Calcitonin Gene-Related Peptide Inhibitors for Migraine Prophylaxis

Systematic Review

October 2018

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Executive Summary

Background

Calcitonin gene-related peptide (CGRP) is a neuropeptide that is thought to play a role in migraine pathophysiology; thus, blocking CGRP has been studied as a mechanism for preventing migraine headache. CGRP inhibitors are monoclonal antibodies that target the CGRP receptor (erenumab) or CGRP ligand (eptinezumab, fremanezumab, and galcanezumab). The U.S. Food and Drug Administration (FDA) has approved 3 drugs in this class (erenumab, fremanezumab, and galcanezumab) and 1 additional drug (eptinezumab) is in development.

PICO and Key Questions

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

1. What is the efficacy and effectiveness of CGRP inhibitors for migraine prophylaxis?
2. What is the frequency of adverse events with CGRP inhibitors for migraine prophylaxis?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which CGRP inhibitors differ in efficacy, effectiveness, or frequency of adverse events?
4. What are the characteristics of ongoing studies of CGRP inhibitors?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, and several other websites to identify eligible studies. We rated the methodological quality of eligible RCTs and systematic reviews using standard instruments adapted from national and international quality standards.[1-3] We rated the quality of the body of evidence for each drug and indication (chronic vs. episodic) for 6 outcomes, when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[4,5] We used EpiInfo (version 7.2.2.6) to calculate risk differences (RD) and risk ratios (RR) and Microsoft Excel to calculate mean differences for various continuous efficacy outcomes when these data were not included by study authors.

Key Findings

We identified 13 placebo-controlled randomized trials and 2 systematic reviews for this review. Three RCTs reported on 2 drugs (erenumab[6], fremanezumab[7,8]) for prophylaxis of chronic migraine and 10 RCTs reported on 4 drugs (eptinezumab,[9] erenumab,[10-12] fremanezumab,[13,14] galcanezumab[15-19]) for prophylaxis of episodic migraines. We identified no studies that compared 1 CGRP inhibitor to another. We rated all primary research studies as fair

methodological quality, primarily because of the risk of bias from extensive manufacturer involvement in design, conduct, analysis, and preparation of manuscripts. One systematic review evaluated the effectiveness and safety of CGRP inhibitors and included a network meta-analysis[20]; we evaluated this review as good methodological quality. The other systematic review[21] also evaluated the effectiveness and safety of CGRP inhibitors; we evaluated this review as poor methodological quality because of limited information regarding study inclusion criteria, no literature flow diagram, and no methodological quality assessment of included studies.

Efficacy and Effectiveness of CGRP Inhibitors (Key Question 1)

- Compared to a placebo, erenumab and fremanezumab resulted in a statistically significant decrease in migraine days per month for chronic migraine at 12 weeks; the difference from a placebo ranged from -1.7 days to -2.5 days across 3 RCTs. We evaluated this evidence as moderate quality.
- Compared to a placebo, 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 a placebo ranged from -0.9 days to -2.8 days across 9 RCTs. We evaluated this evidence as moderate quality.
- Compared to a placebo, eptinezumab resulted in no statistically significant difference in migraine days per month at 12 weeks in 1 RCT; we evaluated this evidence as low quality.
- Compared to a placebo, CGRP inhibitors resulted in significant improvements on various measures of quality of life and function, although estimates in some studies lacked precision and were not statistically significant. The measures included the Headache Impact Test (HIT-6), the Migraine Disability Assessment (MIDAS), the Migraine Physical Function Impact Diary (MPFID), and the Migraine-Specific Quality of Life Questionnaire (MSQL). The magnitude of the treatment effect varied by measure and study. For chronic migraine prophylaxis, we evaluated the body of evidence for the HIT-6 at 12 weeks as moderate quality for fremanezumab; no studies evaluated quality-of-life outcomes for erenumab. For episodic migraine prophylaxis, we evaluated the body of evidence for the HIT-6 as low quality for eptinezumab at 12 weeks, and we rated the body of evidence for the MIDAS as moderate quality for erenumab, fremanezumab, and galcanezumab at 12 to 24 weeks.
- Compared to a placebo, most CGRP inhibitors also demonstrated significant treatment effects on most other measures of efficacy at 12 to 24 weeks, including fewer days of acute medication use, fewer headache days, and a higher percentage of participants with a 50% reduction in migraine days per month.
- In indirect comparisons through a network meta-analysis, for chronic migraine, erenumab and fremanezumab were not significantly different from each other and topiramate 100 mg and onabotulinum toxin A on measures of migraine days per month, days using acute medications, and headache days per month. In indirect comparisons of safety outcomes, erenumab and fremanezumab had a similar incidence of all-cause discontinuations, discontinuations because of adverse events, and frequency of serious adverse events compared to each other and with topiramate 100 mg and onabotulinum toxin A.

- In indirect comparisons through a network meta-analysis, for episodic migraine, erenumab, fremanezumab, and galcanezumab were not significantly different from each other and topiramate 100 mg and 200 mg, amitriptyline 25 mg to 100 mg, and propranolol 160 mg on days of acute medication use and percentage of participants with a 50% reduction in migraine days per month; however, these CGRP inhibitors were statistically significantly more effective in reducing migraine days per month than topiramate 50 mg. In indirect comparisons of safety outcomes, erenumab, fremanezumab, and galcanezumab had a similar incidence of discontinuations because of adverse events and frequency of serious adverse events compared to each other and with the other migraine preventive medications; erenumab had statistically significantly less frequent all-cause discontinuations compared to topiramate 200 mg; all-cause discontinuations were similar among all other comparisons.
- No studies reported employment or health care utilization outcomes.

Adverse Events From CGRP Inhibitors (Key Question 2)

- The frequency of serious adverse events and discontinuations because of adverse events in active treatment groups was similar to a placebo at 12 to 24 weeks across all drugs and doses. We evaluated the body of evidence on serious adverse events and discontinuations because of adverse events as having very low quality, primarily due to very serious concerns regarding imprecision because serious adverse events and discontinuations were rare and because of study limitations from the risk of bias stemming from extensive manufacturer involvement in the study design, conduct, and analysis.
- Treatment-related liver injury was uncommon and was similar between active treatment and placebo groups.
- The frequency of all-cause adverse events at 12 to 24 weeks was similar between active treatment and placebo groups.

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

- Few studies reported findings by subgroups. Three studies (all on fremanezumab) reported similar efficacy among participants not taking concomitant preventive medication compared to the full study population, which also included participants taking concomitant preventive medication.

Ongoing Studies (Key Question 4)

We identified 15 ongoing studies of CGRP inhibitors; all of which are placebo-controlled randomized trials.

- 3 studies are for eptinezumab (2 chronic, 1 episodic)
- 3 studies are for erenumab (all episodic)
- 5 studies are for fremanezumab (1 chronic, 1 episodic, 3 combined)
- 4 studies are for galcanezumab (1 chronic, 1 episodic, 2 combined)
- Most ongoing studies are blinded and have follow-up periods of between 12 and 24 weeks; some have longer follow-up periods (up to 1.5 years)

Conclusions

The evidence showed that in short-term follow-up, erenumab and fremanezumab were more effective than a placebo for chronic migraine prophylaxis and had similar frequency of adverse events compared to a placebo. Erenumab, fremanezumab, and galcanezumab were also more effective than a placebo for episodic migraine prophylaxis and had a similar frequency of adverse events compared to a placebo. The evidence is limited for eptinezumab because there is only 1 RCT. The magnitude of treatment effect and safety of CGRP inhibitors is similar to the effects of other available migraine preventive agents based on indirect comparisons. Providers, patients, or both are likely to view the clinical significance of the magnitude of treatment effect differently, depending on the severity and disability of their headache condition, the patient's ability to tolerate other preventive medications, and other factors. Additional placebo-controlled studies of CGRP inhibitors are in progress, but none will report efficacy outcomes at follow-up longer than 6 months or adverse events at follow-up longer than 1.5 years. We identified no ongoing head-to-head studies.

List of Brand Name and Generic Drugs

Table 1 describes current CGRP inhibitors and FDA status.

Table 1. List of CGRP Inhibitors

Generic Drug (Alternative Names)	Manufacturer	Dose(s)	Form	Frequency	FDA Status
Erenumab (Aimovig, AMG 334)	Amgen Inc./ Novartis	70 mg, 140 mg	Subcutaneous injection	Every month	BLA approved May 17, 2018
Fremanezumab[a] (Ajovy, TEV-48125, LBR-101)	Teva Pharmaceutical Industries Ltd.	225 mg, 675 mg, 900 mg	Subcutaneous injection	Every month or 3 months	BLA approved September 14, 2018
Galcanezumab (Emgality, LY2951742)	Eli Lilly and Company	120 mg[b]	Subcutaneous injection	Every month	BLA approved September 27, 2018
Eptinezumab (ALD403)	Alder Biopharmaceuticals, Inc.	100 mg, 300 mg	Intravenous infusion	Every 3 months	BLA review in late 2018 or early 2019

Notes. [a] Various doses and dosing regimens were evaluated in phase 2 and 3 studies. The FDA-approved label dose is 225 mg every month or 675 mg every 3 months. Abbreviations. [b] The FDA-approved label dose is an initial loading dose of 240 mg followed by a monthly dose of 120 mg. Abbreviations. BLA: biologic license application; FDA: U.S. Food and Drug Administration.

