95% CI; P value)	
Freedom from pain[a] (1,351) [Co-primary study endpoint]	2 h post-dose	10.4 (6.5 to 14.2; *P* < .0001)	
Freedom from most bothersome symptom[b] (1,351) [Co-primary study endpoint]	2 h post-dose	8.3 (3.4 to 13.2; *P* = .0009)	
Pain relief[c] (1,351)	2 h post-dose	16.1 (10.8 to 21.3; *P* < .05)	
Sustained pain relief (1,351)	2–24 h post-dose	20.1 (15.1 to 25.2; *P* < .05)	
Sustained freedom from most bothersome symptom (1,351)	2–24 h post-dose	9.3 (4.9 to 13.7; *P* < .05)	
No rescue medication (1,351)	24 h post-dose	15.0 (10.7 to 19.3; *P* < .05)	
Sustained pain relief (1,351)	2–48 h post-dose	16.9 (12.0 to 21.9; *P* < .05)	
Sustained freedom from most bothersome symptom (1,351)	2–48 h post-dose	6.7 (2.5 to 11.0; *P* < .05)	
Freedom from photophobia (1,351)	2 h post-dose	8.8 (3.7 to 13.9; *P* < .05)	
Pain relief (1,351)	90 min post-dose	12.4 (7.1 to 17.6; *P* < .05)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sustained freedom from pain (1,351)	2–24 h post-dose	10.1 (6.9 to 13.4; *P* < .05)	
Freedom from most bothersome symptom (1,351)	90 min post-dose	5.8 (1.2 to 10.4; *P* < .05)	
Freedom from pain (1,351)	90 min post-dose	7.8 (4.4 to 11.1; *P* < .05)	
Freedom from phonophobia (1,351)	2 h post-dose	11.5 (5.3 to 17.7; *P* < .05)	
Sustained freedom from pain (1,351)	2–48 h post-dose	8.0 (4.9 to 11.1; *P* < .05)	
Pain relief (1,351)	60 min post-dose	5.5 (0.5 to 10.6; *P* < .05)	
Freedom from nausea (1,351)	2 h post-dose	5.9 (–0.9 to 12.7; *P*> .05)	
No pain relapse (1,351)	2–48 h post-dose	13.3 (–0.4 to 27.1; *P* not tested because of hierarchical gate-keeping analysis procedure)	
Functioning and Quality of Life (N analyzed)		**Risk difference from placebo (95% CI; P value)**	
Ability to function normally[d] (1,351)	2 h post-dose	12.3 (7.4 to 17.2; *P* < .05)	
Sustained ability to function normally (1,351)	2–24 h post-dose	12.7 (8.3 to 17.2; *P* < .05)	
Sustained ability to function normally (1,351)	2–48 h post-dose	10.6 (6.3 to 14.9; *P* < .05)	
Ability to function normally (1,351)	90 min post-dose	8.9 (4.3 to 13.6; *P* < .05)	
Ability to function normally (1,351)	60 min post-dose	6.4 (2.3 to 10.6; *P* < .05)	
Dodick et al., 2019[18] (ACHIEVE-I)		**Ubrogepant 50-mg**	**Ubrogepant 100-mg**
Migraine or Headache Events (N analyzed)		**N (%), OR (95% CI) Compared to Placebo**	
Freedom from pain[a] (1,327) [Co-primary study endpoint]	2 h post-dose	50-mg: 81 (19.2) Placebo: 54 (11.8)	100-mg: 95 (21.2) Placebo: 54 (11.8)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
		OR 1.83 (1.25 to 2.66, *P* = .002) RD *7.4% (2.6% to 12.1%, P = .001)*	OR 2.04 (1.41 to 2.95, *P* < .001) RD *9.4% (4.6% to 14.2%, P <.001)*
Absence of the most bothersome symptom[b] (1,327) [Co-primary study endpoint]	2 h post-dose	50-mg: 162 (38.6) Placebo: 126 (27.8) OR 1.70 (1.27 to 2.28, *P* = .002) RD *10.8% (4.6 to 17.0, P <.001)*	100-mg: 169 (37.7) Placebo: 126 (27.8) OR 1.63 (1.22 to 2.17, *P* = .002) RD *10.0% (3.9 to 16.1, P <.001)*
Pain relief[c] (1,327)	2 h post-dose	50-mg: 256 (60.7) Placebo: 224 (49.1) OR 1.69 (1.28 to 2.23, *P* = .002)	100-mg: 275 (61.4) Placebo: 224 (49.1) OR 1.69 (1.28 to 2.21, *P* = .002)
Sustained pain relief[e] (1,327)	2–24 h post-dose	50-mg: 150 (36.3) Placebo: 93 (20.8) OR 2.25 (1.65 to 3.07, *P* = .002)	100-mg: 165 (38.0) Placebo: 93 (20.8) OR 2.39 (1.77 to 3.24, *P* = .002)
Sustained freedom from pain[f] (1,327)	2–24 h post-dose	50-mg: 53 (12.7) Placebo: 39 (8.6) OR 1.57 (1.01 to 2.44, *P* = NE)	100-mg: 68 (15.4) Placebo: 39 (8.6) OR 1.95 (1.28 to 2.97, *P* = .004)
Absence of photophobia (1,327)	2 h post-dose	50-mg: 172 (40.7) Placebo: 143 (31.4) OR 1.63 (1.22 to 2.19, *P* = NE)	100-mg: 205 (45.8) Placebo: 143 (31.4) OR 1.81 (1.36 to 2.42, *P* = .004)
Absence of phonophobia (1,327)	2 h post-dose	50-mg: 245 (57.9) Placebo: 215 (47.1) OR 1.56 (1.16 to 2.09, *P* = NE)	100-mg: 244 (54.5) Placebo: 215 (47.1) OR 1.47 (1.10 to 1.95, *P* = NE)
Absence of nausea (1,327)	2 h post-dose	50-mg: 297 (70.2) Placebo: 284 (62.3) OR 1.31 (0.96 to 1.79, *P* = NE)	100-mg: 310 (69.2) Placebo: 284 (62.3) OR 1.35 (1.00 to 1.83, *P* = NE)
Functioning and Quality of Life (N analyzed)		**N (%), OR (95% CI)**	
Response of "no disability, able to function normally" the Functional Disability Scale[g] (1,327)	2 h post-dose	50-mg: 171 (40.6) Placebo: 136 (29.8) OR 1.67 (1.22 to 2.27)	100-mg: 192 (42.9) Placebo: 136 (29.8) OR 1.93 (1.42 to 2.61)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Lipton et al., 2019[19] (ACHIEVE-II)		**Ubrogepant 50-mg**	
Migraine or Headache Events (N Analyzed)		**N (%) RD (95% CI) and OR (95% CI) Compared to Placebo**	
Freedom from pain[a] (920) [Co-primary study endpoint]	2 h post-dose	50-mg: 101 (21.8) Placebo: 65 (14.3) RD 7.5% (2.6 % to 12.5%, *P* = .01) OR 1.62 (1.14 to 2.29)	
Freedom from the most bothersome symptom[b] (920) [Co-primary study endpoint]	2 h post-dose	50-mg: 180 (38.9) Placebo: 125 (27.4) RD 11.5% (5.4% to 17.5%, *P* = .01) OR 1.65 (1.25 to 2.20)	
Pain relief achieved (920)[c]	2 h post-dose	50-mg: 291 (62.7) Placebo 220 (48.2) ARD 14.5% (8.1% to 20.8%, *P* = .01) OR 1.77 (1.35 to 2.32, *P* NR)	
Pain relief achieved (920)[c]	2 h to 24 h post-dose	50-mg: 165 (36.7) Placebo: 93 (21.0) ARD 15.8% (9.9% to 21.6%, *P* = .01) OR 2.16 (1.59 to 2.92)	
Sustained pain freedom (920)[h]	2 h to 24 h post-dose	50-mg: 66 (14.4) Placebo: 37 (8.2) ARD 6.2% (2.1% to 10.4%, *P* = .01) OR 1.85 (1.20 to 2.83)	
Absence of photophobia	2 h post-dose	50-mg: 203 (43.8) Placebo 162 (35.5) ARD 8.2% (1.9% to 14.5%, *P* = .02) OR 1.52 (1.14 to 2.02, *P* NR)	
Absence of phonophobia	2 h post-dose	25-mg: 233 (53.6) Placebo: 211 (46.3)	50-mg: 251 (54.1) Placebo: 211 (46.3)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
		ARD 7.3% (0.7% to 13.8%, *P* NR) OR 1.38 (1.04 to 1.83)	ARD 7.8% (1.4% to 14.2%, *P* = 0.4) OR 1.39 (1.05 to 1.84)
Absence of nausea	2 h post-dose	25-mg: 307 (70.6) Placebo: 319 (70.0) ARD 0.6% (-5.4% to 6.6%, *P* NR) OR 1.10 (0.81 to 1.49)	50-mg: 331 (71.3) Placebo: 319 (70.0) ARD 1.4% (-4.5% to 7.3%, *P* = .95) OR 1.12 (0.83 to 1.51)
Functioning and Quality of Life (N analyzed)			
NR			
Lipton et al., 2019[16]		**Rimegepant 75-mg**	
Migraine or Headache Events (N Analyzed)		**N (%) RD and RR (95% CI) Compared to Placebo**	
Freedom from pain[a] (1,027) [Co-primary study endpoint]	2 h post-dose	75-mg: 105 (19.6) Placebo: 64 (12.0) RD 7.6% (3.3% to 11.9%, *P* < .001) RR *1.6 (1.2 to 2.2, P < .001)*	
Freedom from the most bothersome symptom[b] (1,027) [Co-primary study endpoint]	2 h post-dose	75mg: 202 (37.6) Placebo: 135 (25.2) RD 12.4% (6.9% to 17.9%, *P* < .001) RR *1.5 (1.3 to 1.8, P <.001)*	
Freedom from photophobia (966)	2 h post-dose	75-mg: 183 (37.4) Placebo: 106 (22.3) RD 15.1% (9.4% to 20.8%, *P* < .001)	
Freedom from phonophobia (736)	2 h post-dose	75-mg: 133 (36.7) Placebo: 100 (26.8) RD 9.9% (3.2% to 16.6%, *P* = .004)	
Pain relief[c] (1,027)	2 h post-dose	75-mg: 312 (58.1) Placebo: 229 (42.8)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
		RD 15.3% (9.4% to 21.2%, *P* < .001)	
Freedom from nausea (691)	2 h post-dose	75-mg: 171 (48.1) Placebo: 145 (43.3) RD 4.8% (-2.7% to 12.2%, *P* = NE)	
Use of rescue medication (1,027)	24 h post-dose	75-mg: 113 (21.0) Placebo: 198 (37.0) RD -16.0% (-21.3% to -10.6%, *P* = NE)	
Sustained freedom from pain (1,027)	2 to 48 h post-dose	75-mg: 53 (9.9) Placebo: 32 (6.0) RD 3.9% (0.7% to 7.1%, *P* = NE)	
Sustained pain relief (1,027)	2 to 48 h post-dose	75-mg: 195 (36.3) Placebo: 121 (22.6) RD 13.7% (8.3% to 19.1%, *P* = NE)	
Pain relapse[i] (169)	2 to 48 h post-dose	75-mg: 52 (49.6) Placebo: 32 (50.0) RD -0.4% (-15.8% to 15.1%, *P* = NE)	
Functioning and Quality of Life (N analyzed)		**N (%), RD (95% CI) Compared to Placebo**	
Ability to function normally	2 h post-dose	75-mg: 175 (32.6) Placebo: 125 (23.4) RD 9.2% (3.9% to 14.6%, *P* = NE)	
Marcus et al., 2014[14]		**Rimegepant 75-mg: vs Placebo**	**Rimegepant 75-mg : vs Sumatriptan**
Migraine or Headache Events (N analyzed)		**N (%), RD, and RR (95% CI) Compared to Placebo**	
Pain free[j] (389) [Primary study endpoint]	2 h post-dose	Rimegepant: 27 (31.4) Placebo: *32* (15.3); *P* < .05 RD *16.2% (5.2% to 27.1%)* RR *2.1 (1.3 to 3.2)*	Rimegepant: 27 (31.4) Sumatriptan: 35[k] (35.0) RD *-3.6% (-17.2 to 9.9%)* RR *0.90 (.6 to 1.4)*

