Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value

Final Evidence Report

July 3, 2018

Prepared for

ICER Staff and Consultants	University of Illinois, Chicago Modeling Group
Alexandra G. Ellis, PhD Senior Scientist, HTA and Economic Evaluation Institute for Clinical and Economic Review **Ifeoma Otuonye, MPH** Research Lead, Evidence Synthesis Institute for Clinical and Economic Review **Varun Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Matt Seidner, BS** Program Manager Institute for Clinical and Economic Review **David Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Surrey M. Walton, PhD** Associate Professor of Pharmacy Department of Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago College of Pharmacy **Todd A. Lee, PhD, PharmD** Professor and Interim Head Department of Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago College of Pharmacy **Danny Quach, PharmD** Graduate Student Department of Pharmacy Systems, Outcomes and Policy University of Illinois at Chicago College of Pharmacy

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About ICER

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical and patient advocacy experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/cgrp-stakeholder-list/

Expert Reviewers

Meghan Buzby, MBA
Executive Director
American Migraine Foundation
No personal conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers. The AMF receives funding from Allergan, Amgen, Avanir, electroCore, Eli Lilly, Promius, and Teva for the operation of its American Registry for Migraine Research (ARMR) database. Note: Meghan Buzby reviewed only Sections 1 and 5 of this document.

Andrew D. Hershey, MD, PhD, FAHS
Endowed Chair and Director of Neurology, Division of Neurology, Cincinnati Children's Hospital Medical Center; Professor of Pediatrics and Neurology, University of Cincinnati College of Medicine; Headache Medicine Specialist
Dr. Hershey is or will be an investigator for manufacturer-sponsored clinical trials of CGRP inhibitors' use in adolescents (Amgen, Eli Lilly, and Teva); funding for these trials will go to the Cincinnati Children's Hospital and does not affect Dr. Hershey's salary or compensation.

Annette Langer-Gould, MD, PhD
Regional Lead for Clinical and Translational Neuroscience
Southern California Permanente Medical Group, Kaiser Permanente
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers

Sonja B. Potrebic, MD, PhD
Residency Program Director, Headache Specialist, and Co-Assistant Chief of Neurology
Southern California Permanente Medical Group, Kaiser Permanente
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

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List of Acronyms Used in this Report

AAN	American Academy of Neurology
AE	Adverse event
AHS	American Headache Society
BASH	British Association for the Study of Headache
BSCA	Blue Shield of California
CGRP	Calcitonin-related gene peptide
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CrI	Credible interval
DCHS	California Department of Health Care Services
ED	Emergency department
EF	Emotional function
FDA	US Food and Drug Administration
HCUP	Healthcare Cost and Utilization
HIT-6	Headache Impact Test
ICHD	International Classification for Headache Disorders
LCD	Local coverage determination
MIDAS	Migraine Disability Assessment
MSQ	Migraine-Specific Quality of Life Questionnaire
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NCD	National coverage determination
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open-label extension
OR	Odds ratio
PICOTS	Population, interventions, comparisons, outcomes, timing, setting, and study design
QALY	Quality-adjusted life year
RCT	Randomized clinical trial
RFR	Role function-restrictive
RFP	Role function-preventive
SAE	Serious adverse event
SE	Standard error
UHC	United Healthcare
US	United States
USPSTF	United States Preventive Services Task Force
WTP	Willingness-to-pay

Executive Summary

Background

Migraine is a common, recurrent headache disorder that affects approximately 20% of women and 6-10% of men in the United States (US).[1,2] Migraine is among the top 10 causes of years lived with disability.[3,4] For many patients, migraine is a mild intermittent problem controlled with oral analgesics. For patients with severe disease, migraine can lead to greater disability. When patients experience a migraine, they may feel moderate-to-severe pain and other symptoms (e.g., nausea, vomiting, or sensitivity to light or to sound), have a reduced ability to function, or require bed rest.[1] Some patients with migraine experience migraine with aura (visual, sensory, speech/language, motor, brainstem, or retinal symptoms). Between migraine attacks, pain and other symptoms may remain, and patients' neurological function may not return to normal (i.e., pre-headache).[5] Hence, for some patients, the duration of impairment may be longer than the migraine attack itself, which can lead to ongoing disability.[6-8] In patients with more severe disease, migraine also may affect school, employment, choice of leisure activities and foods, or interpersonal relationships.[9-11] In addition, patients with migraine feel stigmatized, which may disrupt quality of life and ability to work.[12]

Patients with migraine can be diagnosed with chronic migraine, which is characterized by 15 or more headache days per month for at least three months, with migraine features present on at least eight days per month.[13] Migraine not subclassified as chronic migraine has been called episodic migraine, although this term is not a clinical diagnosis. In the US, approximately 10% of patients with migraine have chronic migraine.[1,14]

Despite its high prevalence and impairment, migraine is often not recognized or effectively treated.[14,15] Patients typically try multiple therapies, including non-pharmacologic therapies (e.g., exercise, changes in diet, relaxation techniques, cognitive behavioral therapy[6]) and pharmacologic therapies. Pharmacologic therapies can be categorized broadly into those used for treatment once symptoms have started ("acute" or "abortive" medications) and those used to decrease the frequency or severity of migraines ("preventive" or "prophylactic" therapies). Although there are no strict guidelines on who should receive preventive therapy, those who have four or more days with headaches per month with some impairment may be considered candidates for preventive therapy.[1] Effective preventive pharmacologic therapies include some antidepressants (amitriptyline, venlafaxine), anti-seizure medications (divalproex sodium, sodium valproate, topiramate), and beta-blockers (propranolol, metoprolol).[16] Patients with chronic migraine may also use onabotulinum toxin A (Botox®, Allergan plc) injections for prevention.[17] Patients on preventive therapy frequently discontinue or switch treatments due to lack of efficacy or tolerability.[6] Because of a delayed response in many of these therapies, adequate therapeutic trials

of preventive therapies may require two to six months of treatment.[18] Without adequate treatment, patients with episodic migraine are more likely to progress to chronic migraine.[19]

The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation, and CGRP has been observed to increase during a migraine.[20-22] In May 2018, erenumab (Aimovig™ Amgen, Inc. and Novartis AG), a fully human monoclonal antibody that binds to the CGRP receptor, was approved by the US Food and Drug Administration (FDA) as a preventive therapy in both episodic and chronic migraine patients.[23,24] Fremanezumab (Teva Pharmaceuticals) and galcanezumab (Eli Lilly and Company), two humanized monoclonal antibodies that target the CGRP ligand, have also been studied in migraine patients,[25-28] with a decision by the FDA expected in the second half of 2018.[29,30] The potential use of CGRP inhibitors as a preventive therapy has generated great interest from clinicians, patients, and their families. Nevertheless, uncertainties remain regarding the effectiveness of CGRP inhibitors compared with existing preventive therapies and with each other, and how well the cost of CGRP inhibitors will align with patient benefits. This report reviews the clinical evidence and potential economic impact of CGRP inhibitors for chronic and episodic migraine.

Insights Gained from Discussions with Patients and Patient Groups

Below, we provide a summary of the main themes from discussions with patients and individual patient submissions. We note that these themes may not represent the experiences of all patients with migraine, particularly those who are less burdened by the condition.

Migraine prevents patients from having normal lives:

- The pain and other symptoms from migraine attacks can last from hours to days.
- Migraine alters patients' decisions, and many patients do not plan or commit to future events, including joining the workforce, because of the uncertainty surrounding when the next attack will occur.
- Living and working spaces need to be adapted (e.g., installation of black-out curtains)
- Patients frequently reported feeling frustrated, depressed, defeated, isolated, or a burden to society; some patients experience suicidal thoughts.
- Patients can miss many days of work or school per month due to migraine attacks.
- At work or school, patients struggle to concentrate, remember things, or speak clearly, which affects performance and employment.
- Relationships with family and friends are strained because of unpredictability of migraine attacks, difficulties participating in activities, and financial pressures from migraine-related medical expenses.
- Patients feel stigmatized and that migraine pain is not taken seriously.

Relief provided by existing preventive treatments is often temporary:

- Patients have tried extensive lists of preventive and acute treatments (including drug and non-drug therapies, and lifestyle changes).
- Some treatments work for a time, but they either stop working or are not tolerable.
- Side-effects from some interventions can be as debilitating as migraine.

Patients struggle to access effective care or treatment:

- Difficulties arise in finding a physician who understands migraine and migraine pain.
- Due to high costs and access restrictions, patients may not have a sufficient supply of acute treatment (e.g., triptans); patients may ration treatment and choose the "important" days to take treatment.
- Patients feel discouraged because treatment strategies follow a "guess and test" procedure, which can take many years before they find an effective treatment.
- Patients reported paying high co-pays for many treatments; some patients must wait for pre-authorization from their insurer.
- Patients are also concerned about the affordability of new preventive treatments.

Patients seek treatments that improve their quality of life:

- For many patients, reduced pain and symptom relief are important steps to improving overall quality of life.
- Patients also reported that fewer side-effects, improved cognitive functioning, and ability to work or take care of family are important outcomes.

Potential Cost-Saving Measures in Chronic or Episodic Migraine

Among the American Headache Society's Choosing Wisely recommendations, the recommendation against performing neuroimaging studies in patients with stable headaches is likely to be cost-saving.[31] In addition, we heard from clinicians that reducing ED visits, for example by directing patients to infusion centers, may also be an area for potential cost-savings.

Comparative Clinical Effectiveness

We evaluated the evidence of the clinical effectiveness, tolerability, and safety of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab) in comparison with no preventive treatment or commonly-used preventive therapies in adults with chronic or episodic migraine who were eligible for preventive migraine therapy. For both episodic and chronic migraine populations, commonly-used preventive therapies included topiramate, propranolol, and amitriptyline. For chronic migraine, onabotulinum toxin A was also included. For the subgroup of patients for whom at least

one prior preventive therapy has failed, we compared each of the CGRP inhibitors to each other, to no preventive treatment (placebo), and to onabotulinum toxin A (chronic migraine only).

Essential to our review was the evidence on the clinical benefits common to migraine trials and reported tolerability/harms. Key outcomes included change from baseline in monthly migraine days, ≥ 50% reduction in migraine days (50% responders), change from baseline in monthly headache days, change from baseline in days using acute medication per month, all-cause discontinuations, discontinuations from adverse events (AEs), serious AEs (SAEs), and any AE reported by ≥ 5% of a trial arm. We also sought data on quality of life measures.

We first describe the evidence on clinical benefits for each population (chronic migraine, episodic migraine). Then we describe the evidence on tolerability and harms collectively.

Clinical Benefits in Chronic Migraine

In chronic migraine, we included 11 trials: one erenumab RCT (Tepper 2017), two fremanezumab RCTs (Bigal 2015a, HALO-CM), and eight trials of onabotulinum toxin A or topiramate.[26,28,32-39] Currently, there are no head-to-head trials of CGRP inhibitors versus any of the comparators of interest. In the three CGRP inhibitor trials and two of the onabotulinum toxin A trials, patients who continued to meet the criteria for chronic migraine during the four-week baseline phase and who showed at least 80% compliance with a daily electronic headache diary continued to the randomized phase. Criteria related to compliance with a daily headache diary was not reported in the other six trials. Both fremanezumab trials and one topiramate trial permitted concomitant preventive migraine therapy, which was not permitted in the other eight trials. Over 80% of the patients were female and the average age was approximately 40 years. The included patients had a history of chronic migraine for an average of 20 years. Five trials excluded patients with medication overuse headaches, whereas four other trials reported the proportion of patients with medication overuse headache, which ranged from 41%-68%. Neither fremanezumab trial reported this information. At baseline, the mean number of migraine days per month ranged from 16 to 19. The time point of analysis ranged from 12 to 26 weeks.

Table ES1 summarizes the results from the network meta-analyses (NMAs) synthesizing the individual trial results. Overall, there were greater reductions in monthly migraine days, monthly headache days, and days using acute medication per month for all interventions versus placebo. Results comparing CGRP inhibitors to active therapies were not statistically different.