Background

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.[22-24] Unlike other available preventive treatments (e.g., antihypertensive agents, antidepressants, antiepileptics), CGRP inhibitors were developed specifically to prevent migraines. The FDA approved the first CGRP inhibitor (erenumab) in May 2018 and approved fremanezumab and galcanezumab in September 2018. One additional CGRP inhibitor (eptinezumab) is currently in development, with FDA review expected in late 2018 or early 2019. Erenumab is a fully human monoclonal antibody that binds to the CGRP receptor; eptinezumab, fremanezumab, and galcanezumab are humanized monoclonal antibodies that target the CGRP ligand.[20,21]

CGRP inhibitors are currently being studied for prophylaxis in people with chronic or episodic migraine headaches. The definition of migraine is based on the International Classification of Headache Disorders (3rd edition) and is divided into migraine with or without aura (i.e., sensory disturbances such as light flashes, blind spots, and tingling).[25] 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.[20] 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).

State Medicaid program administrators are interested in a review of the evidence of the efficacy and adverse events of CGRP inhibitors for migraine prophylaxis to aid in managing this new drug class.

PICO

Populations

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

Comparators

- CGRP inhibitors compared to each other (head-to-head)
- Other migraine prophylaxis (i.e., selected antidepressants [amitriptyline and venlafaxine], anticonvulsants [divalproex, topiramate, and valproic acid and derivatives], beta blockers [propranolol and metoprolol], and onabotulinum toxin A)
- 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 ability
- 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 including total adverse events, treatment-related events, and events that are likely not treatment related
- Serious adverse events (i.e., 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)
- Withdrawals or discontinuations because of adverse events

Setting

- Inpatient
- Outpatient/clinic
- Office
- Home

Study Designs

- Randomized controlled trials (RCTs)
- Prospective cohort studies
- Systematic reviews (with or without a meta-analysis)

Key Questions

1. What is the efficacy and effectiveness of CGRP inhibitors for migraine prophylaxis?
2. What is the frequency of adverse events with CGRP inhibitors for migraine prophylaxis?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which CGRP inhibitors differ in efficacy, effectiveness, or frequency of adverse events?
4. What are the characteristics of ongoing studies of CGRP inhibitors?

Methods

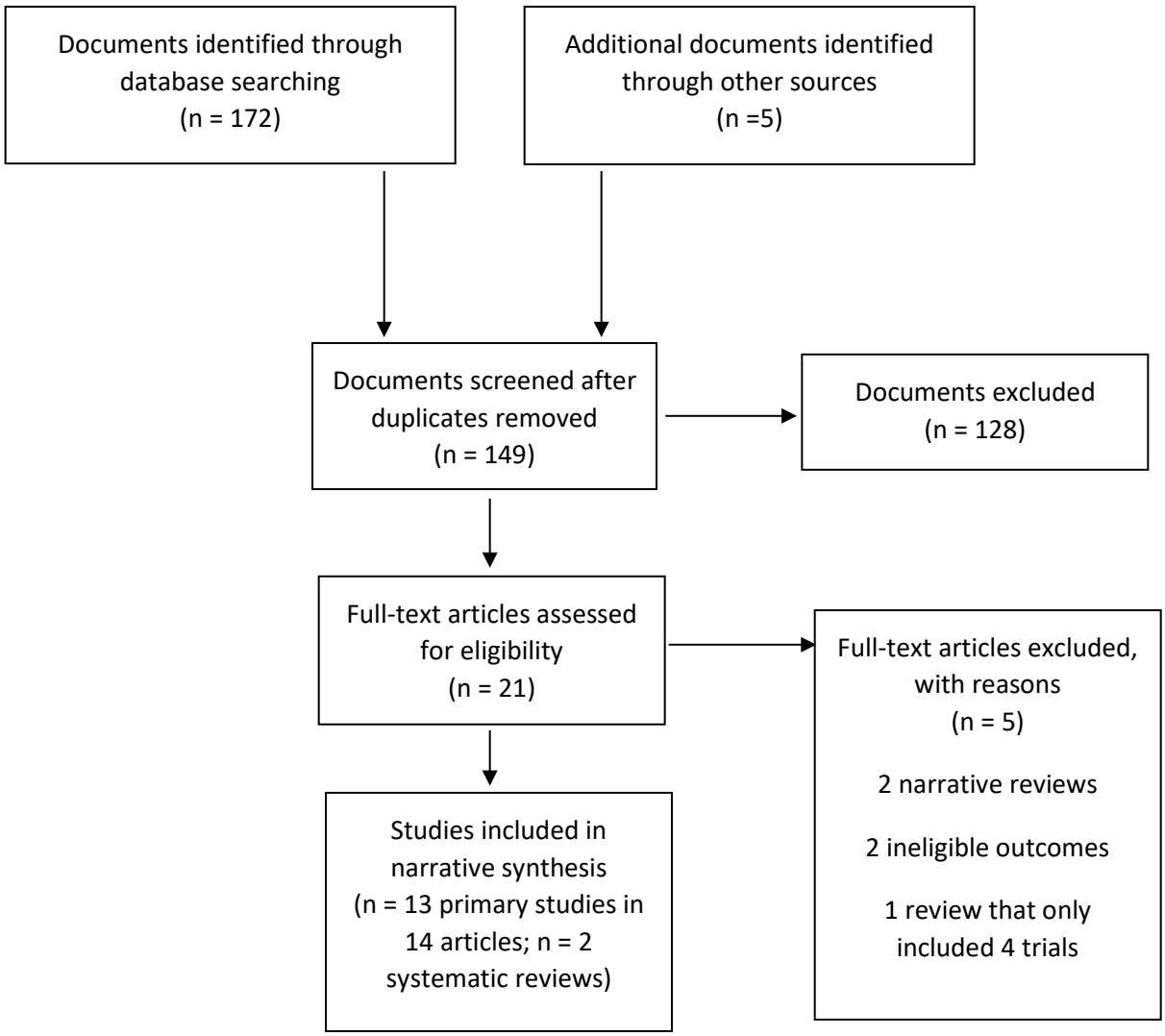
We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, and several other websites to identify eligible studies. We rated the methodological quality of eligible RCTs or systematic reviews using standard instruments adapted from national and international quality standards.[1-3] We rated the quality of the body of evidence for each drug and indication (chronic vs. episodic) for 6 outcomes, when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[4,5] For continuous efficacy measures, we extracted the difference between the intervention and the placebo reported by studies or used Microsoft Excel to calculate 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, and odds ratios [OR]) and used EpiInfo (version 7.2.2.6) to calculate RD and RR and

associated 95% confidence intervals (CI) based on data provided in the study when not reported by authors. For adverse event outcomes, we extracted frequencies and percentages.

Findings

We identified 13 primary research studies (published in 14 articles) and 2 systematic reviews for this review (Figure 1). Three placebo-controlled randomized trials reported on 2 drugs (erenumab[6], fremanezumab[7,8]) for prophylaxis of chronic migraine and 10 placebo-controlled randomized trials reported on 4 drugs (eptinezumab,[9] erenumab,[10-12] fremanezumab,[13,14] galcanezumab[15-19]) for prophylaxis of episodic migraines. Pharmaceutical manufacturers sponsored all trials included in this review. We rated the methodological quality of all included primary research studies as fair, primarily because of the risk of bias from extensive manufacturer involvement in design, conduct, analysis, and preparation of manuscripts. In the rest of this section, we summarize the efficacy (Key Question 1) and adverse events (Key Question 2) by indication (chronic vs. episodic migraine) and by drug, including findings for subgroups of interest (Key Question 3). We summarize efficacy and adverse event findings from the 2 systematic reviews[20,21] and describe ongoing studies (Key Question 4) in the last part of this section.

Figure 1. Literature Flow Diagram



Chronic Migraine Prophylaxis

Table 2 provides the Summary of Findings (GRADE) for the primary research evidence for chronic migraine prophylaxis. 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, we rated the evidence as moderate quality because of serious concerns about study limitations from risk of bias from manufacturer involvement. We rated the evidence for serious adverse events and discontinuations because of adverse events as very low quality because of the same risk of bias concerns and because of very serious concerns about imprecision from infrequent events. Table 3 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for the 3 placebo-controlled trials that reported on the use of or erenumab[6] or fremanezumab.[7,8] We assessed each individual study as fair methodological quality because of the risk of bias from manufacturer involvement. Detailed

evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes).