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sustained pain freedom (386)	2 to 24 h post-dose	Rimegepant: 24 (27.9) Placebo: 15 (7.4) *P* < .001	Rimegepant: 24 (27.9) Sumatriptan: 26 (26.0)
Sustained pain freedom (386)	2 to 48 h post-dose	Rimegepant: 24 (27.9) Placebo: 15 (7.4) *P* < .001	Rimegepant: 24 (27.9) Sumatriptan: 26 (26.0) *P* NR
Pain relief[l] (386)	2 h post-dose	Rimegepant: 62 (72.1) Placebo: 104 (51.2) *P* < .001	Rimegepant: 62 (72.1) Sumatriptan: 72 (72) *P* NR
Sustained pain relief (386)	2 to 24 h post-dose	Rimegepant: 60 (69.8) Placebo: 86 (42.4) *P* < .001	Rimegepant: 60 (69.8) Sumatriptan: 63 (63.0) *P* NR
Nausea free (390)	2 h post-dose	Rimegepant: 58 (67.4) Placebo: 104 (51.2) *P* = .007	Rimegepant: 58 (67.4) Sumatriptan: 60 (60) *P* NR
Photophobia free (390)	2 h post-dose	Rimegepant: 36 (41.9) Placebo: 49 (24.1) *P* = .003	Rimegepant: 36 (41.9) Sumatriptan: 47 (47) *P* NR
Phonophobia free (390)	2 h post-dose	Rimegepant: 45 (52.3) Placebo: 57 (28.1) *P* < .001	Rimegepant: 45 (52.3) Sumatriptan: 49 (49) *P* NR
Use of rescue medication (395)	2 to 48 h post-dose	Rimegepant: 21 (24.4) Placebo: 106 (50.7) *P* NR	Rimegepant: 21 (24.4) Sumatriptan: 31 (31.0) *P* NR
Functioning and Quality of Life (N analyzed)			
NR			