Table ES1. NMA Results in Trials of Chronic Migraine Patients

	Monthly Migraine Days	Days Using Acute Medications	Monthly Headache Days
Placebo	Reference	Reference	Reference
Erenumab 70 mg monthly	**-2.4 (-4.8, 0.0)**	-1.9 (-4.3, 0.6)	NA
Erenumab 140 mg monthly	**-2.4 (-4.8, 0.0)**	**-2.5 (-4.9, 0.0)**	NA
Fremanezumab 675 mg quarterly	-1.3 (-3.5, 0.9)	-1.4 (-3.8, 1.0)	-1.5 (-3.7, 0.8)
Fremanezumab 675/225 mg monthly	-1.7 (-3.5, 0.1)	**-2.2 (-4.1, -0.3)**	**-1.8 (-3.6, -0.1)**
Onabotulinum toxin A 155U quarterly	**-2.0 (-3.6, -0.3)**	NA	**-2.1 (-3.5, -0.6)**
Topiramate 100 mg/day	-1.7 (-4.2, 0.8)	-1.3 (-3.5, 0.7)	-1.1 (-3.6, 1.4)

NA: not available

Results are expressed as the mean change from baseline (95% credible interval) for each intervention vs. placebo. The average placebo responses across the CGRP inhibitor trials were reductions of 4.0 migraine days, 2.0 days using acute medication, and 3.3 monthly headache days. Results in bold indicate statistically significant results.

We also reviewed monthly migraine day data for the subpopulation of chronic migraine patients who experienced the failure of at least one preventive therapy prior to the start of the trial. Manufacturers of erenumab and fremanezumab submitted the data in confidence. As per ICER's data in confidence policy, these results are redacted in this report, but will be unredacted no later than December 2019.

Clinical Benefits in Episodic Migraine

For episodic migraine, 18 trials were included: eight placebo-controlled trials of CGRP inhibitors assessing erenumab (Sun 2016, STRIVE, ARISE), fremanezumab (Bigal 2015b, HALO-EM), or galcanezumab (Skljarevski 2018, EVOLVE-1, EVOLVE-2), and 10 trials assessing oral preventive therapies.[25,40-56] Currently, there are no head-to-head trials of CGRP inhibitors versus any of the oral preventive therapies. The trials included a four-week baseline period followed by a 12- to 26-week randomized phase. In all eight CGRP inhibitor trials, patients who continued to meet episodic migraine criteria during the baseline phase and who showed at least 80% compliance with an electronic headache diary continued to the randomized phase. Criteria related to compliance with a daily headache diary was not reported in the trials of oral preventive therapies. Across the trials, over 80% of the patients were female and the average age was approximately 40 years. The included patients had a history of migraine for an average of 20 years. All eight CGRP inhibitor trials excluded patients who had experienced no therapeutic response to more than two classes of migraine preventive therapies. Patients in four CGRP inhibitor trials (Sun 2016, Skljarevski 2018, EVOLVE-1, EVOVLE-2) were required to discontinue any migraine preventive therapies at baseline, whereas patients in four trials (ARISE, STRIVE, HALO-EM, Bigal 2015b) were allowed stable doses of preventive migraine therapies. Bigal 2015b had the highest proportion of patients on concomitant preventive therapy (30%) whereas the proportion was 3% to 6% in the erenumab trials. At

baseline, the mean number of migraine days per month was 8 in the CGRP inhibitor trials, except for Bigal 2015b which had a higher baseline frequency of 12 migraine days per month. In the trials of oral preventive therapies, the average number of migraine days per month at baseline ranged from 5 to 12 days per month. The time point of analysis ranged from 12 to 26 weeks.

Table ES2 summarizes the results from the NMAs synthesizing the individual trial results. Overall, there were greater reductions in monthly migraine days, higher odds of 50% response, and greater reductions in days using acute medication per month for all interventions versus placebo. Results comparing CGRP inhibitors to oral preventive therapies were not statistically different.

Table ES2. NMA Results in Trials of Episodic Migraine Patients

	Monthly Migraine Days	Days Using Acute Medications	50% Responders
Placebo	Reference	Reference	Reference
Erenumab 70 mg monthly	**-1.3 (-1.8, -0.8)**	**-0.9 (-1.4, -0.4)**	**1.9 (1.4, 2.5)**
Erenumab 140 mg monthly	**-1.9 (-2.7, -1.2)**	**-1.6 (-2.4, -0.9)**	**2.2 (1.4, 3.3)**
Fremanezumab 675 mg quarterly	**-1.2 (-2.2, -0.3)**	**-1.1 (-2.0, -0.3)**	**1.7 (1.1, 2.7)**
Fremanezumab 225 mg monthly	**-1.6 (-2.5, -0.8)**	**-1.2 (-2.0, -0.4)**	**1.9 (1.4, 2.9)**
Galcanezumab 120 mg monthly	**-1.8 (-2.4, -1.2)**	**-1.8 (-2.4, -1.2)**	**2.5 (1.9, 3.3)**
Galcanezumab 240 mg monthly	**-1.8 (-2.5, -1.2)**	**-1.7 (-2.3, -1.1)**	**2.4 (1.7, 3.2)**
Topiramate 50 mg/day	-0.2 (-1.0, 0.6)	-0.4 (-1.3, 0.4)	**1.6 (1.1, 2.3)**
Topiramate 100 mg/day	**-1.2 (-1.7, -0.7)**	**-1.0 (-1.4, -0.5)**	**2.7 (2.1, 3.5)**
Topiramate 200 mg/day	**-1.0 (-1.5, -0.4)**	**-0.7 (-1.3, -0.2)**	**2.3 (1.7, 3.1)**
Amitriptyline 25-100 mg/day	-1.1 (-2.2, 0.1)	-1.2 (-2.4, 0.1)	**2.0 (1.2, 3.2)**
Propranolol 160 mg/day	**-1.2 (-2.0, -0.4)**	**-1.1 (-1.9, -0.3)**	**2.7 (1.7, 4.1)**

Results are expressed as the mean change from baseline (95% credible interval) for monthly migraine days and days using acute medications for each intervention vs. placebo. For 50% responders, results are expressed as odds ratios (95% credible intervals) for each intervention vs. placebo. The average placebo responses across the CGRP inhibitor trials were reductions of 2.8 migraine days and 1.8 days using acute medications; a 50% response was estimated to occur in 37% of patients receiving placebo. Results in bold indicate statistically significant results.

In addition, we reviewed data for the subpopulation of episodic migraine patients who experienced the failure of at least one preventive therapy prior to the start of the trial. Manufacturers of erenumab and fremanezumab submitted the data in confidence. As per ICER's data in confidence policy, these results are redacted in this report, but will be unredacted no later than December 2019.

For longer-term outcomes, one-year data from an open-label extension (OLE) of erenumab were available. Over one year of therapy, the mean reduction in migraine days per month was 5.0 (standard deviation of 4.2). After 64 weeks, 65% of patients achieved at least a 50% reduction in migraine days, 42% achieve at least a 75% reduction in migraine days, and 26% achieved a 100% reduction in migraine days.

Tolerability and Harms

Tolerability and harms assessed include all-cause discontinuations, discontinuations due to AEs, SAEs, and any AE reported by at least 5% of a trial arm. Overall, the CGRP inhibitors were well-tolerated and harms were generally non-serious and uncommon. Across the trials, there were no differences in the meta-analyzed odds of discontinuing for any cause, discontinuing due to adverse events, or experiencing serious adverse events with the CGRP inhibitors versus other preventive therapies.

Across the CGRP inhibitor trials, the most commonly reported AEs involved injection-site events (injection pain and injection-site reactions including erythema, induration, and pruritis) in up to 30% of patients at 12 or 24 weeks. Nasopharyngitis and upper respiratory tract infection were reported in less than 12% of patients in erenumab, fremanezumab, and galcanezumab trials. In the trials of other preventive therapies, the most commonly reported AEs were fatigue, cognitive symptoms (including cognitive difficulties, difficulty with memory, concentration, language), paresthesia, taste perversion, and weight change. These AEs were not frequently observed in the CGRP inhibitor trials.

In the OLE of erenumab, 28% of patients discontinued therapy after one year, with 4% discontinuing due to adverse events. Commonly reported AEs by one year included nasopharyngitis (17%), upper respiratory tract infection (11%), back pain (7%), and influenza (7%).

Controversies and Uncertainties

The currently available trials of erenumab, fremanezumab, and galcanezumab show treatment benefits with few harms. However, these trials assessed outcomes by 12 or 24 weeks, and there remains uncertainty in any durability of effects and adverse events from prolonged use. These interventions are the first in the CGRP inhibitor class, and some concerns exist about the long-term effects of continuous blocking of CGRP or its receptor.[57-59] In its review of erenumab, the FDA specifically requested postmarketing surveillance data for liver toxicity, myocardial infarction, and stroke among patients receiving erenumab.[24] Furthermore, there is a paucity of evidence on optimal duration of preventive treatments, both for the existing preventives and the CGRP inhibitors. Although benefits from treatment may continue after discontinuation, such data were not reported in the trials. If patients, particularly those with chronic migraine, are expected to take CGRP inhibitors for a long duration (greater than one year), studies with longer follow-up are needed.[59]

We understand that there remains a gap between those outcomes reported in the trials and the outcomes that patients seek. Patients expressed their desire for an improvement in their disability by reducing the burden of their condition on their daily life activities. Furthermore, chronic migraine tends to be more burdensome due to the sheer number of symptoms experienced from

the higher average monthly migraine days.[60] However, quality of life measures were infrequently reported across the trials. When reported, the follow-up periods were short. MIDAS, one of the quality of life measures reported in trials, was evaluated no longer than three months (12 weeks). As a result, it was difficult to definitively ascertain an improvement of a long-term outcome with a short-term follow-up period.

The designs of the CGRP inhibitor trials also raise concerns about generalizability of the results to clinical practice. First, the four-week baseline period used in the CGRP inhibitor trials required patients to comply with a headache diary. It is unclear how the efficacy results from these trials would apply to those who did not comply with a headache diary. Second, the efficacy and safety of CGRP inhibitors in migraine patients who are pregnant and those with comorbidities, particularly cardiovascular diseases, have not been evaluated. The FDA requires prospective pregnancy registries to compare the maternal, fetal, and infant outcomes of women with migraine exposed to erenumab.[24] As migraine is associated with a higher prevalence of comorbidities including cardiovascular disease than in the general population, data on these patients are also of interest.[61] Third, we have limited subgroup data on patients for whom prior preventive treatments have failed. The CGRP inhibitor trials excluded those patients who experienced failures from as few as two or three previous treatments. However, these patients are the most in need of an effective and tolerable preventive therapy and are most likely to receive a CGRP inhibitor in practice.

Summary and Comment

Results from clinical trials and from our NMAs suggest that preventive treatment with the CGRP inhibitors provide some clinical benefit in patients with chronic or episodic migraine. Few harms were seen in these short-term trials. In terms of limitations of this evidence base, the trials compared CGRP inhibitors to placebo, restricted the patient population to those for whom no more than two or three other preventive therapies had failed, and were short-term in duration. The generalizability of the results is limited and may not apply to many of the patients who would likely be treated with CGRP inhibitors, such as those who have tried more than three preventive therapies and those with comorbidities. In addition, the short-term trials limit our certainty about the safety of these agents with a novel mechanism of action, particularly related to AEs that may manifest after a longer duration of treatment. Hence, we rated the evidence as follows:

- Among patients with chronic migraine who are eligible to receive preventive therapy, we rated the evidence on the net benefit of erenumab and fremanezumab as insufficient ("I") compared to oral agents or to onabotulinum toxin A. Among patients with chronic migraine for whom prior preventive therapy has failed, we rated the net benefit of erenumab and fremanezumab as comparable or better ("C+") compared to no treatment, weighing uncertainties about potential harms of CGRP inhibitors against the need for therapy in patients with frequent migraine and no other preventive treatment options.

- Among patients with episodic migraine who are eligible to receive preventive therapy, we rated the evidence on the net benefit of erenumab, fremanezumab, and galcanezumab as insufficient ("I") compared to oral agents. Among patients with episodic migraine for whom oral preventive therapies have failed, we rated the net benefit of erenumab and fremanezumab as promising but inconclusive ("P/I") compared to no treatment, again weighing uncertainties about potential harms of CGRP inhibitors against the need for therapy in patients without other preventive treatment options but with less frequent migraine than in the chronic migraine population.
- Given the limited amount of data currently available, we rated the evidence on net benefit of galcanezumab as insufficient ("I") for all other populations and comparisons.
- We rated the evidence on net benefit of erenumab versus fremanezumab as insufficient ("I") for all populations and comparisons due to the lack of direct evidence and weighing uncertainties about potential longer-term benefits and harms of each intervention.

Long-Term Cost Effectiveness

We conducted an analysis to estimate the incremental cost-effectiveness of two CGRP inhibitors, erenumab and fremanezumab, compared to no preventive treatment in patients with chronic and episodic migraine for whom one to three previous preventive therapies had failed. We did not model galcanezumab given the lack of currently available data including data in the subpopulation of patients for whom prior preventive therapy had failed.