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

Outcome	Quality of the Evidence	Relationship	Rationale
Erenumab vs. Placebo			
Migraine days per month (1 RCT[6])	Moderate	Statistically significant improvements with active doses compared to placebo	Downgraded 1 level for study limitations No serious concerns in any domain
Days with acute migraine medication use per month (1 RCT[6])	Moderate		
Percentage with at least 50% reduction in number of migraine days per month (1 RCT[6])	Moderate		
Serious adverse events (1 RCT[6])	Very low	Similar percentages for active doses and placebo	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuation due to adverse events (1 RCT[6])	Very low		
Fremanezumab vs. Placebo			
Migraine days per month (2 RCTs[7,8])	Moderate	Statistically significant improvements with active doses compared to placebo	Downgraded 1 level for study limitations
Days with acute headache medication use per month (2 RCTs[7,8])	Moderate		
Percentage with at least 50% reduction in number of migraine days per month (1 RCT[8])	Moderate		
Mean change in HIT-6 (1 RCT[8])	Moderate		
Serious adverse events (2 RCTs[7,8])	Very low	Similar percentages for active doses and placebo	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (2 RCTs[7,8])	Very low		

Notes. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used. Abbreviations. CGRP: calcitonin gene-related peptide inhibitors; HIT-6: Headache Impact Test (6 item).

Table 3. Summary of Evidence: Placebo-Controlled Randomized Trials of CGRP Inhibitors for Chronic Migraine Prophylaxis

Study; Registration Number; Trial Name	Dose, Frequency[a] and N Randomized	Primary Endpoint; Difference From Placebo (95% CI)	N (%) With at Least 1 Serious Adverse Event[b]	N (%) With Adverse Event Leading to Discontinuation
Erenumab				
Tepper et al., 2017[6] 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)[c] 140 mg: -2.5 (-3.5 to -1.4)[c]	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[7] NCT02021773	225 mg[d] 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[e]; 225 mg: -22.7 (-44.3 to -1.2)[c] 900 mg: -30.4 (-51.9 to -9.0)[c]	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[8] NCT02621931 HALO CM	225 mg[d] SC = 379 675 mg quarterly SC = 376 Placebo SC = 375 Total N = 1,130	Mean change in headache days per month[f] 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)

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] Indicates a statistically significant result based on an alpha equal to .05. [d] Patients in the 225-mg group received 675 mg at baseline and 225 mg at weeks 4 and 8. [e] This study 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. [f] 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. CGRP: calcitonin gene-related peptide inhibitors; CI: confidence interval; SC: subcutaneous.

Erenumab

Study Characteristics

One phase 2 RCT (Tepper et al.) conducted among 667 participants at multiple sites in North America evaluated 70 mg and 140 mg of erenumab compared to a placebo in a 12-week period.[6] We rated this study as fair methodological quality because of the risk of bias from conflicts of interest. This study enrolled adults between ages 18 and 65 with a history of chronic

migraine in the previous 3 months and during the 4-week run-in phase.[6] 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.[6] The use of other drugs for migraine prevention was prohibited in the 2 months prior to run-in and during the treatment phase.[6] Study investigators allowed the use of non-study migraine prevention drugs if prescribed for non-migraine indications (e.g., depression, high blood pressure) and the dose was stable in the month prior to screening.[6] Study investigators allowed participants to use acute migraine treatment during the study period.[6]

Findings

The study authors observed the same statistically significant decrease in mean change in migraine days per month from baseline (primary study endpoint) for both active treatment groups (-2.5 [95% CI, -3.5 to -1.4]) compared to the placebo group (Table 3).[6] All secondary migraine and headache event efficacy endpoints (e.g., days of acute migraine medication use and percentage of participants with at least a 50% reduction in migraine headache days per month) demonstrated a similar effect, and all endpoints except for mean change in headache (of any severity) hours per month for the 70 mg dose were statistically significant (Appendix B2).[6] The study did not report any quality of life or function outcomes. Adverse events were comparable between the active treatment groups and placebo group (Table 3 and Appendix B3).[6] This study did not report any subgroup findings.

Fremanezumab

Study Characteristics

One phase 2b RCT(Bigal et al.[7]) conducted among 264 participants at multiple sites in the U.S. and 1 phase 3 RCT (HALO CM[8]) conducted among 1,130 participants at multiple sites in North America and Europe evaluated fremanezumab. Bigal et al. compared monthly doses of 225 mg and 900 mg with a placebo,[7] whereas HALO CM compared monthly (225 mg) and quarterly (675 mg) doses to a placebo.[8] Both 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.[7,8] Both studies used an active treatment phase of 12 weeks and 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.[7,8]

Findings

Both RCTs reported statistically significant decreases in the primary efficacy endpoints (mean change in headache hours per month from baseline in Bigal et al.[7] and mean change in headache days per month from baseline in HALO CM[8]) for both active treatment groups compared to a placebo (Table 2). The secondary and exploratory migraine and headache event efficacy endpoints reported in Bigal et al. consistently demonstrated a favorable effect for both active treatment groups when compared to a placebo group, but not all findings were statistically significant.[7] The secondary migraine or headache efficacy endpoints reported in

HALO CM all demonstrated statistically significant decreases, consistent with the primary study endpoint.[8] HALO CM reported statistically significant decreases in the HIT-6 for both the monthly dose (mean difference from placebo -2.4) and the quarterly dose (mean difference from placebo -1.9).[8] Bigal et al. did not report any quality of life or function outcomes. In a subgroup of participants not taking concomitant preventive therapy, HALO CM 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.[8]

Findings were comparable between active treatment groups and the placebo group for serious adverse events and discontinuations due to adverse events in both RCTs (Table 2).[7,8] In Bigal et al., the percentage of participants with at least 1 treatment-related adverse event was higher in the active treatment groups (29% in the 225-mg dose group, 32% in the 900-mg dose group) compared to the placebo group (17%).[7] These percentages were more similar in HALO CM (51% in the 225-mg group, 49% in the 675-mg group, and 42% in the placebo group; Appendix Table B3).[8]

Episodic Migraine Prophylaxis

Table 4 provides the summary of findings (GRADE) for the primary research evidence for episodic migraine prophylaxis. We rated the evidence for mean migraine headache days per month as moderate quality for erenumab, fremanezumab, and galcanezumab (because of serious concerns about study limitations from risk of bias from manufacturer involvement) and low quality for eptinezumab (because of study limitations from risk of bias from manufacturer involvement, selective outcome reporting, and serious concerns for imprecision). We rated the evidence for adverse event outcomes as very low quality for all drugs (because of study limitations from the risk of bias from manufacturer involvement and very serious concerns for imprecision). Table 5 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for the 10 placebo-controlled randomized trials that reported on the use of eptinezumab,[9] erenumab,[10-12] fremanezumab,[13,14] or galcanezumab.[15-19] We assessed each individual study as fair methodological quality because of the risk of bias from manufacturer involvement; in addition, 1 RCT had selective outcome reporting.[9] Detailed evidence tables are in Appendix Tables B4 (study characteristics), B5 (efficacy outcomes), and B6 (adverse event outcomes).

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

Outcome	Quality of the Evidence	Relationship	Rationale
Eptinezumab			
Migraine days per month (1 RCT[9])	Low	Statistically significant improvements at 5 to 8 weeks, but not at 9 to 12 weeks compared to placebo	Downgraded 1 level for study limitations and 1 level for imprecision
Percentage with at least 50% reduction in number of migraine days per month (1 RCT[9])	Low	No significant difference compared to placebo	
HIT-6 (1 RCT[9])	Low	No significant difference compared to placebo	
Serious adverse events (1 RCT[9])	Very low	Similar percentage compared to placebo	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuation due to adverse events (1 RCT[9])	Very low	None observed in placebo or active treatment groups	
Erenumab			
Migraine days per month (3 studies[10-12])	Moderate	Statistically significant improvements with active doses compared to placebo	Downgraded 1 level for study limitations
Days with acute migraine medication use per month (3 RCTs[10-12])	Moderate		
Percentage with at least 50% reduction in number of migraine days per month (3 RCTs[10-12])	Moderate		
MIDAS score (2 RCTs[10,12])	Moderate		
Serious adverse events (3 RCTs[10-12])	Very low	Similar percentages for active doses and placebo	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuation due to adverse events (3 RCTs[10-12])	Very low		

Outcome	Quality of the Evidence	Relationship	Rationale
Fremanezumab			
Migraine days per month (2 RCTs[13,14])	Moderate	Statistically significant improvements with active doses compared to placebo	Downgraded 1 level for study limitations
Days with acute headache medication use per month (2 RCTs[13,14])	Moderate		
Percentage with at least 50% reduction in number of migraine days per month (2 RCTs[13,14])	Moderate		
MIDAS Score (2 RCTs[13,14])	Moderate		
Serious adverse events (2 RCTs[13,14])	Very low	Similar percentages for active doses and placebo	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (2 RCTs[13,14])	Very low		
Galcanezumab			
Migraine days per month (4 RCTs[15-19])	Moderate	Statistically significant improvements with active doses compared to placebo	Downgraded 1 level for study limitations
Days with acute headache medication use per month (2 RCTs[18,19])	Moderate		
Percentage with at least 50% reduction in number of migraine days per month (4 RCTs[15-19])	Moderate		
MIDAS Score (2 RCT[18,19])	Moderate		
Serious adverse events (4 RCTs[15-19])	Very low	Similar percentages for active doses and placebo	Downgraded 1 level for study limitations and 2 levels for imprecision
Discontinuations due to adverse event (3 RCTs[15-17,19])	Very low		

Notes. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used.
Abbreviations. CGRP: calcitonin gene-related peptide inhibitors; HIT-6: Headache Impact Test (6 item); MIDAS: Migraine Disability Assessment.