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Voss et al., 2016[17]		Ubrogepant 50-mg	Ubrogepant 100-mg
Migraine or Headache Events (N Analyzed)		N (%), RD, and RR (95% CI)	
Pain freedom[a] (321)[Co-primary study endpoint]	2 h post-dose	50-mg: 22 (21.0) Placebo: 10 (8.9), *P* < .05 RD *12.0% (2.6 to 21.4)* RR *2.4 (1.2 to 4.7)*	100-mg: 26 (25.5) Placebo: 10 (8.9), *P* < .01 RD *16.6% (12.4 to 22.4)* RR *2.9 (1.4 to 5.6)*
Headache response[c] (321) [Co-primary study endpoint]	2 h post-dose	50-mg: 60 (57.1) Placebo: 50 (44.6), *P* > .05 RD *12.5% (-0.7% to 25.7%)* RR *1.28 (1.0 to 1.7)*	100-mg: 60 (58.8) Placebo: 50 (44.6) RD *14.2% (0.9% to 27.5%,)* RR *1.3 (1.0 to 1.7)*
Absence of phonophobia (321)	2 h post-dose	50-mg: 59 (56.2) Placebo: 47 (42.0)	100-mg: 62 (60.8) Placebo: 47 (42.0)
Absence of photophobia (321)	2 h post-dose	50-mg: 50 (47.6) Placebo: 34 (30.4)	100-mg: 56 (54.9) Placebo: 34 (30.4)
Absence of nausea (321)	2 h post-dose	50-mg: 72 (68.6) Placebo: 70 (62.5)	100-mg: 72 (70.6) Placebo: 70 (62.5)
Sustained pain freedom[m] (321)	2 to 24 h post-dose	50-mg: 16 (15.1) Placebo: 7 (6.2)	100-mg: 22 (21.6) Placebo: 7 (6.2)
Sustained pain freedom (321)	2 to 48 h post-dose	50-mg: 15 (14.2) Placebo: 7 (6.2)	100-mg: 21 (20.6) Placebo: 7 (6.2)
Sustained pain relief[n] (321)	2 to 24 h post-dose	50-mg: 48 (45.7) Placebo: 32 (28.3)	100-mg: 47 (46.1) Placebo: 32 (28.3)
Sustained pain relief (321)	2 to 48 h post-dose	50-mg: 45 (42.9) Placebo: 28 (25.0)	100-mg: 44 (43.1) Placebo: 28 (25.0)
Total migraine freedom[o] (321)	2 h post-dose	50-mg: 21 (20.0) Placebo: 9 (8.0)	100-mg: 24 (23.5) Placebo: 9 (8.0)
Total migraine freedom (321)	2 to 24 h post-dose	50-mg: 15 (14.2) Placebo: 6 (5.3)	100-mg: 21 (20.6) Placebo: 6 (5.3)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Total migraine freedom (321)	2 to 48 h post-dose	50-mg: 14 (13.2) Placebo: 6 (5.3)	100-mg: 20 (20.6) Placebo: 6 (5.3)
Functioning and Quality of Life (N analyzed)			
NR			