For erenumab and fremanezumab, we built separate semi-Markov models for chronic and episodic migraine. The general characteristics of the population in each model reflected the average patient who experiences chronic or episodic migraine in the US. The intervention arm of each model includes three health states: 1) CGRP inhibitor treatment, 2) no preventive treatment, and 3) death. The comparator arm includes two health states: 1) no preventive treatment and 2) death. Each of the health states included estimates of the number of migraine days per month. The treatment effect estimates for monthly migraine days reflect the data from the subset of patients for whom one to three prior preventive therapies failed. These data were submitted as academic-in-confidence data by the respective manufacturers and are currently redacted in tables and text. We used trial-specific data on the change in distribution of migraine-severity due to treatment effect since no real-world data currently exists for the CGRP inhibitors. Estimates of treatment effects for days using acute medications and treatment discontinuations were derived from the NMAs of trial data as described in the Clinical Review. Where necessary, data used in the model that were based on periods of four weeks were adjusted to reflect a 30-day period.

The wholesale acquisition cost (WAC) for erenumab is $6,900 per year.[62] There were conflicting reports on whether discounts will be offered and the magnitude of the discounts. We applied an industry-wide average discount rate of 27% to the annual WAC for a rounded annual cost of $5,000

which was used for both CGRP inhibitors.[63] In each health state, the models also included estimates of the daily costs of acute migraine treatments ($25 for chronic migraine patients and $21 for episodic migraine patients),[64] costs of other health care services used to treat migraines, and costs of AEs from the treatments. Utilities were a function of migraine severity for each migraine day along with non-migraine days each month across the health states along with disutility from adverse events. The utility weights were estimated using the EQ-5D in a population of adults in the US who were in good physical health and had experienced migraine in the two months preceding enrollment.[65] We combined the distribution of migraine severity and the utility weights to determine the utilities associated with a migraine day.

The base-case analyses were performed from a health system payer perspective (i.e., focus on direct medical care costs only) and were based on monthly cycles over a two-year time horizon. The outcomes included in the model were quality adjusted life years (QALYs), reduction in migraine days, and total costs for interventions and comparators. We used these outcomes to generate incremental cost-effectiveness ratios of cost per QALY gained and cost per migraine day avoided, comparing CGRP inhibitors to the comparators. Both costs and QALYs were discounted at a rate of 3% per annum.

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for each of the relevant inputs in the model. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 10,000 simulations and calculating 95% credible range estimates for each model outcome based on the results. Additionally, we performed a threshold analysis by systematically altering the price of the CGRP inhibitors to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds. We also conducted several scenario analyses including those that evaluated the impact of productivity losses and the cost-effectiveness relative to other preventive treatments.

Details regarding inputs, model assumptions and their rationale, sensitivity analyses, and scenario analyses are available in Section 4 of the report.

Base-Case Results

Below we present the results of the cost-effectiveness analyses. In order to preserve the confidential data used in the generation of these results, several tables have been redacted. In addition, incremental cost-effectiveness ratios have been rounded to the nearest $10,000 when confidential data were used or when the ratios exceeded one million dollars per QALY gained, and to the nearest $1,000 when only publicly-available data were used. Willingness-to-pay threshold prices and the value-based price benchmarks in Section 6 have been rounded to two significant digits. Cost per migraine-free day gained results have been rounded to the nearest $10.

Treatment with CGRP inhibitors resulted in higher total costs, more migraine-free days, and increased QALYs compared to no preventive treatment in both chronic and episodic migraine patients for whom at least one (and up to three) previous preventive therapies had failed. In both comparisons for the CGRP inhibitors, the drug costs were responsible for the majority of total costs over the two-year period. The drug costs and total costs were lower in the fremanezumab treated group because of higher discontinuation rates when compared to erenumab.

The base case incremental cost-effectiveness ratios for erenumab in chronic migraine for patients among whom prior preventive therapy failed was approximately $90,000 per QALY gained compared to no preventive treatment. The analogous results for fremanezumab were approximately $120,000 per QALY gained compared to no preventive treatment. For patients with episodic migraine among whom prior preventive therapy failed, the incremental cost-effectiveness ratios for the CGRP inhibitors compared to no preventive treatment were approximately $150,000 per QALY gained for erenumab and for fremanezumab.

Table ES3. Base-Case Results [Note: This table is redacted to ensure the confidentiality of the data used in generating results]

Table ES4. Incremental Cost-Effectiveness Ratios for the Base Case*

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-free Day Gained
Chronic Migraine			
Erenumab 140mg monthly	No Preventive Treatment	$90,000	$100
Fremanezumab 625/225mg monthly	No Preventive Treatment	$120,000	$140
Episodic Migraine			
Erenumab 140mg monthly	No Preventive Treatment	$150,000	$160
Fremanezumab 225mg monthly	No Preventive Treatment	$150,000	$150

*To ensure the confidentiality of the data used to generate the results, results are rounded to the nearest $10,000 for cost per QALY gained and to the nearest $10 for cost per migraine-free day gained

Sensitivity and Scenario Analyses Results

In the one-way sensitivity analyses, for both chronic and episodic migraine models, monthly migraine day reduction associated with the treatments were the most influential variable, followed by drug and administrative costs associated with the treatments, the impact of treatments on use of acute medications, migraine day utilities, and migraine free day utilities. Variation in other inputs had negligible impact.

We also evaluated the uncertainty in the model parameters simultaneously by conducting a probabilistic sensitivity analysis. In chronic migraine, compared with no preventive treatment, erenumab had an incremental cost effectiveness ratio less than $100,000 per QALY in two-thirds of the simulations (67%) and less than $150,000 per QALY in 96% of the simulations; fremanezumab

had an incremental cost effectiveness ratio less than $100,000 per QALY 23% of the simulations and less than $150,000 per QALY 79% of the simulations. In episodic migraine, compared with no preventive treatment, both treatments rarely (less than 3%) had an incremental cost effectiveness ratio less than $100,000 per QALY and had incremental cost effectiveness ratios below $150,000 per QALY in 34% of the simulations for erenumab and in 44% of the simulations for fremanezumab.

In one scenario analysis, we compared CGRP inhibitors to current preventive treatments for all patients (i.e., not conditional on prior treatment failure). In the chronic migraine population, erenumab 140 mg monthly had an incremental cost-effectiveness ratio of approximately $345,000 per QALY gained while fremanezumab had an incremental cost-effectiveness ratio of approximately $12.78 million per QALY gained. In episodic migraine, erenumab 140 mg monthly had an incremental cost-effectiveness ratio of approximately $395,000 per QALY gained, fremanezumab 225 mg monthly had an incremental cost-effectiveness ratio of approximately $1.02 million per QALY gained, and galcanezumab 240 mg monthly had an incremental cost-effectiveness ratio of approximately $389,000 per QALY gained.

In scenarios that employed a modified societal perspective to the base case model and included the impact of reduced migraine days on productivity, lower (i.e., more favorable) incremental cost effectiveness ratios were found in all the comparisons. For chronic migraine, the incremental cost of erenumab was $50,000 per QALY gained relative to no preventive treatment, and the incremental cost of fremanezumab relative to no preventive treatment was $80,000 per QALY gained. For episodic migraine, the incremental cost per QALY gained for both erenumab and fremanezumab was approximately $110,000 per QALY gained relative to no preventive treatment.

Threshold Analyses

Table ES5 shows unit drug prices, separately for chronic and episodic migraine, associated with various cost-effectiveness thresholds based on the base case model results.

Table ES5. Resulting Prices for Erenumab and Fremanezumab to Reach Cost per QALY Thresholds

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Chronic Migraine			
Erenumab 140 mg vs. No Preventive Treatment	$3,300	$5,600	$7,900
Fremanezumab 625/225 mg vs. No Preventive Treatment	$2,600	$4,400	$6,200
Episodic Migraine			
Erenumab 140 mg vs. No Preventive Treatment	$1,900	$3,400	$4,800
Fremanezumab 225 mg vs. No Preventive Treatment	$1,900	$3,500	$5,100

Summary and Comment

Relative to no preventive treatment, CGRP inhibitors are predicted to positively impact the health of patients with chronic or episodic migraine for whom prior preventive therapy had failed. In the base-case analyses, where results from patients who have previously failed one to three prior preventive treatments were used to estimate outcomes in patients for whom other preventive therapies are no longer an option, both erenumab and fremanezumab were under a $150,000 per QALY threshold in chronic migraine and approximately $150,000 per QALY gained in episodic migraine, compared to no preventive treatment. Importantly, the analysis results were sensitive to a number of parameters including the costs of the medication and to scenarios that took a societal perspective.

The models were based on clinical trial results that may not hold true for longer time horizons or in particular patient populations different from those seen in the trials. Discontinuation rates may be lower in the clinical trials than would be seen in a general patient population. The price estimates for the drugs may not reflect actual market prices. Costs and disutilities of the AEs were crude estimates, however, they did not substantially impact the estimated cost-effectiveness ratios. The available estimates for the severity distribution of migraines may not reflect the actual patient population.

CGRP inhibitors are projected to have positive impact on migraine days and associated QALYs for episodic and chronic migraine patients. For patients with chronic migraine for whom other preventive treatments have failed, at a price of $5,000 per year, the cost-effectiveness of CGRP inhibitors is below the upper bound of commonly accepted thresholds. In patients with episodic migraine for whom other preventive treatments have failed, cost-effectiveness is near the upper bound of commonly accepted thresholds. In patients with chronic or episodic migraine who have other treatment options available, cost-effectiveness will likely exceed commonly accepted thresholds.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table ES6. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	A monthly (or quarterly), rather than daily, administration may ease the burden of living with migraine for some patients. And, with a more tolerable short-term safety profile, patients may be less likely to discontinue CGRP inhibitors due to tolerability. However, a subcutaneous self-injection rather than oral ingestion may add complexity of care.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	No impact identified.
This intervention will significantly reduce caregiver or broader family burden.	CGRP inhibitors may reduce caregiver/family burden regarding migraine attack care or adverse events arising from therapies.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Erenumab, fremanezumab, and galcanezumab are the first monoclonal antibodies targeting the CGRP pathway for migraine prevention. The CGRP inhibitors could be a treatment option for patients for whom other therapies have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Migraine patients may perform their job duties less productively while experiencing migraine (presenteeism), regularly stop showing up for work (absenteeism), or leave the workforce or college. By reducing migraine frequency, CGRP inhibitors may increase some patients' ability to work and improve overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	No impact identified.

Table ES7. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Migraine is among the top ten causes of years lived with disability.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Migraine typically recurs over many years and represents a long-term burden for patients and their families, friends, and colleagues.
This intervention is the first to offer any improvement for patients with this condition.	For some patients, existing preventive therapies have not provided enough relief or have otherwise not been tolerable.

Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Serious adverse events of the CGRP inhibitors appear to be minimal. However, these interventions are the first in the CGRP inhibitor class, and some concerns exist about the long-term effects of continuous blocking of CGRP or its receptor.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	There is a paucity of evidence on optimal duration of preventive treatments, both for the existing preventives and the CGRP inhibitors. The long-term effects of CGRP inhibitors are starting to be assessed but are limited at this time.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Despite guidelines recommending against opioids as a first line acute treatment, many migraine patients are frequently prescribed opioids. Patients and patient advocacy groups expressed concern about the opioid epidemic and its associated health and cost consequences in the migraine population.

Value-Based Benchmark Prices

The value-based benchmark prices for erenumab and fremanezumab are presented in Table ES8. The value-based prices were calculated using a blended population of patients with chronic and episodic migraine for whom prior preventive therapy had failed. Specifically, it was assumed that the proportion of those eligible for treatment with the CGRP inhibitors in the United States would be comprised of 19.4% with chronic migraine and 80.6% with episodic migraine. Calculations for population estimates are described in the Potential Budget Impact section below.

Table ES8. Value-Based Benchmark Prices for Erenumab and Fremanezumab*

	Annual WAC	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY	Discount from WAC Required to Achieve Threshold Prices
Erenumab 140 mg	$6,900	$3,700	$5,300	23% to 46%
Fremanezumab 625/225 mg	$6,900	$3,700	$5,200	25% to 46%

*Annual prices are rounded to the nearest $100 in order to ensure the confidentiality of the data used to generate the results

Potential Budget Impact

We used the results from the cost-effectiveness model to estimate the potential total budgetary impact of erenumab and fremanezumab separately in patients in the US with chronic migraine or episodic migraine for whom at least one preventive treatment has failed. We used the same estimated net price (based on a 27% discount from the WAC price of erenumab) used in the cost-effectiveness analyses, the WAC, and the three threshold prices for each CGRP inhibitor in our

estimates of potential budget impact. All costs were undiscounted and estimated over a five-year time horizon.