Table 5. Summary of Evidence: Placebo-Controlled Randomized Clinical Trials of CGRP Inhibitors for Episodic Migraine Prophylaxis

Study; Registration Number Trial Name	Dose, Frequency[a] and N Randomized	Primary Endpoint; Difference From Placebo (95% CI)	N (%) With at Least 1 Serious Adverse Event[b]	N (%) With Adverse Event Leading to Discontinuation
Eptinezumab				
Dodick et al., 2014[9] 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*)	NR
Erenumab				
Dodick et al., 2018[10] 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[11] 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[12] 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)
Fremanezumab				
Bigal et al., 2015[13] 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[14] NCT02629861	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)

Study, Trials Registration Number	Dose, Frequency[a] and N Randomized	Primary Study Endpoint; Difference From Placebo (95% CI or SE and P Value)	N (%) With at Least 1 Serious Adverse Event[b]	N (%) With Adverse Event Leading to Discontinuation
Galcanezumab				
Dodick et al., 2014[15] 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[16] Oakes et al., 2018[17] NCT02163993	120 mg SC = 70 300 mg SC = 67 Placebo = 137 Total N = 410[f]	Mean change in migraine days per month from baseline at weeks 9 to 12[g]; 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[18] 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*)[h] 240 mg: 0 (*0*)[h] Placebo: 2 (*0.5*)[h]
Skljarevski et al., 2018[19] NCT02614196 EVOLVE-2	120 mg SC[i] = 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. We calculated values in italics from data presented in article. [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 dose groups; these are not included because they are outside the FDA-approved dosing range. [f] Study also included 5-mg and 50-mg dose groups; these are not included because they are outside of the dosing range that is being considered for FDA approval based on phase 3 studies. [g] This was a secondary endpoint; the primary endpoint was the posterior probability of greater improvement in migraine days compared to placebo for at least 1 dose of at least 95%; this endpoint was met (posterior probability

99.6%). [h] Study only reported serious adverse events leading to discontinuation. [i] A loading dose of 240 mg was used for the first dose. Abbreviations. ARISE: A Phase 3, Randomized, Double-blind Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention; EVOLVE-1: Evaluation of LY2951742 in the Prevention of Episodic Migraine 1; IV: intravenous; NR: not reported; SC: subcutaneous; STRIVE: Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention.

Eptinezumab

Study Characteristics

One phase 2 RCT (Dodick et al.) conducted among 174 participants at multiple sites in the U.S. evaluated eptinezumab.[9] This study compared a single 1,000-mg intravenous dose with a placebo and used a 4-week run-in phase and a 12-week follow-up period for efficacy outcomes and a 24-week follow-up period for safety outcomes.[9] No concomitant regular use of preventive migraine medication was allowed within 3 months prior to screening or during the study period.[9]

Findings

The primary endpoints for this study were safety outcomes.[9] All efficacy outcomes reported were secondary, including the outcome the authors reported as their primary efficacy endpoint (mean change in monthly migraine days from baseline at 5 to 8 weeks).[9] 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.[9] Using data provided in the study, we calculated the CIs as -2.0 to 0.04; we calculated the P value as 0.06 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).[9] The authors observed no significant differences in the other reported efficacy outcomes (Appendix Table B5).[9] The percentage of participants with total and serious adverse events was similar between active treatment and placebo groups (Appendix Table B6).[9]

Erenumab

Study Characteristics

Two phase 3 RCTs (ARISE, N = 577[10]) and (STRIVE, N = 955[11]) and 1 phase 2 RCT (Sun et al., N = 267[12]), all conducted at multiple sites in North America and Europe, evaluated erenumab. All studies evaluated a monthly dose of 70 mg compared to a placebo; STRIVE[11] also evaluated a monthly dose of 140 mg. 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.[10-12] The double-blind active treatment phase was 12 weeks in 2 studies[10,12] and 24 weeks in 1 study.[11] ARISE[10] and STRIVE[11] allowed concomitant use of 1 migraine preventive treatment as long as use was stable prior to enrollment.

Findings

All 3 studies reported statistically significant decreases in the primary efficacy endpoint (mean change in monthly migraine days from baseline) for active doses compared to a placebo.[10-12]

The treatment effect ranged from -1.0 to -1.4 days for the 70-mg dose and was -1.9 days (95% CI, -2.3 to -1.4) for the 140-mg dose.[10-12] All 3 studies also demonstrated statistically significant decreases for the active treatment groups compared to the placebo group for the mean change in acute migraine medication use (mean difference from placebo ranging from -0.6 to -1.4) and in the percentage of participants with a 50% or greater reduction in mean number of migraine headache days per month (ORs ranging from 1.59 to 2.81; we calculated RRs ranging from 1.35 to 1.89).[10-12] Sun et al. also reported 12 additional migraine or headache event or symptom outcomes; findings from these additional outcomes were mixed (Appendix Table B5).[12]

Across the 3 studies, the study authors observed larger improvements for the active treatments compared to placebos on the 4 quality of life and function outcomes reported, but findings were mixed with respect to precision and statistical significance of the estimates.[10-12] These outcomes were secondary outcomes in all the studies, and the authors designed studies with sample sizes for adequate statistical power on the primary study endpoints.[10-12] ARISE[10] and Sun et al.[12] reported these outcomes using the HIT-6, MIDAS or modified MIDAS, and the MSQL instruments. ARISE reported statistically significant larger mean improvements for active treatment compared to a placebo for overall scores and for nearly all domain scores for these instruments.[10] Sun et al. also reported larger improvements for active treatment compared to a placebo; no differences were statistically significant.[12]

ARISE[10] and STRIVE[11] reported functional outcomes using the MPFID. Only ARISE reported the MPFID overall score; the study authors reported a statistically significant improvement for active treatment compared to a placebo (mean difference -1.4 [95% CI, -2.6 to -0.2]).[10] The authors of both studies observed statistically significant improvements for active treatment compared to a placebo on the 2 MPFID domain scores,[10,11] but findings were not statistically significant for the MPFID everyday activities domain in ARISE.[10] The ARISE authors reported on the percentage of participants with at least a 5-point improvement on each of the 2 MPFID domain scores; the percentage was higher in the active treatment group compared to the placebo group, but these findings were not statistically significant (Appendix Table B5).[10]

All 3 studies observed similar percentages of adverse events across all active dose and placebo groups (Appendix Table B6).[10-12] No studies reported findings for any subgroups of interest to this review.

Fremanezumab

Study Characteristics

One phase 2b RCT(Bigal et al.[13]) conducted among 297 participants at multiple U.S. sites and 1 phase 3 RCT (Dodick et al.[14]) conducted among 875 participants at multiple sites in 9 countries evaluated fremanezumab. Bigal et al. evaluated a monthly dose of 225 and a monthly dose of 675 mg compared to a placebo.[13] Dodick et al. evaluated a monthly dose of 225 mg and a quarterly dose of 675 mg.[14] 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.[13,14] 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.[13,14]

Findings

Both studies reported statistically significant decreases in the primary efficacy endpoint (mean change in monthly migraine days from baseline).[13,14] The mean difference from the placebo ranged from -1.3 days to -2.8 days across doses.[13,14] Authors of both studies reported a statistically significant reduction in days of acute headache medication use; the mean difference from the placebo across active doses ranged from -1.3 days to -1.8 days.[13,14] Dodick et al. reported a higher percentage of participants with a reduction of 50% or more in migraine headache days per month (RD compared to placebo 19.8% [95% CI, 12.1% to 27.6%] for 225-mg dose; 16.5% [95% CI, 8.9% to 24.1%] for 675-mg quarterly dose).[13] Both studies demonstrated statistically significant improvements in other secondary headache event or symptom endpoints (Appendix Table B4) with 1 exception (Dodick et al., mean change in days with nausea and vomiting for the 675-mg dose).[13,14] 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.[13,14]

Both studies reported changes in quality of life and function using the MIDAS instrument.[13,14] The authors of both studies observed a statistically significant improvement in the MIDAS overall score across all doses compared to a placebo.[13,14]