Notes. [a] *Refers to change in the severity of headache pain from moderate or severe pain to no pain.* [b] *Refers to most bothersome symptom (nausea, phonophobia, or photophobia) reported as absent instead of present.* [c] *Refers to change in severity of headache pain from moderate or severe pain to mild or no pain.* [d] *Refers to normal function as opposed to mild impairment, severe impairment, or required bedrest.* [e] *Refers to pain relief after initial dose without the use of optional second dose or rescue medication.* [f] *Refers to freedom from pain after initial dose without the use of optional second dose or rescue medication.* [g] *Refers to ability to perform normal activities.* [h] *Refers to pain freedom at 2 hours with no administration of either rescue medication or the second dose of medication with no occurrence thereafter.* [i] *Refers to return of headache pain of any intensity after being pain-free for 2 hours after the dose during 2 to 48 hours after initial dose.* [j] *Refers to headache pain intensity level reported as no pain.* [k] *Depicted on a figure, actual value NR.* [l] *Refers to headache pain intensity level reported as no pain or mild pain.* [m] *Refers to no use of rescue medications and no mild, moderate or severe headache pain.* [n] *Refers to no use of rescue medications and no moderate or severe headache pain.* [o] *Refers to pain freedom with no photophobia, phonophobia, nausea, or vomiting. Abbreviations. ARD: adjusted risk difference; CGRP: calcitonin gene-related peptide; CI: confidence interval; h: hours; min: minutes; NE: not evaluated; NR: not reported; OR: odds ratio; RD: risk difference; RR: risk ratio; .*

Table B9. Adverse Events From CGRP Inhibitors in Randomized Trials Evaluating Acute Migraine Treatment