The candidate populations eligible for treatment with the CGRP inhibitors included adults with chronic or episodic migraine for whom at least one preventive therapy had failed. To estimate the size of the potential candidate populations for treatment, we first estimated the size of the US adult population by gender for years 2018 to 2022 using population projection data published by the US Census Bureau[66] and age-range-specific prevalence of chronic and episodic migraine from a two-year longitudinal, population-based study.[40,41] We considered all chronic migraine patients eligible for active preventive therapy. For episodic migraine, 38.8% of the episodic population were considered eligible for active preventive therapy.[67] An estimated 45% of patients with migraine using preventive therapy failed at least one preventive therapy.[68] Using these estimates, our target population eligible to be treated with CGRP inhibitors was approximately 4.5 million people with episodic migraine and approximately 1.1 million people with chronic migraine.

Since people with migraine often cycle through several preventive therapies, we assumed that each sub-cohort (i.e., 20% of the prevalent cohort) remained in the model for two years, and a new cohort entered the model every year, resulting in larger patient populations for years two through five. We thus used only year one and two undiscounted costs for interventions and no preventive treatment.

We assessed the budget impact of CGRP inhibitors jointly in chronic and episodic migraine. Results presented here used CGRP inhibitor prices (WAC, estimated net price, and the three WTP threshold prices) weighted by the size of the prevalent population.

For erenumab, the annual average potential budget impact per patient at its WAC ($6,900 annually) and estimated net price ($5,000 annually, assuming an approximate 27% discount from estimated WAC) were approximately $4,200 and $2,100 respectively, relative to no current preventive treatment. The per-patient annual budget impact ranged from approximately $1,000 using the price to reach $50,000 per QALY (~$2,200 annually) to approximately $3,200 using the price to reach the $150,000 per QALY (~$5,300) threshold (Table ES9). The total potential annual budget impact across the entire eligible migraine populations when using erenumab at its assumed net price relative to no active preventive treatment was estimated at approximately $5.9 billion. At other prices of erenumab, the total population annual budget impact ranged from approximately $2.1 billion using the price to reach the $50,000 per QALY threshold (~$2,200 annually) to approximately $8.4 billion using the WAC ($6,900 annually). As shown in Figure ES1, approximately 11% and 16% of the total annual eligible migraine population could be treated with erenumab at its WAC and assumed net price without crossing the ICER annual budget impact threshold of $915 million. At the annual prices to reach the cost-effectiveness thresholds between $150,000 and $50,000 per QALY, between 15% and 44% of the entire eligible migraine population could be treated annually.

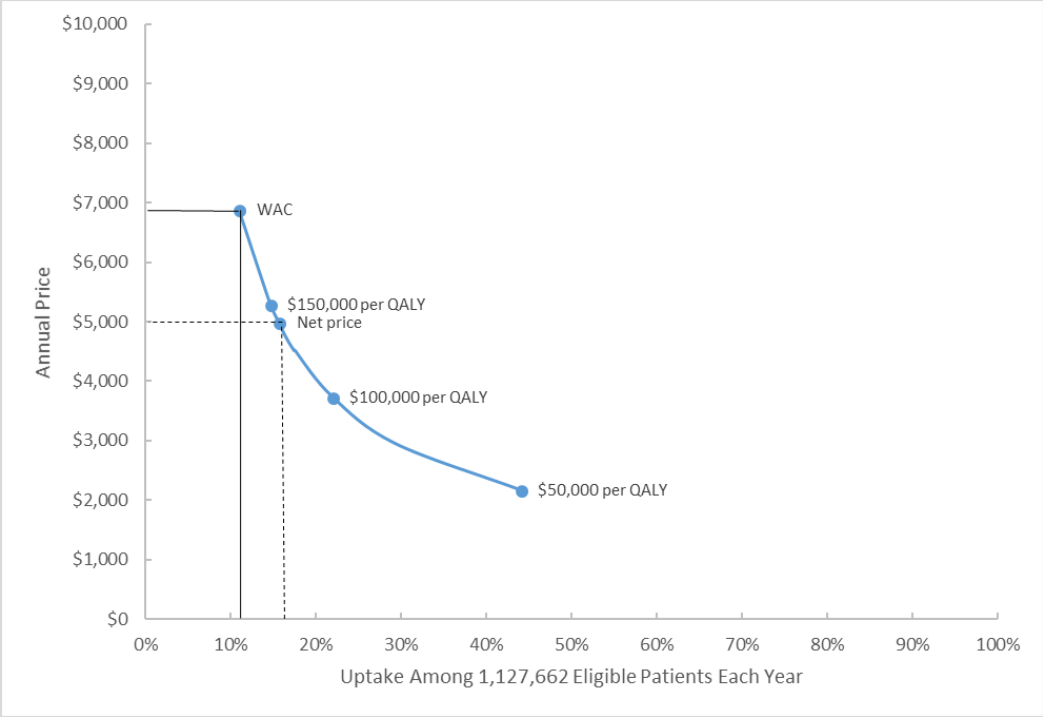
Table ES9. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Erenumab in Migraine Patients for Whom At Least One Previous Preventive Therapy Has Failed

	Average Annual Per Patient Budget Impact				
	WAC	Assumed Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$6,041	$3,432	$4,961	$3,906	$2,851
No Active Preventive Treatment	$1,803				
Difference	$4,238	$2,147	$3,159	$2,103	$1,048

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Budget impact weighted by predicted prevalent populations of chronic and episodic migraine

Figure ES1. Potential Budget Impact Scenarios at Different Prices of Erenumab in Migraine Population Eligible for Preventive Treatment for Whom At Least One Previous Preventive Therapy Has Failed



For fremanezumab, the annual average potential budget impact per patient at its estimated WAC ($6,900 annually) and estimated net price ($5,000 annually, assuming an approximate 27% discount from estimated WAC) were approximately $3,000 and $2,100 respectively, relative to no current preventive treatment. The per patient annual budget impact ranged from approximately $800 using the price to reach $50,000 per QALY (~$2,100 annually) to approximately $2,200 using the price to reach $150,000 per QALY (~$5,200 annually) threshold (Table ES10). The total potential annual budget impact across the entire eligible migraine populations when using fremanezumab at

its estimated net price relative to no active preventive treatment was estimated at approximately $4.2 billion. At other prices of fremanezumab, this total population annual budget impact ranged from approximately $1.5 billion using the price to reach the $50,000 per QALY threshold ($2,100 annually) to approximately $5.9 billion using the estimated WAC ($6,900 annually). The lower per-patient and population potential budget impact of treatment with fremanezumab as compared to erenumab was primarily driven by the higher discontinuation rate of fremanezumab. As shown in Figure ES2, approximately 15% and 22% of the total annual eligible migraine population could be treated with fremanezumab at its estimated WAC and estimated net price without crossing the ICER annual budget impact threshold of $915 million. At the annual prices to reach the cost-effectiveness thresholds between $150,000 and $50,000 per QALY, between 21% and 62% of the entire eligible migraine population could be treated annually.

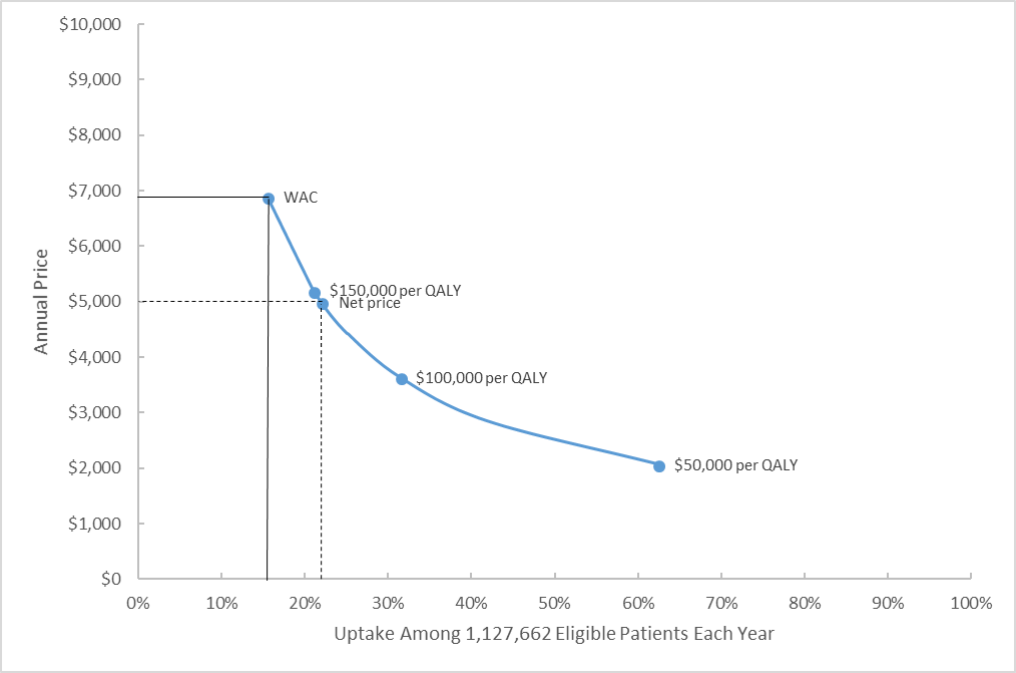
Table ES10. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Fremanezumab in Migraine Patients for Whom At least One previous Preventive Therapy Has Failed

	Average Annual Per Patient Budget Impact				
	Estimated WAC	Estimated Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Fremanezumab	$4,842	$3,942	$4,038	$3,296	$2,555
No Active Preventive Treatment	$1,803				
Difference	$3,040	$2,140	$2,235	$1,494	$752

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Budget impact weighted by predicted prevalent populations of chronic and episodic migraine

Figure ES2. Potential Budget Impact Scenarios at Different Prices of Fremanezumab in Migraine Population Eligible for Preventive Treatment for Whom At Least One Previous Preventive Therapy Has Failed



Detailed budget impact results for both CGRP inhibitors are available in section 7.3 of this report.

Access and Affordability

As illustrated in these analyses, treating the entire patient population eligible for treatment with CGRP inhibitors would have a substantial budget impact. However, at the June 14 public meeting, clinical experts indicated that uptake is unlikely to exceed levels that would threaten access and affordability, as CGRP inhibitors use a novel mechanism of action with an unknown long-term safety profile, are injectable, and patients who do not benefit from therapy are likely to discontinue treatment. As such, ICER is not issuing an access and affordability alert at this time. However, given the budget impact potential, all stakeholders should closely monitor the use of CGRP inhibitors in the event that actual uptake exceeds expectations.

California Technology Assessment Forum Votes

The California Technology Assessment Forum (CTAF) Panel deliberated on key questions raised by ICER's report at a public meeting on June 14, 2018 in Los Angeles, California. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Patient population for questions 1-4: Adult patients with 15 or more headache days per month (i.e., chronic migraine).

1) Is the evidence adequate to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab?

Yes: 0 votes	***No: 13 votes***

2) Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies (e.g., amitriptyline, topiramate, or propranolol)?

Yes: 0 votes	***No: 13[a] votes***

3) Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and onabotulinum toxin A (Botox®, Allergan)?

Yes: 0 votes	***No: 13 votes***

4) For patients who have no other options for preventive therapy, is the evidence adequate to demonstrate a net health benefit for treatment with CGRP inhibitors compared with no treatment?

Yes: 10 votes	No: 3 votes

Patient population for questions 5-7: Adult patients with 14 or fewer migraine days per month

5) Is the evidence adequate to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab?

Yes: 1 votes	***No: 12 votes***

6) Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies (e.g., amitriptyline, topiramate, or propranolol)?

Yes: 0 votes	***No: 13 votes***

7) For patients who have no other options for preventive therapy, is the evidence adequate to demonstrate a net health benefit for treatment with CGRP inhibitors compared with no treatment?

Yes: 4 votes	***No:9 votes***

Patient population for questions 8-9: Adult patients with migraine for whom other preventive treatments have failed.

[a] One Panelist's vote was not recorded during the meeting and was provided after the session concluded.

8) Does treating patients with CGRP inhibitors offer one or more of the following "other benefits?" (select all that apply)

Reduced complexity	4/13
Reduce important health disparities	2/13
Reduce caregiver/family burden	12/13
Novel mechanism of action or approach	13/13
Significant impact on improving return to work/overall productivity	13/13
Other important benefits or disadvantages	3/13

9) Are any of the following contextual considerations important in assessing CGRP inhibitors' long-term value for money? (select all that apply)

Care of individuals with condition of high severity	11/13
Care of individuals with condition with high lifetime burden of illness	9/13
First to offer any improvement	1/13
Compared to comparator, there is significant uncertainty about long-term risk of serious side effects	11/13
Compared to the comparator, significant uncertainty about magnitude or durability of the long-term benefits of this intervention	12/13
Other important contextual considerations.	6/13

Patient population for question 10: Adult patients with 15 or more headache days per month (i.e., chronic migraine) for whom other preventive therapies have failed.

10) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with erenumab versus no treatment?