The percentage of participants reporting serious adverse events was similar across active dose and placebo groups in both studies (range 0% to 2.4%).[13,14] Dodick et al. reported somewhat higher percentages of treatment-related adverse events in the 2 active dose groups (47.6% for 225 mg; 47.1% for 675 mg quarterly) compared to the placebo group (37.2%).[14] Bigal et al. reported a similar percentage across treatment groups (range 23% to 27%).[13]

Galcanezumab

Study Characteristics

One phase 2 RCT (Dodick et al.[15] [N = 218]) and 1 phase 2b RCT (Skljarevski et al.,[16] Oakes et al.[17] [N = 274]), both conducted at multiple U.S. sites, evaluated galcanezumab. Two phase 3 RCTs evaluated galcanezumab[18,19]; one RCT (Stauffer et al., [EVOLVE-1, N = 862]) was conducted at multiple sites in North America and the other RCT (Skljarevski et al., [EVOLVE-2, N =915]) was conducted at multiple sites in North American, Europe, South America, and Asia. Dodick et al.[15] evaluated 150 mg every 2 weeks and Skljarevski et al. evaluated 120 mg and 300 mg every month but did not report migraine or headache event efficacy outcomes for the 300-mg dose.[16] EVOLVE-1 and EVOLVE-2 evaluated 120 mg and 240 mg every month.[18,19] All studies used a run-in phase (range 28 to 40 days) during which no study medications were administered.[15,16,18,19] The double-blind active treatment phase was 12 weeks in 2 studies[15,16] and 6 months in 2 studies.[18,19] No studies allowed concomitant migraine prophylaxis treatment.

Findings

All 4 studies reported statistically significant decreases in the mean change in monthly migraine days from baseline, which was the primary efficacy endpoint in 3 of the studies.[15,18,19] However, we note that 1 study reported findings using 90% CIs.[15] Across the 4 studies, the mean difference from a placebo ranged from -0.9 days to -2.0 days across doses.[15,16,18,19] Three studies also reported a statistically significantly higher percentage of participants reporting a 50% or greater reduction in migraine days for all active doses compared to a placebo. Dodick et al. reported an OR of 2.88 (90% CI, 1.78 to 4.69); we calculated the RR with a 95% CI as 1.56 (1.22 to 2.00).[15] EVOLVE-1 and EVOLVE-2 reported a similar treatment effect as Dodick et al., for both the 120-mg and 240-mg doses (Appendix Table B5).[18,19] The fourth study, Skljarevski et al., reported the percentage of participants with at least a 50% reduction in migraine days as 75.8% in the 120-mg dose group compared to 61.9% in the placebo group; the authors reported this difference as statistically significant (P = .03).[16] We calculated the RR as 1.22 (95% CI, 1.01 to 1.49). EVOLVE-1 reported on the change in days of acute headache medication use from baseline; the mean difference from placebo was -1.8 (95% CI, -2.3 to -1.3) for the 120-mg dose and -1.6 (95% CI, -2.1 to -1.1) for the 240-mg dose.[18] Similar findings were observed for this outcome in EVOLVE-2.[19] All studies also demonstrated statistically significant improvements in other secondary headache event or symptom endpoints (Appendix Table B5) with 1 exception (Skljarveski et al., mean change in headache days per month for 120 mg dose).

Across the 4 studies, multiple quality of life and functional outcomes were reported, but findings were mixed with respect to precision and statistical significance of estimates (Appendix 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. EVOLVE-1 and EVOLVE-2 reported statistically significant improvements on the MSQL (overall and domain-specific scores), the MIDAS, and the Patient Global Impression Survey (PGIS) for both active doses compared to a placebo.[18,19] As part of exploratory efficacy endpoints, Dodick et al. 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 around the estimates using available data.[15] Skljarevski et al. reported no significant difference in the MSQL overall score between either the 120-mg or 300-mg dose compared to a placebo (actual mean difference from the placebo not reported), but did report a statistically significant improvement on the HIT-6 for the 120-mg dose (calculated mean difference from placebo -2.7 [P = .04]) but not for the 300-mg dose (mean difference not reported and we were unable to calculate it using available data).[16]

All 4 studies observed similar percentages of adverse event outcomes across all active dose and placebo groups (Appendix Table B6).[15,16,18,19] No studies reported findings for any subgroups of interest to this review.

Findings from Systematic Reviews

We identified 2 systematic reviews for inclusion in this review.[20,21] The Institute for Clinical and Economic Review (ICER) published an evidence report in May 2018[20]; we assessed this review as good methodological quality. The Canadian Agency for Drugs and Technologies in Health (CADTH) published a report in February 2018[21]; we assessed this review as poor methodological quality because the study inclusion and exclusion criteria were not clearly stated, no literature flow diagram indicating how many studies were screened and excluded was provided, and the authors did not perform any quality assessment on the included studies.

Study Characteristics

The ICER review searched various sources through May 2, 2018, and included 11 trials for chronic migraine (1 erenumab, 2 fremanezumab, 8 for onabotulinum toxin A or topiramate) and 16 trials for episodic migraine (3 erenumab, 2 fremanezumab, 1 galcanezumab, and 10 other preventive therapies).[20] All CGRP inhibitor trials in the ICER review are included in our review of primary studies presented in the preceding sections.

The CADTH report searched various sources through December 18, 2017, and included results from 5 studies for chronic migraine and 10 studies for episodic migraine.[21] This review included studies that published results in press releases and conference abstracts and studies not yet completed, in addition to completed studies published in peer-reviewed literature. As a result, 2 additional studies for chronic migraine that were not included in our primary research review presented in the preceding sections were included in the CADTH report. This includes a phase 2 RCT comparing intravenous eptinezumab 100 mg or 300 mg to a placebo; the results were published in a conference abstract.[26] The clinical trials entry for this study reported the study completion date was November 2016.[27] The other study was a phase 3 RCT comparing subcutaneous galcanezumab 120 mg or 240 mg to a placebo. The estimated completion date for this study is May 2021.[28] For episodic migraine, the CADTH report included results from a phase 2 RCT comparing intravenous eptinezumab 100 mg or 300 mg to a placebo, which was published in a press release and conference abstract.[29]

Efficacy Findings: Chronic Migraine

The ICER report study authors conducted a network meta-analysis for the outcomes of 1) change in monthly migraine days per month, 2) days using acute medications, and 3) monthly headache days.[20] A network meta-analysis allows for an indirect comparison of therapies. Table 6 presents the pairwise comparisons of each drug and placebo. The authors reported greater reductions in these outcomes for all active treatments relative to a placebo, and most were statistically significant.[20] The magnitude of reductions relative to the placebo was similar for CGRP inhibitors and the other migraine preventive therapies, and no significant indirect comparisons between CGRP inhibitors and other drugs were observed for any of the 3 efficacy outcomes evaluated.[20]

The CADTH report qualitatively summarized findings across included studies. The report authors concluded that participants with chronic migraine who received active treatment had between 2 to 2.5 fewer migraine days each month compared to a placebo.[21]

Table 6. Outcomes for Various Drugs Relative to a Placebo From a Network Meta-analysis of Preventive Therapies for Chronic Migraine[20]

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]
Onabotulinum toxin A 155 U 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. Abbreviations. NR: not reported; U: unit. Source. Institute for Clinical and Economic Review. Calcitonin gene-related peptide (CGRP) inhibitors as preventive treatments for patients with episodic or chronic migraine: effectiveness and value. Evidence report. May 2018.

Efficacy Findings: Episodic Migraine

The ICER report study authors conducted a network meta-analysis for the outcomes of 1) change in monthly migraine days per month, 2) days using acute medications, and 3) percentage of participants reporting a 50% or more reduction in monthly migraine days.[20] Table 7 presents the pairwise comparisons from this analysis. 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.[20] 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.[20] 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.[20]

Table 7. Outcomes for Various Agents Relative to a Placebo From a Network Meta-analysis of Preventive Therapies for Episodic Migraine[20]

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]

Notes: [a] Results reported as statistically significant. Abbreviations. OR: odds ratio. Source. Institute for Clinical and Economic Review. Calcitonin gene-related peptide (CGRP) inhibitors as preventive treatments for patients with episodic or chronic migraine: effectiveness and value. Evidence report. May 2018.