Outcome	Treatment Groups[a]		
Ailani et al., 2020[20] (open-label extension to ACHIEVE-I & II)	Usual Care[b]	Ubrogepant 50-mg	Ubrogepant 100-mg
N (%) with treatment-emergent[c] AE over 52 weeks	NR	268 (66.3)	297 (72.6)
N (%) with at least 1 treatment-related AE over 52 weeks	NR	42 (10.4)	43 (10.5)
N (%) with at least 1 SAE/N events over 52 weeks	NR	9 (2.2)	12 (2.9)
N (%) with adverse events leading to discontinuation over 52 weeks	NR	9 (2.2)	11 (2.7)
N (%) with treatment-related liver injury over 52 weeks (liver enzymes 3 times or more the upper limit of normal; determination of whether elevations were study related was adjudicated by a blinded panel of liver experts)	4 (1.0) (4 determined unlikely related)	5 (1.3) (3 determined unlikely related and 2 possibly related)	11 (2.7) (10 determined unlikely related and 1 probably related)
Croop et al., 2019[15]	Placebo	Rimegepant 75-mg	
N (%) with at least 1 AE	73 (11)	90 (13)	
N (%) with at least 1 treatment-related AE	36 (5)	47 (7)	
N (%) with at least 1 SAE/N events	0 (0)	0 (0)	
N (%) events reported by ≥ 1% of either group	3 (<1) nausea 4 (1) urinary tract infection 7 (1) dizziness	11 (2) nausea 10 (1) urinary tract infection 6 (1) dizziness	
N (%) with treatment-related liver injury	1 in each group had transaminase concentration greater than 3 times the upper limit of normal, there was no signal of hepatotoxicity and both events were assessed as unrelated to the study medication. No participants had bilirubin greater than two times the upper limit of normal.		
Dodick et al., 2019[18] (ACHIEVE-I)	Placebo	Ubrogepant 50-mg	Ubrogepant 100-mg
N (%) with at least 1 AE within 48 hours	62 (12.8)	44 (9.4)	79 (16.3)
N (%) with at least 1 treatment-related AE within 48 hours	41 (8.5)	27 (5.8)	58 (12.0)

Outcome	Treatment Groups[a]		
N (%) with at least 1 SAE/N events within 48 hours	0 (0)	0 (0)	0 (0)
N (%) with discontinuation due to AE within 48 hours	0 (0)	0 (0)	0 (0)
N (%) with at least 1 AE within 30 days	113 (23.3)	126 (27.0)	139 (28.7)
N (%) with at least 1 treatment-related AE within 30 days	49 (10.1)	36 (7.7)	68 (14.0)
N (%) with at least 1 SAE/N events within 30 days	0 (0)	3 (0.6) 1 Appendicitis 1 Pericardial effusion 1 Spontaneous abortion	2 (0.4) 2 Appendicitis 1 Seizure
N (%) with AE leading to discontinuation within 30 days	0 (0)	0 (0)	0 (0)
N (%) with treatment-related liver injury (liver enzymes 3 times or more the upper limit of normal; determination of whether elevations were study related was adjudicated by a blinded panel of liver experts)	1 (determined to possibly be related)	2 (determined unlikely to be related)	3 (1 case determined to possibly be related, other cases were determined unlikely to be related)
Lipton et al., 2019[19] (ACHIEVE-II)	**Placebo**		**Ubrogepant 50-mg**
N (%) Treatment-emergent AEs (48 hr post-dose)	51 (10.2)		63 (12.9)
N (%) SAEs (48 hr post-dose)	0		0
N (%) AE leading to discontinuation (48 hr post-dose)	0		0
N (%) Treatment-emergent AEs (30 days post-dose)	112 (22.4)		133 (27.3)
N (%) SAEs (30 days post-dose)	0		0
N (%) AE leading to discontinuation (30 days post-dose)	0		0
N (%) with treatment-related liver injury	1 (adjudicated by blinded panel to be possibly related to treatment)		3 (all were adjudicated by blinded panel to be unlikely to be related to study drug)
Lipton et al., 2019[16]	**Placebo**		**Rimegepant 75-mg**

Outcome	Treatment Groups[a]		
N (%) with at least 1 AE	77 (14.2)	93 (17.1)	
N (%) with at least 1 SAE	2 (0.4) (chest pain, urinary tract infection)	1 (0.2) (back pain)	
N (%) Serum AST or ALT above ULN	12 (2.2)	13 (2.4)	
N (%) Serum AST or ALT > 3 × ULN	0 (0)	0 (0)	
N (%) Total bilirubin > 2 × ULN	0 (0)	0 (0)	
Marcus et al., 2014[14]	**Placebo**	**Sumatriptan 100-mg**	**Rimegepant 75-mg**
N (%) with at least 1 AE	NR[d]	NR	NR
N (%) with at least 1 SAE/N events	2 (pneumonia, postlumbar puncture headache; neither were considered to be treatment-related)		
N (%) with discontinuation due to AE	0 (0)	0 (0)	0 (0)
N (%) with treatment-related liver injury	1(total bilirubin ≥ 2 times the upper limit of normal)	0 (0)	1 (mild increase in a hepatic enzyme on day 7 that resolved by day 64)
Voss et al., 2016[17]	**Placebo**	**Ubrogepant 50-mg**	**Ubrogepant 100-mg**
N (%) with at least 1 AE within 48 hours post-dose	28 (24.8)	23 (21.5)	30 (29.4)
N (%) with at least 1 drug-related AE within 48 hours post-dose	23 (20.4)	18 (16.8)	25 (24.5)
N (%) with at least 1 AE within 14 days post-dose	33 (29.2)	30 (28.0)	32 (31.4)
N (%) with at least 1 drug-related AE within 14 days post-dose	23 (20.4)	19 (17.8)	25 (24.5)
N (%) with at least 1 SAE/N events	0 (0)	0 (0)	0 (0)
N (%) with treatment-related liver injury	0 (0)	0 (0)	0 (0)