Low: 0 votes	***Intermediate: 12 votes***	High: 1 votes

Patient population for question 11: Adult patients with 14 or fewer migraine days per month for whom other preventive therapies have failed.

11) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with erenumab versus no treatment?

Low: 6 votes	***Intermediate: 7 votes***	High: 0 votes

Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on CGRP inhibitors for patients with chronic or episodic migraine to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, a representative from a pharmacy benefit manager, a purchaser representative, and representatives from Amgen and Teva. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Payers

- Given that CGRP inhibitors have a new mechanism of action, are entering clinical use without long-term safety and efficacy data and were labeled by the FDA using language that could suggest that all patients with migraine are eligible for treatment, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments.
- When responsible pricing is accomplished and the net price of CGRP inhibitors aligns with the estimated added benefit for patients, prior authorization criteria should be relatively streamlined and allow documentation of eligibility through a clinician statement that patients have attempted adequate trials of two to three other preventive therapies rather than requiring extensive submission of clinical documents.
- Payers should negotiate discounts to seek the best value for patients and the health system by bringing the net price into traditional cost-effectiveness ranges. Adequate discounts may require preferential formulary placement for one particular CGRP inhibitor, but payers should maintain options for clinicians and patients to seek coverage for more than one CGRP inhibitor.
- Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups.

Manufacturers

- Following the example set by the launch of the first CGRP inhibitor, manufacturers should continue to exercise restraint in pricing and price negotiation with payers so that net prices align reasonably with the added benefits for patients. Consideration of price increases in future years should be transparently justified by new clinical evidence of superior performance.
- Manufacturers should exercise restraint in marketing CGRP inhibitors to incorporate the reality that patients will be required to have tried other preventive options first.

Promotional material for patients and for clinicians should refrain from building unrealistic expectations of a cure.

- Manufacturers and researchers should support studies that evaluate the efficacy of CGRP inhibitors in the patients most likely to receive them: those for whom more than three prior preventive therapies have failed.
- Manufacturers and researchers should conduct studies directly comparing CGRP inhibitors and other treatment options using standardized research protocols and outcome assessments to permit real-world, long-term outcome assessment.

Patient Advocacy Organizations

- Patient groups should advocate early during trial development to ensure evidence on the outcomes most important to patients is available at the time of product launch.

Providers

- Clinicians should be aware of the uncertainties in long-term efficacy and potential harms when prescribing CGRP inhibitors.

1. Introduction

1.1 Background

Migraine

Migraine is a common, recurrent headache disorder that affects approximately 20% of women and 6-10% of men in the United States (US).[1,2] Although migraine affects individuals of any age, the highest prevalence in adults has been observed in those aged 18-44.[1,2] Patients experience migraines (sometimes referred to as migraine episodes or "migraine attacks"), which are often unpredictable. In some patients, migraine is associated with allodynia or specific triggers. Common triggers include stress, hormones in women, hunger (missed or delayed meals), too little or too much sleep, lack of regular exercise, dietary elements (wine, caffeine, monosodium glutamate, artificial sweeteners, nitrates), and odors (perfumes, cigarette smoke).[69-71]

Migraine is among the top 10 causes of years lived with disability.[3,4] Because the frequency, duration, and intensity of migraine symptoms vary by individual and fluctuate over time, the burden of migraine may be more severe for some patients than others. For many patients, migraine is a mild intermittent problem controlled with oral analgesics. For patients with severe disease, migraine can lead to greater disability.[72]

When patients experience a migraine, they may feel moderate-to-severe pain and other symptoms (e.g., nausea, vomiting, or sensitivity to light or to sound, vertigo, tinnitus, hyperacusis, aphasia), have a reduced ability to function, or require bed rest.[1] Some patients with migraine experience migraine with aura (visual, sensory, speech/language, motor, brainstem, or retinal symptoms). If unable to get relief, patients may seek emergency care. Headaches are among the top five reasons for emergency department (ED) visits, accounting for approximately 3% of all ED visits.[2] Between migraine attacks, pain and other symptoms may remain, and patients' neurological function may not return to normal (i.e., pre-headache).[5] Hence, for some patients, the duration of impairment may be longer than the migraine attack itself, which can lead to ongoing disability.[6-8] In patients with more severe disease, migraine also may affect school, employment, choice of leisure activities and foods, or interpersonal relationships.[9-11,73,74] In addition, patients with migraine feel stigmatized, which may disrupt quality of life and ability to work.[12]

Patients with migraine can be diagnosed with *chronic migraine*, which is characterized by 15 or more headache days per month for at least three months, with migraine features present on at least eight days per month.[13] Most patients with migraine experience attacks over many years, but the use of "chronic" here refers to patients who have headaches on at least half the days over at least a three-month period. Migraine not subclassified as chronic migraine has been called *episodic migraine*, although this term is not a clinical diagnosis. We use the term “episodic” in this

document to refer to this type of migraine. In the US, approximately 10% of patients with migraine have chronic migraine and 90% have episodic migraine.[1,14] Due to the within-person fluctuation of migraine frequency and the progression of disease, patients may be diagnosed with chronic migraine at different points in time.[75,76]

Despite its high prevalence and impairment, migraine is often not recognized or effectively treated.[14,15] Barriers to appropriate care arise when accessing healthcare professionals, obtaining a correct diagnosis, and receiving appropriate therapy.[14,15] Patients from some racial backgrounds (Native Americans, African Americans, Hispanics), those from lower socioeconomic statuses, and those who are underinsured or uninsured may face higher barriers.[77] When patients do access care, they typically try multiple therapies, including non-pharmacologic therapies (e.g., exercise, changes in diet, relaxation techniques, cognitive behavioral therapy)[6] and pharmacologic therapies. Pharmacologic therapies can be categorized broadly into those used for treatment once symptoms have started ("acute" or "abortive" medications) and those used to decrease the frequency or severity of migraines ("preventive" or "prophylactic" therapies).

Acute Medications

For mild-to-moderate headaches, patients may benefit from simple analgesics including acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen.[78-81] These agents are relatively safe, available, and inexpensive. If patients do not respond to these agents or if they experience more severe headaches, they may use other migraine-specific medications including triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) and ergots (ergotamine, dihydroergotamine).

When usual acute medications do not provide relief, patients may present to the ED.[2] In this setting, patients may receive sumatriptan, dihydroergotamine, ketorolac, antiemetics (chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine), dexamethasone, or opioids (meperidine, tramadol, nalbuphine).[82-85]

Clinicians discourage the frequent use of acute medications for migraines. The use of acute therapy more frequently than 10 days per month is associated with the development of medication overuse headache and chronic daily headache.[19] Opioids and barbiturates are associated with the highest risk for medication overuse headache, although frequent use of NSAIDS and triptans can also lead to chronic migraine and medication overuse headache.[19]

Preventive Therapy

Although there are no strict guidelines on who should receive preventive therapy, those who have four or more days with headaches (headache days) per month with some impairment may be considered candidates for preventive therapy.[1] Preventive therapy aims to reduce the frequency, intensity, or duration of attacks, but preventive therapies usually do not prevent all migraines.

Effective preventive pharmacologic therapies include some antidepressants (amitriptyline, venlafaxine), anti-seizure medications (divalproex sodium, sodium valproate, topiramate), and beta-blockers (propranolol, metoprolol).[16] Patients with chronic migraine may also use onabotulinum toxin A (Botox®, Allergan plc) injections for prevention.[17]

Currently, there is little evidence or guidance on the optimal duration of preventive therapy. Most randomized trials measured outcomes after three months of treatment with few trials following patients beyond six months. In part due to the short timeframe and delayed response observed in these trials, some guidance suggests patients receive adequate therapeutic trials of two to six months with preventive therapy.[18] Patients who benefit from six months of preventive therapy may begin to taper off the therapy,[18,86] although some patients may benefit from prolonged use.[87] Nevertheless, patients frequently discontinue or switch treatments due to lack of efficacy or tolerability.[6,88] Without adequate treatment, patients with episodic migraine are more likely to progress to chronic migraine.[19] Approximately 2.5% of patients with episodic migraine progress to chronic migraine per year.[19]

CGRP Inhibitors

The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation, and elevations of CGRP were observed during a migraine.[20-22] CGRP is a 37-amino acid peptide and functions as a neurotransmitter in the central and peripheral nervous system and as a vasodilator. The involvement of CGRP in migraine was suggested in the 1980s.[20,21] Since then, new agents affecting the CGRP pathway have been developed and studied. Some approaches focused on small molecule CGRP receptor antagonists to be used to treat migraine attacks, or monoclonal antibodies to be used for migraine prevention. However, the development of many of the small molecule CGRP inhibitors have been hindered or terminated due to concerns of toxicity.[89] To date, the development of monoclonal antibodies for migraine prevention has seen fewer challenges related to toxicity.

Currently, erenumab (Aimovig™ Amgen, Inc. and Novartis AG), a fully human monoclonal antibody that binds to the CGRP receptor, has been assessed as a preventive therapy in both episodic and chronic migraine patients.[40,41,90] In May 2018, the US Food and Drug Administration (FDA) approved erenumab as a preventive therapy for patients with migraine (chronic or episodic).[23,24] The launch price for erenumab, $6,900 was lower than both the initial estimates by analysts and the placeholder price used in ICER's draft report. The manufacturer stated that, in choosing this price, they were hoping to ensure access to erenumab for a broader groups of patients and to maintain patient affordability by choosing a price that would be covered by many insurers with a copay rather than coinsurance.[91] Fremanezumab (Teva Pharmaceuticals) and galcanezumab (Eli Lilly and Company), two humanized monoclonal antibodies that target the CGRP ligand, have also been studied in migraine patients.[25-28] A decision by the FDA is expected for fremanezumab in September 2018;[29] and galcanezumab in the third quarter of 2018.[30] The potential use of CGRP

inhibitors as a preventive therapy has generated great interest from clinicians, patients, and their families. Nevertheless, uncertainties remain regarding the effectiveness of CGRP inhibitors compared with existing preventive therapies and with each other, and how well the cost of CGRP inhibitors will align with patient benefits. Therefore, stakeholders will benefit from a comprehensive review of the clinical evidence and potential economic impact.

1.2 Scope of the Assessment

Overview

This report assesses both the comparative clinical effectiveness and economic impacts of CGRP inhibitors for patients with chronic or episodic migraine. The assessment aims to systematically evaluate the existing evidence, taking uncertainty and patient-centered considerations into account. To that aim, the assessment is informed by two research components (a systematic review of the existing evidence and an economic evaluation) developed with input from a diverse group of stakeholders, including patients and their families, clinicians, researchers, representatives from pain and migraine foundations, and manufacturers of the agents of focus in this review. Below, we present the review's scope in terms of the research questions, PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design) elements, and an analytic framework diagram.

Research Questions

The following research questions were developed with input from clinical experts, patients, and patient groups:

- In patients with chronic migraine eligible for preventive therapy, what is the comparative efficacy, safety, effectiveness, and economic impacts of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab) versus each other and commonly-used oral migraine preventive therapies (topiramate, propranolol, and amitriptyline), and onabotulinum toxin A?
- In patients with chronic migraine for whom other preventive therapies have failed, what is the comparative efficacy, safety, effectiveness, and clinical impacts of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab) versus each other, onabotulinum toxin A, and no preventive therapy?
- In patients with episodic migraine eligible for preventive therapy, what is the comparative efficacy, safety, effectiveness, and economic impacts of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab) versus each other and commonly-used oral migraine preventive therapies (topiramate, propranolol, and amitriptyline)?
- In patients with episodic migraine for whom other preventive therapies have failed, what is the comparative efficacy, safety, effectiveness, and economic impacts of CGRP inhibitors

(erenumab, fremanezumab, and galcanezumab) versus each other and no preventive therapy?

Populations

The population of focus for this review is adult patients of at least 18 years of age who experience at least four headache days per month and are eligible for preventive therapy. We evaluated the following two subpopulations separately:

1. Patients experiencing chronic migraine
2. Patients experiencing episodic migraine

As discussed above, adequate therapeutic trials of preventive therapies generally require two to six months of treatment. We heard from clinicians and patients that requiring failure of multiple classes of medications for prevention of episodic migraine prior to treatment with a CGRP inhibitor would typically take more than 18 months and may be overly burdensome. As such, we evaluated subgroups defined by prior failure of at least one other preventive treatment where data allowed.

Interventions

The interventions of interest are prophylactic treatment by subcutaneous injection of erenumab, fremanezumab, and galcanezumab. We included trials of any dose or frequency and assessed regimens separately, including two monthly doses of erenumab (70 mg, 140 mg), two regimens of fremanezumab (675 mg quarterly, 225 mg monthly with or without a 675 mg loading dose), and two monthly doses of galcanezumab (120 mg, 240 mg). The CGRP inhibitors may be used alone or in combination with existing preventives (i.e., as add-on).