The CADTH report qualitatively summarized findings across included studies. The report authors concluded that participants with episodic migraine taking a CGRP inhibitor had between 1 and 2 fewer migraine days each month compared to a placebo.[21]

Adverse Event Findings: Chronic and Episodic Migraine

The ICER report authors conducted network meta-analyses for all-cause discontinuations, discontinuations for adverse events, and frequency of serious adverse events.[20] Discontinuations because of adverse events ranged from 0% to 30% between 4 and 26 weeks among participants in the placebo group and from 0% to 5% from 12 and 24 weeks for the CGRP inhibitor group, and from 0% to 49% for other migraine preventive medications.[20]

The ICER report authors also conducted network meta-analyses for 1) all-cause discontinuations, 2) discontinuations for adverse events, and 3) frequency of serious adverse events.[20] No significant differences from a placebo in all-cause discontinuation were observed for any drug (CGRP or other).[20] Participants allocated to topiramate (100 mg or 200 mg daily), amitriptyline

(75 to 150 mg per day), or onabotulinum toxin A (100 to 200 U quarterly) were statistically significantly more likely to discontinue treatment because of adverse events compared to the placebo group (ORs ranged from 2.6 to 3.7).[20] Participants allocated to CGRP inhibitors, propranolol, and topiramate 50 mg per day had no significant differences in the frequency of discontinuation compared to the placebo group (ORs ranged from 1.0 to 1.7).[20] Amitriptyline was the only drug with a significantly higher frequency of serious adverse events compared to the placebo.[20] No significant differences between CGRP inhibitors and other active drugs were observed in indirect comparisons for all-cause discontinuations in chronic migraine.[20] 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.[20] For both chronic and episodic migraine, CGRP inhibitors had no statistically significant differences with other active treatments for discontinuations because of adverse events or in the frequency of serious adverse events in indirect comparisons.[20]

The CADTH report authors summarized the frequency of serious adverse events as 1% to 2% in the active treatment groups and stated that withdrawal because of adverse events was infrequent.[21]

Ongoing Studies

We identified 15 ongoing phase 2 or 3 studies of CGRP inhibitors, all of which are placebo-controlled RCTs; most but not all studies are blinded (Table 8). Three studies are on eptinezumab (2 for chronic and 1 for episodic migraine), 3 studies are on erenumab (all for episodic), 5 studies are on fremanezumab (1 episodic, 1 chronic, 3 combined), and 4 studies are on galcanezumab (1 chronic, 1 episodic, 2 combined). Eleven studies have a primary endpoint that is an efficacy outcome and 4 studies have a primary endpoint that is a safety outcome. Most studies have planned follow-up of between 12 weeks and 24 weeks, although some studies focused on safety outcomes have follow-up planned at 1.5 years.

Table 8. 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				
NCT02559895 A Multicenter Assessment of ALD403 in Frequent Episodic Migraine (PROMISE 1) Phase 3	Dose 1, 2, 3 Placebo; Blinded	N = 900 (Actual) 12 to 56 weeks	December 2017 (Actual)	Change in frequency of migraine days at 12 weeks
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
NCT02275117 A Multicenter Assessment of ALD403 in Chronic Migraine Phase 2	Dose 1, 2, 3, 4 Placebo; Blinded	N = 617 (Actual) 12 to 49 weeks	November 2016 (Actual)	Change in migraine days from baseline to week 12
Erenumab				
NCT02630459 A Safety and Efficacy Study to Evaluate AMG 334 in Migraine Prevention (Episodic) Phase 2	Dose 1, 2, 3 Placebo; Blinded	N = 475 (Actual) 24 weeks	June 2019 (Estimated)	Change in mean monthly migraine days from baseline to 24 weeks
NCT03333109 Study of Efficacy and Safety of AMG 334 in Adult Episodic Migraine Patients (EMPOwER) Phase 3	Dose 1, 2 Placebo; Blinded	N = 880 (Estimated) 12 weeks to 24 weeks	February 2020 (Estimated)	Change in mean monthly migraine days from baseline to 12 weeks
NCT03096834 A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies (LIBERTY) (Episodic) Phase 3	Dose 1 Placebo; Blinded	N = 220 (Estimated) 12 weeks	January 2021	Percentage of participants with a 50% reduction of monthly migraine days from baseline to week 12

Registry Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Fremanezumab				
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	December 2018	Change in mean monthly migraine days from baseline to 12 weeks
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	Percentage of participants with adverse events at 533 ± 15 days
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	April 2019	Change in mean monthly headache days of at least moderate severity from baseline to 12 weeks
NCT03308968 An Efficacy and Safety Study of Fremanezumab in Adults With Migraine (FOCUS) Phase 3	Dose 1, 2 Placebo; Blinded	N = 838 (Actual) 12 weeks to 24 weeks	September 2019	Change in mean monthly migraine days 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)	February 2020	Percentage of participants with adverse events at 562 days

Registry Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Galcanezumab				
NCT02959177 A Study of LY2951742 (Galcanezumab) in Japanese Participants With Episodic Migraine Phase 2	Dose 1, 2 Placebo; Blinded	N = 451 (Estimated) 6 months	February 2019	Change in monthly migraine days from baseline to month 6
NCT02614261 Evaluation of Galcanezumab in the Prevention of Chronic Migraine (REGAIN) Phase 3	120 mg, 240 mg Placebo; Blinded	N = 1,113 3 months	May 2021	Change in monthly migraine days from baseline to month 3
NCT02959190 A Study of LY2951742 (Galcanezumab) in Japanese Participants With Migraine Phase 3	Dose 1, 2 Open label	N = 300 (Estimated) 12 months	August 2019	Percentage of participants who discontinue treatment by month 12
NCT02614287 A Safety Study of Galcanezumab in Participants With Migraine, With or Without Aura Phase 3	120 mg, 240 mg Open label	N = 270 12 months	December 2018	Percentage of participants who discontinue treatment by month 12

Notes. [a] As indicated on Clinicaltrials.gov.

Discussion

For chronic migraine, the evidence for erenumab and fremanezumab suggests a favorable treatment effect compared to a placebo at least through 12 weeks of follow-up. For episodic migraine, the evidence for erenumab, fremanezumab, and galcanezumab suggests a favorable treatment effect compared to a placebo at least through 12 weeks of follow-up, and longer in some studies. Erenumab, fremanezumab, and galcanezumab appear safe, with relatively few serious adverse events and discontinuations because of adverse events. 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 of generally 12 to 24 weeks.

The evidence for eptinezumab is limited to only 1 RCT for episodic migraine. Although the evidence from this study suggests that the drug is relatively safe, the authors did not observe any significant difference compared to a placebo in monthly migraine days at 12 weeks. The

estimates from this study were imprecise, and the study might not have had an adequate sample size for evaluating efficacy outcomes.

The magnitude of the treatment effect of CGRP inhibitors is modest across all studies, generally between 0.9 to 2.8 days reduction compared to placebos, with slightly larger treatment effects among participants with chronic migraine compared to episodic migraine. The magnitude of the treatment effect of CGRP inhibitors is similar to the treatment effects of other available migraine preventive agents.[20] 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, 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.[30] All but 1 of the studies reporting this outcome have between-group differences of more than 2 points compared to a placebo, suggesting a clinically important improvement.

Across the body of evidence, all studies were of fair methodological quality and most studies were adequately statistically powered for most of the efficacy outcomes reported. 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. 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. All studies were industry sponsored, some authors were employed by the manufacturer, and non-employee 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, recent findings from a Cochrane systematic review suggest that industry sponsorship is associated with more favorable results than sponsorship by other sources.[31]

We identified 15 ongoing studies; all of which are placebo-controlled and will offer additional evidence on efficacy up to 24 weeks and safety up to 1.5 years. We identified no ongoing studies that compare CGRP inhibitors to each other or another migraine prevention therapy.

Limitations of the Evidence

Most of the included trials 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. 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; 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 prevention drugs, and 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.

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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,* and *CGRP inhibitors*. We did not limit searches of evidence sources by any dates.

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
- Ovid Medline
- Veterans Administration Evidence-based Synthesis Program (ESP)

We conducted gray literature searches of Google and Google Scholar using the following search terms *eptinezumab*, *erenumab*, *fremanezumab*, *galcanezumab*, *ALD403*, *Aimovig*, *AMG 334, TEV-48125*, *LBR-101*, *LY2951742,* and *CGRP inhibitors*.

Ovid Medline Search Strategy

Database: Ovid MEDLINE(R) <1946 to July Week 1 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 13, 2018>

Search Strategy:

1. Eptinezumab.mp.
2. ALD403.mp.
3. Erenumab.mp.
4. Aimovig.mp.
5. AMG 334.mp.
6. Fremanezumab.mp.
7. TEV-48125.mp.
8. LBR-101.mp.
9. Galcanezumab.mp.
10. LY2951742.mp.
11. CGRP inhibitors.mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Limit 12 to English language
14. Animals/

15. Humans/
16. 14 not 15
17. 12 not 16

Cochrane Library Search Strategy

Database: Cochrane Reviews and Protocols through July 31, 2018

1. Calcitonin gene-related peptide inhibitors
2. CGRP inhibitors
3. Migraine headache prevention
4. Migraine headache prophylaxis
5. 1 or 2 or 3 or 4

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,* and *CGRP inhibitors*:

- ClinicalTrials.gov
- ISRCTN Registry
- WHO-ICTRP Registry
- U.S. Food and Drug Administration
- Teva Pharmaceuticals
- Amgen
- Novartis
- Eli Lilly and Company
- Arteaus Therapeutics

Inclusion Criteria

Populations

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

Comparators

- CGRP inhibitors compared to each other (head-to-head)
- Other migraine prophylaxis (i.e., selected antidepressants [amitriptyline and venlafaxine], anticonvulsants [divalproex, topiramate, and valproic acid and derivatives], beta blockers [propranolol and metoprolol], and onabotulinum toxin A)
- 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 (e.g., total adverse events, treatment-related events [e.g., injection site pain or erythema, liver toxicity])
- Serious adverse events (i.e., 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)
- Withdrawals due to adverse events

Setting

- Inpatient
- Outpatient/clinic
- Office
- Home

Study Designs

- Randomized controlled trials (RCTs)
- Prospective cohort studies
- Systematic reviews (with or without a meta-analysis)

Exclusion Criteria

We excluded studies if they were not published in English.