Notes. Calculated values are indicated with italics. [a] All active treatments and placebos administered monthly unless otherwise specified. [b] Included usual care for acute migraine headache treatment as directed by the participant's usual care clinician. [c] Refers to events that occurred or increased in intensity on or after the initial dose and before visit 16 or 30 days after the last visit or treatment. [d] The incidence of overall adverse events was reported as comparable across groups. Abbreviations. AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CGRP: calcitonin gene-related peptide; NR: not reported; SAE: serious adverse event; ULN: upper limit of normal.

Table B10. Characteristics of Studies Evaluating CGRP Inhibitors for Cluster Headache Prevention

Author, Year Registry Number	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
Goadsby et al., 2019[10] NCT02397473	Phase 3, double-blind, parallel-assignment RCT Galcanezumab (dose at month 0 and month 1) 300-mg SC = 49 Placebo SC = 57 Total N = 106 (study stopped early by sponsor because of fewer participants entering active cluster headache periods than anticipated)	Age; by group: 300-mg: 47 (11) Placebo: 45 (11) Female, by group: 300-mg: 8 (16) Placebo: 10 (18) Baseline cluster headache attacks days per week, by group: 300-mg: 17.8 (10.1) Placebo: 17.3 (10.0) Inclusion: Men and women ages 18 to 65 years with history of episodic cluster headache as defined by ICHD-3; able to distinguish cluster headache attacks from other headache disorders; cluster headache attack frequency of at least one every other day; at least 4 total attacks and no more than 8 attacks per day during 7 consecutive days of the prospective baseline period; and have had a cluster headache period that had lasted at least 6 weeks.	10 to 15 days 8 weeks 8 weeks No concomitant preventive medications for cluster headache were permitted.	35 sites in Europe and North America Eli Lilly and Company Fair

Author, Year Registry Number	Study Design Drug and Comparator (N Randomized)	Demographic Characteristics Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Baseline Run-in Duration Treatment Duration Follow-Up Duration Ongoing Preventive Therapy	Sites Sponsor Quality Rating
		Exclusion: Recent participation in a clinical trial; current or any previous use of any CGRP antibody, antibody to the CGRP receptor, or antibody to nerve growth factor, concurrent use of other therapeutic monoclonal antibodies; another distinct trigeminal autonomic cephalalgia or a history of migraine variants that could have been due to cerebral ischemia.		

Abbreviations. CGRP: calcitonin gene-related peptide; ICHD-3 = International Classification of Headache Disorders, 3rd edition; NCT: U.S. National Clinical Trial; RCT: randomized controlled trial; SC: subcutaneous.

Table B11. Efficacy of CGRP Inhibitors in Randomized Trials Evaluating Cluster Headache

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups
Goadsby et al., 2019[10]		Galcanezumab 300-mg
Headache Events (N analyzed)		Mean difference from placebo (95% CI; P value)
Mean change in frequency of cluster headache attacks per week from baseline [Primary study endpoint] (106)	Weeks 1 to 3	-3.5 (-0.2 to -6.7; *P* = .04)
Mean change in frequency of cluster headache attacks per week from baseline (106)	Week 8	1.3 (−1.2 to 3.8; *P* NR)
Percentage of participants with 50% or greater reduction in the frequency of cluster headache attacks per week (106)	Week 3	%; OR (95% CI), *P* Value
		Placebo 53%; 300-mg 71%; 2.4 (1.0 to 5.7), *P* = .046
Percentage of participants with 50% or greater reduction in the frequency of cluster headache attacks per week (106)	Week 8	Placebo 88%; 300-mg 74%; 0.4 (0.1 to 1.3); *P* NR

Abbreviations. CGRP: calcitonin gene-related peptide; CI: confidence interval; NR: not reported; OR: odds ratio.

Table B12. Adverse Events From CGRP Inhibitors in Randomized Trials Evaluating Cluster Headache

Outcome	Treatment Groups	
Goadsby et al., 2019[10]	Placebo	Galcanezumab 300-mg
N (%) with at least 1 adverse event	19 (33)	21 (43)
N (%) with at least 1 serious adverse event/N events	0 (0)	0 (0)
N (%) with discontinuation due to adverse event	1 (2)	2 (4)
N (%) with treatment-related liver injury (alanine aminotransferase normal at baseline but above upper limit of normal at any post-baseline visit)	1 (2)	2 (5)
N (%) with treatment-related liver injury (aspartate aminotransferase normal at baseline but above upper limit of normal at any post-baseline visit)	0 (0)	1 (2)
N (%) with treatment-related liver injury (total bilirubin normal at baseline but above upper limit of normal at any post-baseline visit)	1 (2)	0 (0)

Abbreviation. CGRP: calcitonin gene-related peptide.