Comparators

For each population and subgroup, we compared the CGRP inhibitors to each other, to commonly-used migraine preventive therapies, and to no preventive therapy as data permit. For the episodic migraine population, the commonly-used preventives include topiramate, propranolol, and amitriptyline. For the chronic migraine population, the commonly-used preventives include topiramate, propranolol, amitriptyline, and onabotulinum toxin A.

Outcomes

The outcomes of interest for the clinical review include:

- Frequency, intensity, and duration of migraine events
- Pain
- Other symptoms: nausea, vomiting, dizziness, and sensitivity to light, sound, smell, or touch

- Cognitive functioning/impairment
- Disability
- Health-related 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, absenteeism)
- Use of rescue therapies
- Number of ED and primary care visits
- Adherence/treatment discontinuation
- Tolerability
- Harms/adverse events (AEs)

All endpoints related to each of the above outcomes were of interest for the clinical review. For example, the outcome "frequency of migraine events" encompasses endpoints for the percentage of patients with at least 50% fewer migraines per month (i.e., 50% responders) and the mean change in the number of migraine days per month, among others. The outcomes incorporated into the economic model are described in Section 4.

Timing

Evidence on intervention effectiveness and harms are derived from studies of any follow-up duration.

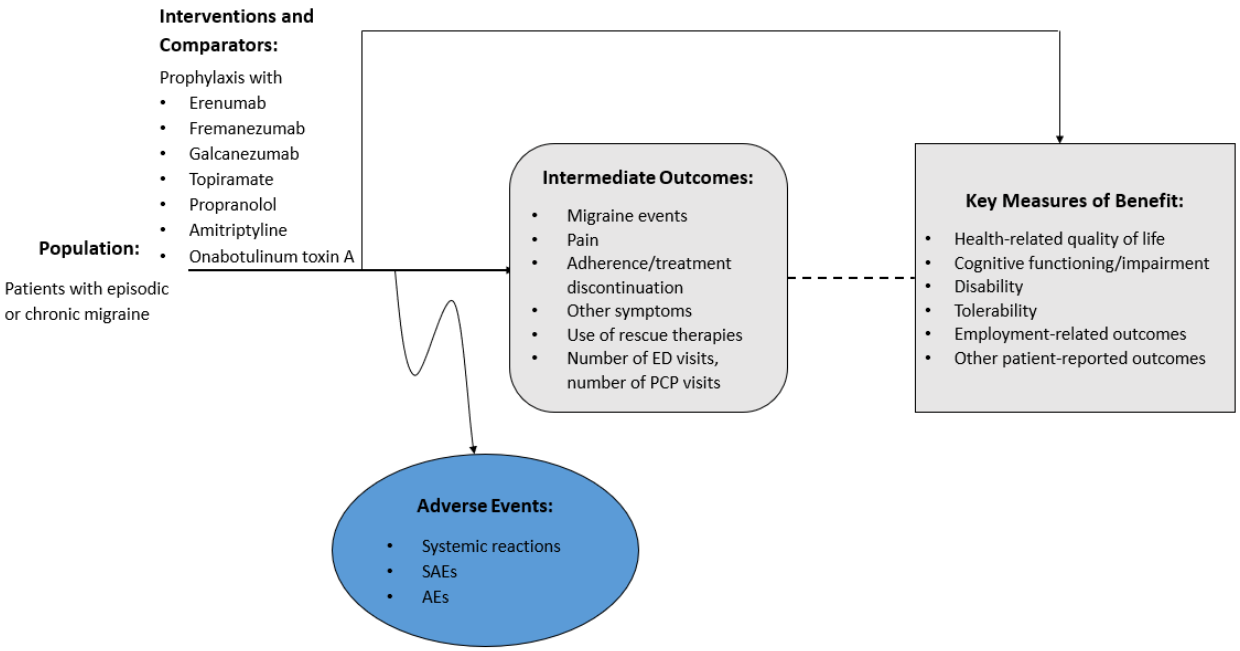
Settings

All relevant settings were considered, including inpatient, outpatient/clinic, office, and home settings.

Analytic Framework

The analytic framework for this review is depicted below.

Figure 1.1. Analytic Framework: CGRP Inhibitors for Chronic or Episodic Migraine



AE: adverse event, ED: Emergency Department, PCP: Primary Care Physician, SAE: serious adverse event

The diagram (Figure 1.1) begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., migraine events), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[92]

1.3 Definitions

Select International Classification of Headache Disorders (ICHD) Third Edition Criteria for Migraine Diagnoses[93]

- **Migraine without aura:** Patients with migraine without aura have at least five attacks meeting the following criteria: headache lasting four to 72 hours without treatment or without successful treatment, headache with at least two characteristics (unilateral location, pulsating quality, moderate or severe pain, aggravated by or caused avoidance of routine physical activity), at least one symptom of nausea/vomiting or sensitivity to light or sound.

- **Migraine with aura:** Patients with migraine with aura have at least two attacks meeting the following criteria: presence of aura (visual, sensory, speech/language, motor, brainstem, or retinal symptoms, each fully reversible), and at least two characteristics (aura symptom spreads gradually over at least five minutes, each aura symptom lasts five to 60 minutes, at least one aura symptom is unilateral, a headache accompanies the aura or follows within 60 minutes).
- **Chronic migraine:** Patients with chronic migraine have headaches (migraine-like or tension-type-like) on at least 15 days per month for more than three months. Patients have had at least five attacks meeting criteria for migraine without aura or migraine with aura. In addition, on at least eight days per month for more than three months, patients have experienced migraines with characteristics and symptoms of migraine with or without aura, or headache believed to be a migraine at onset and relieve by a triptan or ergot derivative.
- **Probable migraine:** Patients with probable migraine fulfill all but one criteria for migraine without aura or migraine with aura.
- **Medication overuse headache:** Patients with medication overuse headache are those with an existing headache disorder who experience headaches on at least 15 days per month and have regularly overused drugs taken for acute or symptomatic treatment of headaches for more than three months.

Episodic migraine: Patients diagnosed with migraine who do not meet the criteria for chronic migraine. Note that this term is not a clinical diagnosis.

Preventive therapy: Any routinely-given therapy used with the goal of reducing the frequency, intensity, or duration of attacks.

Acute medication: Pharmacologic agent used to treat a migraine attack, sometimes referred to as "abortive" medication.

Headache Impact Test (HIT-6): A six-item questionnaire developed to measure the burden and level of disability in migraine patients. The questionnaire asks patients about their head pain, social, work and cognitive functioning, vitality, and psychological distress. An overall severity level is generated, with scores ranging from 36 to 78 and higher scores indicate more severe impact. The HIT-6 can be found online (http://campaign.optum.com/optum-outcomes/what-we-do/disease-specific-health-surveys/hit-6.html)

Migraine Disability Assessment (MIDAS): A five-item questionnaire developed to help patients measure the number of days that migraines impacted their lives. The questionnaire asks patients about the number of days during last three months that they were inhibited by their headaches in different forms. An overall level of disability is generated based on the total number of days affected. The specific questions are:

1. On how many days in the last three months did you miss work or school because of your headaches?
2. How many days in the last three months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question one where you missed work or school.)
3. On how many days in the last three months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?
4. How many days in the last three months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question three where you did not do household work.)
5. On how many days in the last three months did you miss family, social or leisure activities because of your headaches?

Migraine-Specific Quality of Life Questionnaire (MSQ): A 14-item questionnaire that measures the health-related quality of life in migraine patients. The questionnaire asks patients about three essential aspects (domains) over the past month: role function-restrictive (RFR), role function-preventive (RFP), and emotional function (EF). RFR includes seven questions regarding how migraines limit daily social and work-related activities. RFP includes four questions regarding how migraines prevent these activities. EF includes three questions about the patients' emotions. Raw scores for each domain are rescaled to 0 to 100, with higher values indicating a better quality of life.

1.4 Insights Gained from Discussions with Patients and Patient Groups

We heard from many migraine patients about how living with migraine affects their everyday lives, how current treatments provide only temporary relief, how accessing effective care or treatment is challenging, and what outcomes are most important. Below, we provide a summary of the main themes from these patient submissions and discussions. We note that this is a summary of the submissions we received and may not represent the experiences of all patients with migraine, particularly those who are less burdened by the condition.

Migraine prevents patients from having normal lives:

- The pain and other symptoms from migraine attacks can last from hours to days.
- Migraine alters patients' decisions, and many patients do not plan or commit to future events, including joining the workforce, because of the uncertainty surrounding when the next attack will occur.
- Living and working spaces need to be adapted (e.g., installation of black-out curtains)
- Patients frequently reported feeling frustrated, depressed, defeated, isolated, or a burden to society; some patients experience suicidal thoughts.

- Patients can miss many days of work or school per month due to migraine attacks.
- At work or school, patients struggle to concentrate, remember things, or speak clearly, which affects performance and employment.
- Relationships with family and friends are strained because of unpredictability of migraine attacks, difficulties participating in activities, and financial pressures from migraine-related medical expenses.
- Patients feel stigmatized and that migraine pain is not taken seriously.

Relief provided by existing preventive treatments is often temporary:

- Patients have tried extensive lists of preventive and acute treatments (including drug and non-drug therapies, and lifestyle changes).
- Some treatments work for a time, but they either stop working or are not tolerable.
- Side-effects from some interventions can be as debilitating as migraine.

Patients struggle to access effective care or treatment:

- Difficulties arise in finding a physician who understands migraine and migraine pain.
- Due to high costs and access restrictions, patients may not have a sufficient supply of acute treatment (e.g., triptans); patients may ration treatment and choose the "important" days to take treatment.
- Patients feel discouraged because treatment strategies follow a "guess and test" procedure, which can take many years before they find an effective treatment.
- Patients reported paying high co-pays for many treatments; some patients must wait for pre-authorization from their insurer.
- Patients also are concerned about the affordability of new preventive treatments.

Patients seek treatments that improve their quality of life:

- For many patients, reduced pain and symptom relief are important steps to improving overall quality of life.
- Patients also reported that fewer side-effects, improved cognitive functioning, and ability to work or take care of family are important outcomes.

In addition, patients and patient advocacy groups directed us to a national survey "Migraine in America" conducted by migraine.com.[94] The survey includes patients with either episodic or chronic migraine and asks a range of questions pertaining to living with migraine. The responses echoed many of the concerns we heard above, including the challenges in dealing with uncertainty of migraine attacks and in ability to function.

1.5. Potential Cost-Saving Measures in Chronic or Episodic Migraine

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/).

The American Headache Society (AHS) has several Choosing Wisely recommendations for clinicians that have the potential to reduce waste by avoiding unnecessary or inappropriate services:[31]

- Do not perform neuroimaging studies in patients with stable headaches that meet criteria for migraine
- Do not perform computed tomography (CT) imaging for headache when magnetic resonance imaging (MRI) is available, except in emergency settings
- Do not recommend surgical deactivation of migraine trigger points outside of a clinical trial
- Do not prescribe opioid or butalbital-containing medications as first-line treatment for recurrent headache disorders
- Do not recommend prolonged or frequent use of over-the-counter pain medications for headache

While each of these recommendations may help to reduce unnecessary services, only the first recommendation focused on reducing neuroimaging is likely to be cost-saving. In addition, we heard from clinicians that reducing ED visits, for example by directing patients to infusion centers, may also be an area for potential cost savings.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for therapies for migraine prevention, we reviewed publicly-available coverage policies for amitriptyline, propranolol, topiramate, and onabotulinum toxin A from the Centers for Medicare and Medicaid Services (CMS), California Department of Health Care Services (DHCS), and from regional and national commercial insurers (Aetna, Anthem, Blue Shield of California [BSCA], Cigna, Health Net, Humana, Kaiser Permanente, and United HealthCare [UHC]). At the time the revised Evidence report was published, we were unable to survey policies pertaining to CGRP inhibitors, as the FDA had yet to issue a decision on fremanezumab and galcanezumab at the time this report was published, and payers had not yet posted policies pertaining to the use of erenumab.