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.[1,2] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the methodological quality of a study, a third rater resolved the disagreement.

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).[4,5] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. 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[7] NCT02021773	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 onabotulinum toxin A 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

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
Silberstein et al. 2017[8] HALO CM NCT02621931	Phase 3 double-blind, parallel-assignment RCT Fremanezumab 225 mg[b] SC = 379 675 mg quarterly SC = 376 Placebo SC = 375 Total N = 1,130	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) 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	4 weeks 12 weeks 12 weeks Use of 1 preventive medication if use was stable for 2 months prior to run-in; this was permitted for up to 30% of enrolled patients	132 sites in 9 countries, including academic neurology clinics, private practices, for-profit research clinics, specialty headache clinics, primary care clinics, and other outpatient clinics 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
Silberstein et al. 2017[8] HALO CM NCT02621931 (continued)		*Exclusion:* Used onabotulinum toxin A 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		
Tepper et al., 2017[6] NCT02066415	Phase 2 double-blind, parallel-assignment RCT Erenumab 70 mg SC = 191 140 mg SC = 190 Placebo SC = 286 Total N = 667	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) 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)	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 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
Tepper et al., 2017[6] NCT02066415 (Continued)		*Inclusion:* Men and women ages 18 to 65 with a history of chronic migraine (with or without aura) defined as ≥ 15 headache days per month in prior 3 months and during run-in phase, of which ≥ 8 were migraine days; ≥ 80% compliance with electronic headache diary during run-in phase *Exclusion:* Migraine onset occurred after age 50 in individuals with history of cluster headache, hemiplegic migraine, or chronic migraine with continuous pain; used > 3 preventive medication categories without efficacy, overused acute medication during run-in phase or used a butalbital-containing analgesic on > 6 days during 3 months prior to run-in, used botulinum toxin within 4 months prior to start of run-in phase		

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. RCT: randomized controlled trial; ICHD-3: International Classification of Headache Disorders, 3rd edition; SC: subcutaneous.

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[7]		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)4	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

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Silberstein et al., 2017[8] 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 headache days 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 migraine days 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)
Mean change in headache days 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 headache days 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[c] from baseline (1,121)	Week 12	-2.4 (0.5; *P* < .001)	-1.9 (0.5; *P* < .001)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Tepper et al., 2017[6]		Erenumab 70 mg	Erenumab 140 mg
Migraine or Headache Event (N analyzed)		*Mean difference from placebo (95% CI; P value)*	
Mean change in migraine days 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 migraine days 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)		*Mean difference from placebo*	
NR	NR	NR	NR

Notes. Outcomes that are italicized are values we calculated based on data provided in the study report. [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]HIT-6 scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability. Abbreviations. CI: confidence interval; HIT-6: Headache Impact Test; NR: not reported; OR: odds ratio; RD: risk difference; RR: risk ratio; SE: standard error.

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

Outcome	Treatment Groups[a]		
Bigal et al., 2015[7]	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	

Outcome	Treatment Groups[a]		
Silberstein et al., 2017[8] 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 1 drug hypersensitivity 1 uterine leiomyoma 1 migraine	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
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)

Outcome	Treatment Groups[a]		
Tepper et al., 2017[6]	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. [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.

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
Bigal et al., 2015[13] NCT02025556	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 migraine days 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 of headache per month with at least 8 of these fulfilling migraine criteria, compliance with electronic headache diary of at least 80% during run-in phase	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
Bigal et al., 2015[13] NCT02025556		*Exclusion:* Chronic migraine, used opioids or barbiturates for more than 4 days during run-in, onabotulinum toxin A use within 6 months, used 3 or more preventive medications without efficacy, clinically significant medical or psychiatric conditions		
Dodick et al., 2018[10] ARISE NCT02483585	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 migraine days 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 migraine days per month and < 15 headache days per month for ≥ 12 months	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

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[10] ARISE NCT02483585 (continued)		*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		
Dodick et al., 2018[14] NCT02629861	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 migraine days 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
Dodick et al., 2018[14] NCT02629861 (continued)		*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 onabotulinum toxin A 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		

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., 2014[15] NCT01625988	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 migraine days per month, by group: 150 mg: 6.7 (2.4) Placebo: 7.0 (2.5) *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 migraine headache days per month, at least 80% compliance of daily electronic headache entries during run-in phase	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
Dodick et al., 2014[15] NCT01625988 (continued)		*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 botulinum toxin A), and clinically significant medical or psychiatric conditions		
Dodick et al., 2014[9] NCT01772524	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 migraine days per month, by group: 1,000 mg: 8.4 (2.1) Placebo: 8.8 (2.7)	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
Dodick et al., 2014[9] NCT01772524 (continued)		*Inclusion:* Ages 18 to 55 with at least a 1-year history of migraine according to ICHD-2, migraine onset prior to age 50, between 5 and 14 migraine days in each of the prior 3 months; and between 5 and 14 migraine days 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		

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
Goadsby et al., 2017[11] STRIVE NCT02456740	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 migraine days 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, migraine onset prior to age 50, and between 4 and 15 migraine days and fewer than 15 headache days per month and at least 80% compliance of daily electronic headache entries during run-in phase	4 weeks 24 weeks 24 weeks[c] Use of 1 medication was permitted if the dose 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
Goadsby et al., 2017[11] STRIVE NCT02456740 (continued)		*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		
Skljarevski et al., 2018[19] EVOLVE-2 NCT02614196	Phase 3, multi-center, double-blind RCT Galcanezumab 120 mg SC[d] = 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 migraine days per month, by group: 120 mg: 9.07 (2.9) 240 mg: 9.06 (2.9) Placebo: 9.2 (3.0)	30 to 40 days 6 months 4 months Ongoing preventive therapy not allowed (wash-out 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
Skljarevski et al., 2018[19] EVOLVE-2 NCT02614196 (continued)		*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 headache days, 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 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[16] Oakes et al., 2018[17] NCT02163993	Phase 2b double-blind, parallel-assignment RCT Galcanezumab[e] 5 mg SC = 68 50 mg SC = 68	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)	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
Skljarevski et al., 2018[16] Oakes et al., 2018[17] NCT02163993 (continued)	120 mg SC = 70 300 mg SC = 67 Placebo = 137 Total N = 410	Baseline migraine days 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 migraine days 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 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		

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
Stauffer et al., 2018[18] EVOLVE-1 NCT02614183	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 migraine days 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 migraine days 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
Stauffer et al., 2018[18] EVOLVE-1 NCT02614183 (continued)		*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[12] NCT01952574	Phase 2 double-blind, parallel-assignment RCT Erenumab[f] 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 migraine days per month, by group: 70 mg: 8.6 (2.5) Placebo: 8.8 (2.7)	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
Sun et al., 2016[12] NCT01952574 (continued)		*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 migraine days and fewer than 15 headache days (≥ 50% of headache days being migraine days) 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 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] A loading dose of 240 mg was used for the first dose. [e] Outcomes from the 5-mg and 50-mg doses 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. [f] Outcomes from the 7-mg and 21-mg doses are not included in this review because they are outside of the FDA-approved dose range for this agent. Abbreviations. ICHD-2 or -3: International Classification of Headache Disorders, 2nd or 3rd revision; IV: intravenous; SC: subcutaneous.