Appendix C. Detailed Findings From Network Meta-analysis

Table C1. Outcomes for Various Drugs Relative to a Placebo From a Network Meta-analysis of Preventive Therapies for Chronic Migraine[43]

Drug	Monthly Migraine Days	Days Using Acute Medications	Monthly Headache Days
	Difference in Days Relative to Placebo (95% Credible Interval)		
Erenumab 70 mg monthly	-2.4 (-4.8 to 0.0)[a]	-1.9 (-4.3 to 0.6)	NR
Erenumab 140 mg monthly	-2.4 (-4.8 to 0.0)[a]	-2.5 (-4.9 to 0.0)[a]	NR
Fremanezumab 675 mg quarterly	-1.3 (-3.5 to 0.9)	-1.4 (-3.8 to 1.0)	-1.5 (-3.7 to 0.8)
Fremanezumab 225 mg monthly[b]	-1.7 (-3.5 to 0.1)	-2.2 (-4.1 to -0.3)[a]	-1.8 (-3.6 to -0.1)[a]
OnabotulinumtoxinA 155 units quarterly	-2.0 (-3.6 to -0.3)[a]	NR	-2.1 (-3.5 to -0.6)[a]
Topiramate 100 mg daily	-1.7 (-4.2 to 0.8)	-1.3 (-3.5 to 0.7)	-1.1 (-3.6 to 1.4)

Notes. [a] Results reported as statistically significant; [b] Initial dose is 675 mg followed by monthly doses of 225 mg. Source. Institute for Clinical and Economic Review (ICER). Calcitonin gene-related peptide (CGRP) inhibitors as preventive treatments for patients with episodic or chronic migraine: effectiveness and value. https://icer-review.org/wp-content/uploads/2017/11/ICER_Migraine_Final_Evidence_Report_070318.pdf. Published July 3, 2018. Abbreviation. NR: not reported.

Table C2. Outcomes for Various Agents Relative to a Placebo From a Network Meta-analysis of Preventive Therapies for Episodic Migraine[43]

Drug	Monthly Migraine Days	Days Using Acute Medications	50% Responders
	Mean Difference in Days Relative to Placebo (95% Credible Interval)		OR (95% Credible Interval)
Erenumab 70 mg monthly	-1.3 (-1.9 to -0.7)[a]	-0.9 (-1.5 to -0.4)[a]	1.9 (1.3 to 2.6)[a]
Erenumab 140 mg monthly	-1.9 (-2.9 to -1.0) [a]	-1.6 (-2.5 to -0.8)[a]	2.2 (1.3 to 3.6)[a]
Fremanezumab 675 mg quarterly	-1.2 (02.3 to -0.1)[a]	-1.1 (-2.1 to -0.1)[a]	1.7 (1.0 to 2.9)[a]
Fremanezumab 225 mg monthly	-1.6 (-2.6 to -0.7)[a]	-1.2 (-2.1 to -0.4)[a]	2.0 (1.3 to 3.1)[a]
Galcanezumab 120 mg monthly	-1.9 (-3.2 to -0.6)[a]	NR	2.0 (0.9 to 4.4)
Topiramate 50 mg daily	-0.2 (-1.1 to 0.7)	-0.4 (-1.5 to 0.5)	1.6 (1.0 to 2.5)[a]
Topiramate 100 mg daily	-1.2 (-1.7 to -0.6)[a]	-1.0 (-1.5 to -0.4)[a]	2.7 (2.0 to 3.7)[a]
Topiramate 200 mg daily	-1.0 (-1.6 to -0.4)[a]	-0.7 (-1.4 to -0.2)[a]	2.3 (1.7 to 3.2)[a]
Amitriptyline 25-100 mg daily	-1.1 (-2.4 to 0.2)	-1.2 (-2.5 to 0.2)	2.0 (1.2 to 3.5)[a]
Propranolol 160 mg daily	-1.2 (-2.2 to -0.3)[a]	-1.1 (-2.0 to -0.2)[a]	2.7 (1.6 to 4.2)[a]

Note. [a] Results reported as statistically significant. Source. Institute for Clinical and Economic Review (ICER). Calcitonin gene-related peptide (CGRP) inhibitors as preventive treatments for patients with episodic or chronic migraine: effectiveness and value. https://icer-review.org/wp-content/uploads/2017/11/ICER_Migraine_Final_Evidence_Report_070318.pdf. Published July 3, 2018. Abbreviations. NR: not reported; OR: odds ratio.