We were unable to locate any National Coverage Determinations (NCDs) from CMS for any of the preventive therapies. A Medicare Authorized Contractor, Noridian Health Care Solutions, has issued a Local Coverage Determination (LCD) for the state of California that authorizes reimbursement for onabotulinum toxin A for patients with chronic migraine, defined as 15 or more headache days per month lasting at least four hours per headache day.[95] The policy from the California DCHS pertaining to Medi-Cal matches the LCD.[96] California DHCS further covers amitriptyline, propranolol, and topiramate at the lowest formulary tier; we were unable to locate formulary information for onabotulinum toxin A.[97]

Each of the commercial payers included in our search covered generic versions amitriptyline, propranolol, and topiramate at the lowest available formulary tier, and did not have utilization management policies for their use in either episodic or chronic migraine.[98-105]

Details of the utilization management policies for onabotulinum toxin A are included in Table 2.1 and are broadly summarized below. We identified publicly-available utilization management policies from all payers except for BSCA and Kaiser Permanente.[106-111] All of the other private insurers required a diagnosis of chronic migraine, defined as at least 15 headache days per month for at least four hours per day; UHC further specified that at least half of the headache days must be classified as migraine or probable migraine days. Prior authorization requirements and step therapy policies were nearly universal across private payers, with Kaiser Permanente being the only payer that did not require them in its formulary.[98,112] Requirements from other payers varied narrowly, with patients commonly being required to attempt treatment with two or three agents from two different classes (e.g., antiepileptics, beta blockers, antidepressants, etc.). Aetna was the only payer that specified a minimum duration for prior therapy attempts of 60 days per medication.

Health Net's policy was the most extensive and required patients to attempt three abortive medications and two preventive medications, all from different classes.

Stopping rules varied widely across payers, though policies for continuation of therapy were consistent. If patients did not respond to therapy, Aetna required discontinuation after a 12-week trial, Anthem after six months, and Cigna after one year. Aetna, Anthem, and Cigna would authorize continued therapy if patients experience a minimum reduction of seven days or 100 hours of migraine per month within those trial periods. Health Net specified only that treatment would be re-authorized for the length of benefit, and the other payers did not include stopping or continuation rules in their policies.

Table 2.1. Representative Private Payer Policies for Onabotulinum Toxin A

Criteria	Aetna	Anthem	Cigna	Humana	UHC	BSCA	Health Net	Kaiser Permanente
Tier	Specialty	Specialty	Excluded	Specialty	NS	NS	NS	2 (branded drugs)
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
ST	Yes	Yes	Yes	Yes	Yes	NS	Yes	No
Number of Headache Days	≥ 15	≥ 15	≥ 15	≥ 15	≥ 15, 50% migraine / probable migraine	NS	≥ 15	NS
Duration of Headaches	> 4 hours/day	> 4 hours/day	> 4 hours/day	> 4 hours/day	> 4 hours/day	NS	4 hours/day	NS
Prior Tx Requirement	≥ 3 agents, ≥ 2 classes for at least 60 days per medication	≥ 2 agents, ≥ 2 classes	≥ 2 agents, ≥ 2 classes	≥ 2 preventive therapies	≥ 2 agents, ≥ 2 classes	NS	≥ 3 acute medications from different classes and ≥ 2 preventive therapies from different classes	NS
D/C Rule	No response after 12 weeks	Inadequate response after 6 months	Inadequate response after 1 year	NS	NS	NS	NS	NS
Continuation Rule	Reduction of 7 days/month or 100 hours/month	Reduction of 7 days/month or 100 hours/month	Reduction of 7 days/month or 100 hours/month	NS	NS	NS	Approved for length of benefit	NS
Additional Criteria	NS	First episode at least 6 months ago	NS	NS	NS	NS	Chronic migraine for at least 3 months. Documentation of significant disability (i.e., inability to work, multiple ED visits)	NS

BSCA: Blue Shield of California**,** D/C: discontinuation, ED: emergency department, NS: not specified, PA: prior authorization, ST: step therapy, Tx: therapy, UHC: United Healthcare

2.2 Clinical Guidelines

We reviewed guidelines on migraine treatment issued by major US and ex-US clinical societies and health technology assessment organizations. Although many of the organizations also provide recommendations on the use of abortive therapies, we have only summarized the guidance that pertain to the prevention of episodic or chronic migraine with pharmacologic therapy. At the time this report was published, we were unable to locate any guideline statements that pertained to CGRP inhibitors. We received feedback on the draft report that the American Migraine Foundation and the American Headache Society were working to publish a consensus document with criteria for identifying patients who clinicians should consider treating with CGRP inhibitors.

American Academy of Neurology (AAN)

Botulinum Neurotoxin for the Treatment of Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache (2016)[17]

In their 2016 guidelines, the AAN recommends that clinicians offer onabotulinum toxin A to patients with chronic migraine, defined as migraine attacks on at least 15 days per month for a period of at least three months, to reduce the number of headache days. Doctors may also consider offering the treatment to improve health-related quality of life, though on the basis of weaker evidence. The authors of the guideline note that there was a large placebo response in clinical trials, and that the magnitude of between-group differences was small, but statistically significant. The AAN considers onabotulinum toxin A to be ineffective as a treatment for episodic migraine and recommends that it not be offered to such patients.

Pharmacologic Treatment for Episodic Migraine Prevention in Adults (2012)[16,113]

The AAN's 2012 guidelines were jointly developed with the American Headache Society (AHS). For the prevention of episodic migraine, the AAN/AHS recommends that clinicians offer antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) or beta blockers (metoprolol, propranolol, timolol). They recommend several other medications as "probably" effective, including antidepressants (amitriptyline, venlafaxine) and other beta blockers (atenolol, nadolol). Additional medications are considered "possibly" effective (lisinopril, candesartan, guanfacine, carbamazepine, and nebivolol), and may be offered to patients.

British Association for the Study of Headache (BASH)

Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache, Medication-Overuse Headache, 2010[114]

In their 2010 guidelines, BASH recommends that prophylactic treatment for migraine be used in addition to acute treatments, and they additionally note that prophylaxis is ineffective for the

treatment of medication overuse headache, which should be ruled out before beginning preventive treatment. The society recommends beta blockers, topiramate, valproate, and amitriptyline as first-line treatments, and that clinicians consider evidence on efficacy, comorbidity, contraindications, and ease of compliance when deciding which treatment to use. Second-line treatments include topiramate and sodium valproate. Onabotulinum toxin A is recommended only for patients who experience more than 15 headache days per month, at least eight of which are migraines, though the guidelines note that there were small, but statistically significant differences, between the active and placebo arms in clinical trials.

BASH recommends that effective treatments be continued for four to six months, then withdrawn over a period of two to three weeks, stating that uninterrupted prophylaxis over the long term is only appropriate in rare cases. Conversely, they recommend that drugs that initially appear to be ineffective be continued for a trial period of six to eight weeks after dose titration, barring unacceptable side effects, as benefit may be delayed.

National Institute for Health and Care Excellence (NICE, United Kingdom)

Management of Migraine (With or Without Aura)[115]

NICE recommends that physicians offer topiramate or propranolol for the prevention of migraine, with the choice of agent being driven by individual patient preference, comorbidities, and risk of experiencing adverse events. Women of childbearing potential should be advised that topiramate may cause fetal malformations and may reduce the effectiveness of hormonal contraceptives. Amitriptyline may also be offered based on patient preference.

Physicians may offer onabotulinum toxin A for the prevention of chronic migraine, defined as headaches on at least 15 days per month with at least eight being classified as migraine, provided the patient has attempted at least three other pharmacologic preventive treatments, and that the patient is being managed for medication overuse. Doctors should stop therapy with onabotulinum toxin A if the patient does not experience at least a 30% reduction in headache days per month after two treatment cycles, or if the patient's migraine converts to episodic migraine (< 15 headache days per month) for three consecutive months.

3. Comparative Clinical Effectiveness

3.1 Overview

In this review of the comparative clinical effectiveness of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab), we systematically identified and synthesized the existing evidence from clinical studies. Full PICOTS criteria were described in Section 1.2. In brief, we evaluated studies of adult patients 18 years of age or older with chronic or episodic migraine who were eligible for preventive migraine therapy. Our review focused on the efficacy, safety, and effectiveness of CGRP inhibitors versus each other or commonly-used preventive therapies. For both episodic and chronic migraine populations, commonly-used preventive therapies included topiramate, propranolol, and amitriptyline. For chronic migraine, onabotulinum toxin A was also included. For the subgroup of patients for whom at least one prior preventive therapy has failed, we compared each of the CGRP inhibitors to each other, to no treatment (placebo), and to onabotulinum toxin A (chronic migraine only).

Essential to our review was the evidence on the clinical benefits common to migraine trials and reported tolerability/harms. We sought evidence on all outcomes listed in Section 1.2. Here, we focused on the primary outcomes listed below.

- Clinical benefits (separately for chronic and episodic migraine)
    - Migraine days per month
    - ≥ 50% reduction in migraine days (50% responders)
    - Headache days per month
    - Days using acute medication per month
    - Quality of life (MIDAS, HIT-6, MSQ)
- Tolerability/harms (pooled studies of chronic or episodic migraine, unless otherwise noted)
    - All-cause discontinuations (separately for chronic and episodic migraine)
    - Discontinuation due to AEs
    - Serious adverse events (SAEs)
    - Any AE reported by ≥ 5% of a trial arm

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on CGRP inhibitors for migraine followed established best methods.[116,117] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[118,119] The PRISMA guidelines include a list of 27 checklist items, which are listed in Appendix Table A1.

We searched MEDLINE and the Cochrane Central Register of Controlled Trials through the Ovid database and searched EMBASE directly for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2-A3. The date of the most recent search is May 2, 2018. Since then, two additional trials assessing galcanezumab (EVOLVE-1 and EVOLVE-2) were published and are also included in the review.

We further supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more details, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Two reviewers independently screened the abstracts and full-texts of studies using DistillerSR, with any differences resolved through consensus. We included relevant published randomized clinical trials (RCTs) of any sample size and non-randomized comparative studies with a minimum of 100 participants. Crossover studies were included only if they reported results prior to crossover. To support the comparative evidence and to gain insights into the duration of treatment benefits and harms, we included non-comparative observational studies with a minimum of 100 participants and six months of follow-up and open-label extensions (OLEs) of RCTs of any size and duration. Studies assessing other headache or migraine conditions including tension-type headaches, cluster headaches, and other secondary headaches arising from another existing condition were excluded. We excluded conference abstracts reporting data available in a full-text peer-reviewed publication.

Data Extraction and Quality Assessment

Data were extracted into the Systematic Review Data Repository™ by one researcher and independently verified by another researcher. Data elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features (e.g., open-label or crossover periods), interventions (drug, dosage, frequency, schedules), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality assessment for each study. Quality assessment was based on US Preventive Services Task Force (USPSTF)[120] criteria that included presence of comparable groups, non-differential loss to follow-up, use of blinding, clear definition of interventions and outcomes, and appropriate handling of missing data. For more information on data extraction and quality assessment, refer to Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix Figure D1).[121]

Assessment of Publication Bias

We assessed the presence of publication bias by utilizing the clinicaltrials.gov database of trials. Search terms included "AMG-334", "erenumab", "TEV-48125", "fremanezumab", and "LY2951742" and "galcanezumab". Evidence of publication bias exists if any registered trials meeting our inclusion criteria that was completed more than two years ago does not have published findings. We did not identify any completed, unpublished trials of CGRP inhibitors, hence we did not find evidence of publication bias. We identified 13 registered, ongoing trials of CGRP inhibitors. These trials are described in the Ongoing Studies section in Appendix C and not included in any of our analyses.

Data Synthesis and Statistical Analyses

Data on outcome results were summarized in evidence tables (see Appendix Tables D9-D18) and synthesized quantitatively and qualitatively in the body of the review. Data from OLEs and observational studies were described narratively only and not included in the quantitative syntheses. Using the available trial data, we conducted network meta-analyses (NMAs) for each outcome of interest, including tolerability and harms, when data existed from at least three trials that were sufficiently similar in population, interventions, outcomes, time point, and other characteristics. Based in part on availability of data from sufficiently similar trials, we conducted NMAs on the following efficacy outcomes, separately for chronic and episodic migraine: the change from baseline in monthly migraine days, 50% responders (episodic migraine only), the change from baseline in monthly headache days (chronic migraine only), and the change from baseline in days per month using acute medications. Due to limited data, 50% responders in the chronic migraine population, monthly headache days in the episodic migraine population, and quality of life data using MIDAS, HIT-6, and MSQ for both populations are described narratively only. We also conducted NMAs for all-cause discontinuations separately for trials of chronic and episodic migraine and NMAs for SAEs and discontinuations due to AEs pooling trials in chronic and episodic migraine. Specific AEs reported by ≥ 5% of patients in a given study were too infrequently reported for an NMA and are described narratively only.

For studies that reported data at multiple time points, we included data at the latest time point for the NMA. Where feasible, we also conducted NMAs separately at monthly time points (e.g., four weeks, eight weeks, 12 weeks); these results are available in Appendix Tables D29-D32. In addition, we conducted network meta-regression analyses with study duration as a covariate; these analyses did not provide a better fit and results are also available in Appendix Tables D29-D32.