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

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Bigal et al., 2015[13]		Fremanezumab 225 mg	Fremanezumab 675 mg
Migraine or Headache Event (N analyzed)		*Mean difference from placebo (95% CI)*	
Mean change in migraine days 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 headache (of any severity) days 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 headache (moderate to severe) days 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)
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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Bigal et al., 2015[13] (continued)		Fremanezumab 225 mg	Fremanezumab 675 mg
Patients with a 50% or greater reduction in migraine days 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 migraine days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2018[10] ARISE		Erenumab 70 mg
Migraine or headache events (N analyzed)		*Mean difference from placebo (95% CI; P value)*
Mean change in migraine days 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 migraine days 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)*
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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2018[10] ARISE (continued)		Erenumab 70 mg
Mean change in mMIDAS score[b] from baseline (570)	Weeks 9 to 12	-1.7 (-3.1 to -0.3; *P* = .02)
Mean change in mMIDAS absenteeism domain score[b] from baseline (570)	Weeks 9 to 12	-0.8 (-1.7 to 0.0; *P* = .06)
Mean change in mMIDAS 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[14]		Fremanezumab 225 mg	Fremanezumab 675 mg quarterly
Migraine or headache events (N analyzed)		*Mean difference from placebo (95% CI; P value)*	
Mean change in migraine days 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 migraine days 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)
Percentage of participants with 50% or greater reduction in migraine days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2014[15]		Galcanezumab 150 mg every 2 weeks
Migraine or Headache Events (N analyzed)		*Mean difference from placebo (90% CI; P value)*
Mean change in migraine days per month from baseline (217) [Primary study endpoint]	Weeks 9 to 12	-1.2 (-1.9 to -0.6; *P* = .003)
Mean change in headache days per month from baseline (217)	Weeks 9 to 12	-1.3 (-2.1 to -0.5; *P*= .01)
Mean change in migraine or probably migraine headache days 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 migraine headache days 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 migraine headache days 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 migraine headache days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2014[15] (continued)		Galcanezumab 150 mg every 2 weeks
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
Dodick et al., 2014[9]		Eptinezumab 1,000 mg
Migraine or Headache Events (N analyzed)		*Mean difference from placebo (95% CI)*
Mean change in migraine days per month from baseline (158) [Primary study endpoint][e]	Weeks 5 to 8	-1.0 (-2.0 to 0.1)[f]
Mean change in migraine days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2014[9] (continued)		Eptinezumab 1,000 mg
Migraine or Headache Events (N analyzed) (continued)		*Mean difference from placebo (95% CI)*
Mean change in headache days 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 migraine headache days 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 migraine headache days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Dodick et al., 2014[9] (continued)		Eptinezumab 1,000 mg
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 migraine headache days per month from baseline (143)	Weeks 9 to 12	1,000 mg: 11 (16) Placebo: 0 (0) RD 16% (8% to 27%) 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Goadsby et al., 2017[11] STRIVE		Erenumab 70 mg	Erenumab 140 mg
Migraine or Headache Events (N analyzed)		*Mean difference from placebo (95% CI)*	
Mean change in migraine days 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 migraine headache days 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* < .0001) RR 1.63 (1.30 to 2.03, *P* < .0001)	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* < .0001) RR 1.89 (1.52 to 2.33, *P* < .0001)
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)
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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Skljarevski et al., 2018[19] EVOLVE-2		Galcanezumab 120 mg	Galcanezumab 240 mg
Migraine or Headache Event (N analyzed)		*Mean difference from placebo*	
Mean change in migraine days 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 migraine headache days 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 migraine headache days 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 migraine headache days 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)*
Functioning and Quality of Life (N analyzed)		*Mean difference from placebo*	
Mean change from baseline in the Role Function-Restrictive (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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Skljarevski et al., 2018[19] EVOLVE-2 (continued)		Galcanezumab 120 mg	Galcanezumab 240 mg
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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Skljarevski et al., 2018[16] Oakes et al., 2018[17]		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 migraine headache days compared to placebo[i] [Primary study endpoint] (258)	Weeks 9 to 12	-4.8[j] (-5.4 to 4.2); 99.6%	NR
Mean change in migraine days 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 migraine days per month from baseline (196)	Weeks 9 to 12	*-1.9 (P < .001)*	NR
Mean change in probable migraine days per month from baseline (196)	Weeks 9 to 12	*-0.4 (P = .049)*	NR
Mean change in headache days 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

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Skljarevski et al., 2018[16] Oakes et al., 2018[17](continued)		Galcanezumab 120 mg	Galcanezumab 300 mg
Percentage of participants with 50% or greater reduction in the mean number of migraine headache days 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) RR: 1.22 (1.01 to 1.49, *P* = .07)	NR
Percentage of participants with greater than 100% reduction in the mean number of migraine headache days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Stauffer et al., 2018[18] EVOLVE-1		Galcanezumab 120 mg	Galcanezumab 240 mg
Migraine or Headache Events (N analyzed)		*Mean difference from placebo (95% CI)*	
Mean change in migraine headache days per month from baseline (843)	Month 1 to 6	-1.9 (-2.5 to -1.4, *P* < .001)	-1.8 (-2.3 to -1.2, *P* < .001)
Mean change in migraine headache days with acute medication use per month from baseline (843)	Month 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)	Month 1 to 6	*-14.0 (P < .001)*	*-13.6 (P< .001)*
Percentage of participants with 50% or greater reduction in the mean number of migraine headache days 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 migraine headache days 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 migraine headache days 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 migraine headache days 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

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]	
Stauffer et al., 2018[18] EVOLVE-1 (continued)		Galcanezumab 120 mg	Galcanezumab 240 mg
Functioning and Quality of Life (N analyzed)		*Mean difference from placebo (SE)*	
Mean change in MSQL score[h] from baseline (NR)	Month 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)	Month 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)	Month 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)	Month 4 to 6	8.3 (1.5, *P* < .001)	7.2 (1.5, *P* < .001)
Mean change in MIDAS score[b] from baseline (NR)	Month 4 to 6	*-6.3 (NR, P < .001)*	*-5.2 (NR, P < .002)*
Mean change in PGI-S score[k] from baseline (750)	Month 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[12]		Erenumab 70 mg
Migraine or Headache Events (N analyzed)		*Mean difference from placebo (95% CI)*
Mean change in migraine (including probable migraine) days 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 headache (including migraine, probable migraine, and non-migraine headache) days 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)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Sun et al., 2016[12] (continued)		Erenumab 70 mg
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)
Monthly incidence of migraine (including probably migraine) days 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 migraine (including probable migraine) days 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[l] from baseline (244)	Week 12	-1.4 (-3.0 to 0.2; *P* = .08)

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups[a]
Sun et al., 2016[12] (continued)		Erenumab 70 mg
Functioning and Quality of Life (N analyzed) (continued)		*Mean difference from placebo (95% CI)*
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[m] from baseline (227)	Week 12	-2.2 (-5.0 to 0.7; *P* = .13)
Mean change in MIDAS question B response[n] from baseline (227)	Week 12	-0.3 (-0.8 to 0.1; *P* = .18)

Notes. We calculated values in italics from data presented in article. [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] 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. [j] The corresponding change in migraine headache days in the placebo group was -3.7 (90% Bayesian credible interval -4.1 to -3.2). [k] PGI-S scores range from 1 to 7, with higher scores indicating a greater severity of illness. [l] PROMIS pain interference scores range from 41.0 to 78.3, with higher scores indicating a greater degree of interference. [m] Responses to MIDAS question A range from 0 to 90, with higher responses indicating a higher frequency of headaches. [n] Responses to MIDAS question B range from 0 to 10, with higher responses indicating a greater degree of headache-related disability. Abbreviations. HIT-6: Headache Impact Test; (m)MIDAS: (Modified) Migraine Disability Assessment; MPFID: Migraine Physical Function Impact Diary; MSQL: Migraine-specific Quality of Life Questionnaire; OR: odds ratio; PGI-S: Patient Global Impression Survey; PROMIS: Patient Reported Outcomes Measurement Information System; RD: risk difference; RR: risk ratio.

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

Outcome	Treatment Groups[a]		
Bigal et al., 2015[13]	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		

Outcome	Treatment Groups[a]	
Dodick et al., 2018[10] 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 1 uterine leiomyoma	3 (1.1)/3 1 migraine 1 intervertebral disc protrusion 1 urinary tract infection
N (%) with treatment-related liver injury	Treatment did not result in any observable effect on liver enzymes.	

Outcome	Treatment Groups[a]		
Dodick et al., 2018[14]	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

Outcome	Treatment Groups[a]	
Dodick et al., 2014[15]	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.	

Outcome	Treatment Groups[a]	
Dodick et al., 2014[9]	Placebo	Eptinezumab 1,000 mg IV single dose
N (%) with at least 1 adverse event	43 (52)	46 (57)
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.	

Outcome	Treatment Groups[a]		
Goadsby et al., 2017[11] 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 post-traumatic 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.		

Outcome	Treatment Groups[a]		
Skljarevski et al., 2018[19] 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

Outcome	Treatment Groups[a]		
Skljarevski et al., 2018[16] Oakes et al., 2018[17]	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)
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.		

Outcome	Treatment Groups[a]		
Stauffer et al., 2018[18] 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[12]	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)	
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: NR: not reported. Notes. [a] All treatments and placebos administered monthly unless otherwise specified

Appendix C. Bibliography of Included Studies

1. Bigal ME, Dodick DW, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol.* 2015;14(11):1081-1090. doi: https://dx.doi.org/10.1016/S1474-4422(15)00249-5.

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Appendix D. Bibliography of Excluded Studies

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