Table C3. Results from Network Meta-analysis of Agents to Treat Acute Migraine Headache

	Lasmiditan	Rimegepant	Ubrogepant	Sumatriptan	Eletriptan	Placebo
Freedom from pain at 2 hours (adjusted OR, 95% Credible Interval)						
Rimegepant	1.43 (0.97 to 2.06)					
Ubrogepant	1.43 (0.93, 2.14)	1.0 (0.69 to 1.46)				
Sumatriptan	0.73 (0.53 to 1.06)	0.51 (0.39 to 0.7)[a]	0.52 (0.37 to 0.74)[a]			
Eletriptan	0.54 (0.36 to 0.85)[a]	0.38 (0.27 to 0.57)[a]	0.38 (0.26 to 0.59)[a]	0.73 (0.57 to 0.97)[a]		
Placebo	3.01 (2.2 to 4.14)[a]	2.11 (1.67 to 2.72)[a]	2.12 (1.58 to 2.88)[a]	4.09 (3.43 to 4.82)[a]	5.6 (4.14 to 7.23)[a]	
Pain relief at 2 hours (OR, 95% Credible Interval)						
Rimegepant	1.16 (0.87 to 1.52)					
Ubrogepant	1.15 (0.85 to 1.58)	1.0 (0.75 to 1.34)				
Sumatriptan	0.84 (0.67 to 1.13)	0.73 (0.58 to 0.96)[a]	0.73 (0.55 to 1)			
Eletriptan	0.61 (0.44 to 0.88)[a]	0.52 (0.38 to 0.76)[a]	0.52 (0.37 to 0.78)[a]	0.72 (0.58 to 0.89)[a]		
Placebo	2.53 (2.04 to 3.25)[a]	2.19 (1.8 to 2.76)[a]	2.19 (1.7 to 2.89)[a]	2.99 (2.65 to 3.34)[a]	4.18 (3.32 to 5.14)[a]	
Sustained freedom from pain at 24 hours (adjusted OR, 95% Credible Interval)						
Rimegepant	1.16 (0.67 to 1.94)					
Ubrogepant	1.26 (0.72 to 2.11)	1.08 (0.67 to 1.74)				
Sumatriptan	0.83 (0.5 to 1.44)	0.71 (0.48 to 1.12)	0.66 (0.41 to 1.12)			
Eletriptan	0.73 (0.34 to 1.53)	0.63 (0.32 to 1.22)	0.59 (0.28 to 1.18)	0.89 (0.44 to 1.69)		
Placebo	2.92 (1.89 to 4.5)[a]	2.51 (1.89 to 3.46)[a]	2.32 (1.62 to 3.46)[a]	3.53 (2.52 to 4.77)[a]	3.97 (2.24 to 7.36)[a]	

	Lasmiditan	Rimegepant	Ubrogepant	Sumatriptan	Eletriptan	Placebo
Freedom from most bothersome symptom at 2 hours (adjusted OR, 95% Credible Interval)						
Rimegepant	1.07 (0.78 to 1.46)					
Ubrogepant	1.03 (0.73 to 1.45)	0.96 (0.69 to 1.33)				
Placebo	1.69 (1.33 to 2.14)[a]	1.58 (1.29 to 1.94)[a]	1.64 (1.28 to 2.12)[a]			
Ability to function normally at 2 hours (adjusted OR, 95% Credible Interval)						
Rimegepant	0.99 (0.71 to 1.39)					
Ubrogepant	1.13 (0.78 to 1.64)	1.14 (0.81 to 1.62)				
Placebo	1.7 (1.32 to 2.2)[a]	1.72 (1.38 to 2.14)[a]	1.51 (1.15 to 1.96)[a]			

Notes. [a] Indicates the 95% credible interval excludes a null effect. The OR listed represent the treatment effect comparing the drug in the column header to the drug in the row header; an OR > 1.0 indicates the column drug is more effective than the row drug, and an OR < 1.0 indicates that the column drug is less effective than the row drug; study authors adjusted the OR for placebo group response rates. Source: Atlas S, Touchette D, Agboola F, et al. Acute treatments for migraine: effectiveness and value. Institute for Clinical and Economic Review. http://icer-review.org/material/acute-migraine-evidence-report/. Published January 8, 2020. Abbreviation. OR: odds ratio.

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Appendix E. Bibliography of Excluded Studies

Exclusion Codes

X1: Ineligible Population

X2: Ineligible Intervention

X3: Ineligible or no comparator

X4: Ineligible outcome

X5: Ineligible setting

X6: Ineligible study design

X7: Ineligible or superseded

X8: Ineligible study protocol or in progress

X9: Non-English full text

X10: Other

- Ailani J, Pearlman E, Zhang Q, Nagy AJ, Schuh K, Aurora SK. Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine: post hoc analyses of 3 randomized double-blind studies. *Eur J Neurol.* 2019. doi: 10.1111/ene.14102. Exclude: X6
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