All NMAs were conducted in a Bayesian framework with random effects on the treatment parameters using the *gemtc* package in R.[122] Continuous outcomes were analysed using a normal likelihood and identity link; binary outcomes were analysed using a binomial likelihood and logit link.[123] Tabular results below were presented for the treatment effects (mean difference or odds ratio [OR]) of each intervention versus placebo along with 95% credible intervals (95% CrI). The expected change from baseline or proportion of patients experiencing the outcome were also presented when anchoring to the average placebo effect observed across the CGRP inhibitor trials. Additional details regarding the analysis methods, as well as network diagrams and league tables with all pairwise results are provided in Appendix D (Appendix Tables D19-D28 and Figures D1-D10).

3.3 Results

Study Selection

Our literature search identified a total of 1,601 potentially relevant references (see Appendix A Figure A1). We included 91 references, of which 80 references presented on comparative clinical trials, four on OLEs, and seven on observational studies. These references consisted of 66 publications and 25 conference abstracts. Primary reasons for study exclusion included use of interventions outside of our scope, wrong study population (e.g., pediatric population), small sample size (sample size < 100 for observational studies), minimum follow-up duration not met (non-comparative observational studies with less than six months of follow-up), and conference abstracts with duplicate data as the full-text publications.

The 80 references of comparative trials correspond to 50 trials, of which 13 trials (39 references) assessed a CGRP inhibitor and 37 trials (41 references) assessed one or more of the comparators of interest. Currently, there are no head-to-head trials of CGRP inhibitors versus any of the comparators of interest. Below, we describe the trials and efficacy results separately for chronic and episodic migraine, followed by a discussion of the tolerability and harms reported in both populations.

Quality of Individual Trials

We rated all CGRP inhibitor trials in chronic or episodic migraine to be of good quality. All trials had comparable arms at baseline, did not have differential attrition, were patient and physician/investigator blinded, had clear definitions of intervention and outcomes, and used an intent-to-treat analysis or a modified version. The trials of erenumab and galcanezumab did not impute missing data in their primary outcomes, whereas the trials of fremanezumab used a form of single imputation. For secondary outcomes, the trials typically used a form of single imputation for continuous (e.g., last observation carried forward) and categorical outcomes (e.g., missing data treated as non-responder), and some trials conducted sensitivity analyses using multiple imputation. Without additional details regarding the validity of the assumptions underlying these

approaches for handling missing data, their effect on the outcomes' reported means and variances are unknown.[124,125]

In both the chronic and episodic migraine populations, trials on the commonly-used preventive therapies had ratings of good (six trials), fair (15 trials), or poor (16 trials). Common reasons for lower ratings include a lack of reporting of the comparability of the arms at baseline, ambiguity in definitions of outcomes, and inadequate reporting of approaches for handling missing data. Detailed information on the ratings can be found in Appendix Tables D7-D8.

Chronic Migraine

Overview of Trials Assessing CGRP Inhibitors

Of the 13 CGRP inhibitor RCTs, four were in chronic migraine. We included one Phase II RCT assessing erenumab (NCT02066415, Tepper 2017),[90,126-129] one Phase II RCT assessing fremanezumab (NCT02021773, Bigal 2015a),[26] and one Phase III RCT assessing fremanezumab (NCT02621931, HALO-CM).[28,130-133] We also identified one unpublished, ongoing Phase III RCT on galcanezumab (NCT02614261, REGAIN).[134,135] Given limited details on its study design and baseline characteristics, we were unable to assess the similarity of REGAIN to the published trials and we did not include the results in any quantitative analysis. Refer to Appendix C for the data available from this trial.

The three erenumab and fremanezumab RCTs were all industry-funded with locations predominantly in North America and Europe. All RCTs included a four-week baseline period, followed by a 12-week randomized, placebo-controlled phase in which patients and investigators were blinded to treatment assignment. Patients were enrolled in the baseline phases of the trials if they had a diagnosis of chronic migraine based on ICHD (third edition, beta) criteria or self-reported history of chronic migraine, defined as ≥ 15 headache days per month with at least eight migraine days per month. Patients who continued to meet the criteria for chronic migraine during the four-week baseline phase and who showed at least 80% compliance with a daily electronic headache diary (i.e., completed the diary on 22 of 28 days or 24 of 28 days in HALO-CM) continued to the randomized phase.

Appendix Tables D1 and D5 contain the key study design and baseline characteristics of the patients included in the randomized phases. Over 80% of the patients were female and the average age was approximately 40 years in each trial. Patients had been living with migraine for approximately 20 years. Across the trials, patients at baseline had an average of 16 to 18 migraine days per month and 16 to 21 headache days per month. At baseline, the average number of days using an acute migraine-specific medication ranged from nine days per month (Tepper 2017, erenumab) to 11 days per month (HALO-CM, fremanezumab); the average number of days using any acute medication ranged from 13 days per month (HALO-CM, fremanezumab) to 16 days per month (Bigal 2015a,

fremanezumab) at baseline. In the erenumab trial, 41% of patients reported medication overuse headache, which was not reported in either fremanezumab trial.

All trials excluded patients who had no therapeutic response after an adequate trial of preventive therapies. In the erenumab trial, patients who experienced the failure of more than three preventive therapy categories were excluded. In the fremanezumab trials, patients who experienced the failure of more than two preventive medication categories or more than three preventive medications across two categories were excluded. At baseline, approximately 68% of patients in the erenumab trial had previously experienced the failure of at least one preventive therapy. These data were not reported in the fremanezumab trials. Patients in the erenumab trial were not allowed to take concomitant migraine preventive therapy during the trial, whereas patients in both fremanezumab trials could continue taking preventive therapy at stable doses. At baseline, approximately 20% of patients in HALO-CM and 40% of patients in Bigal 2015a continued using existing preventive therapies.

The primary efficacy outcome in the erenumab trial (Tepper 2017) was the mean change in monthly migraine days from baseline to the last four weeks of the treatment period (nine to 12 weeks). Patients on erenumab 140 mg and 70 mg experienced larger reductions in monthly migraine days during week nine through 12 than those on placebo (difference with erenumab 70 mg vs. placebo -2.5 [95% CI -3.5, -1.4] and difference with erenumab 140 mg vs. placebo -2.5 [95% CI -3.5, -1.4]).[90] For the two trials of fremanezumab, the primary outcomes were mean change in the average number of headache hours of any severity from baseline to weeks nine to 12 (Bigal 2015a) and mean change from baseline in monthly headache days by 12 weeks after treatment. In Bigal 2015a, patients on fremanezumab 625/225 mg monthly experienced a larger reduction in headache hours during week nine to 12 than those on placebo (difference vs. placebo -22.7 [95% CI -44.3, -1.2]).[26] In HALO-CM, patients on fremanezumab monthly and quarterly dosing experienced a greater reduction in headache days per month during the 12-week treatment phase than those on placebo (difference in fremanezumab monthly vs. placebo -2.1 [standard error, SE 0.3] and difference in fremanezumab quarterly vs. placebo -1.8 [SE 0.3]).[28]

Overview of Trials Assessing Current Preventive Therapies in Chronic Migraine

We included 13 trials (15 references) and one OLE assessing at least one comparator of interest in the chronic migraine population. Four RCTs,[34-37] one crossover trial,[38] and one OLE[136] were included for onabotulinum toxin A versus placebo, two RCTs for onabotulinum toxin A versus topiramate,[39,137] and one RCT for onabotulinum toxin A versus amitriptyline.[138] Four RCTs (six publications) were included for topiramate versus placebo[32,33,139-142] and one RCT compared topiramate and propranolol combination therapy to topiramate alone.[143]

Appendix Tables D2 and D5 contain the key study design and baseline characteristics. Most trials were industry-funded, multi-centered trials conducted predominately in North America and Europe,

except for three single-center trials including one conducted in Brazil (Magalhaes 2010). All trials had a parallel design with a baseline phase followed by a randomized placebo-controlled phase, except for one randomized crossover trial of onabotulinum toxin A with a four-month pre-crossover period (Cady 2014). Eleven of the RCTs had a four-week baseline period, whereas one trial had an eight-week baseline period (Silvestrini 2003). Patients fulfilling specific chronic migraine criteria (ICHD first or second edition) during the baseline phase continued to the randomized phase. In PREEMPT 1 and 2, patients were required to provide headache diary data on at least 20 of the 28 days during baseline. Criteria related to compliance with a daily headache diary was not reported in the other trials. The randomized phase was between nine and 36 weeks, with two onabotulinum toxin A trials having open-label follow-up periods of a year. Overall, the trials included predominantly female patients living with migraine since their adolescence or early twenties. Where reported, the mean age ranged from 30 to 50 years, and mean monthly migraine days ranged from 10 to 25 days at baseline. Most trials did not allow concomitant use of preventive therapies, with the exception of Diener 2007 with approximately 14% of patients using concomitant preventive therapy at baseline. Freitag 2008 and Cady 2014 allowed concomitant preventive therapy but did not report the proportion of patients using it at baseline.

Clinical Benefits

Of the 16 included trials that evaluated preventive therapies in chronic migraine, 15 trials reported outcome data on at least one of the efficacy endpoints described below (change from baseline in monthly migraine days, 50% responders, change from baseline in monthly headache days, or change from baseline in days per month using acute medication). Three of these trials (Sandrini 2011, Mei 2006, Silvestrini 2003) only included patients with medication overuse headache and were excluded from these efficacy analyses. Silberstein 2012 assessed topiramate versus the combination of topiramate plus propranolol. As the combination was not of direct interest for these analyses and the comparison does not add strength to the network, this trial was not included in the analyses.

Of the remaining 11 trials, nine were placebo-controlled and assessed erenumab (one trial), fremanezumab (two trials), onabotulinum toxin A (four trials), or topiramate (two trials), and two trials directly compared topiramate and onabotulinum toxin A. Both fremanezumab trials and one topiramate trial (Silberstein 2007) permitted concomitant preventive migraine therapy, which was not permitted in the other eight trials. Across six of the 11 trials, the included patients had a history of chronic migraine for an average of 20 years, which was lower in one topiramate trial (nine years; Silberstein 2007) or not reported (Cady 2014, Freitag 2008, Diener 2007, Cady 2011). Five trials excluded patients with medication overuse headaches, whereas four other trials reported the proportion of patients with medication overuse headache, which ranged from 41%-68%. Neither fremanezumab trial reported this information. At baseline, the mean number of migraine days per month ranged from 16-18 in the CGRP inhibitor and topiramate trials and was 19 migraine days for

the onabotulinum toxin A trials. The time point of analysis ranged from 12 to 26 weeks. Overall, these 11 trials were deemed sufficiently similar and included in the efficacy analyses below.

Migraine Days per Month

Seven trials reported the mean change from baseline in monthly migraine days. The trials used similar definitions of migraine days: a day with migraine (with or without aura) or probable migraine (lacking one migraine feature) lasting four or more hours (at least 30 minutes in Diener 2007). The CGRP inhibitor trials also considered a day that involved the use of acute migraine-specific medication as a migraine day. One trial of topiramate (Diener 2007) was not included in the analysis due to inconsistent data reported in the publication. Sensitivity analyses that included the data from this trial are available in Appendix Table D29. The timepoint of analysis of the remaining six trials was the last four weeks of the randomization period for the three CGRP inhibitor trials, the full 24-week period for the two onabotulinum toxin A trials, and the full 16-week period for the topiramate trial. Table 3.1 presents the data inputs for the NMA, which included the mean change from baseline and standard error for each arm of the trials. If these data were not reported, we included the reported difference in change from baseline between arms. For the arm-level change from baseline, a negative value indicated a reduction in monthly migraine days. For the difference in change from baseline, a negative value indicated a larger reduction for the intervention versus placebo. Across the trials, patients receiving placebo experienced an average change from baseline of 3.8 to 6.3 fewer migraine days per month. Overall, trials reported greater reductions in monthly migraine days for all interventions versus placebo.

Table 3.1. Data for Change from Baseline in Monthly Migraine Days in Chronic Migraine Patients

Trial	Week	Tx 1	Mean (SE)	Tx 2	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 3	Mean (SE)	Difference vs. Tx 1 (95% CI)
Tepper 2017[90]	12	Placebo	-4.20 (0.40)	Erenumab 70 mg	-6.60 (0.40)	-2.5 (-3.5, -1.4)	Erenumab 140 mg	-6.6 (0.40)	-2.5 (-3.5, -1.4)
Bigal 2015a[26]	12	Placebo	NR	Fremanezumab 675/225 mg*	NR	-1.7 (-3.7, 0.2)			
Silberstein 2017 (HALO-CM)[28]	12	Placebo	-3.80 (0.4)	Fremanezumab 675/225 mg	-5.43 (0.30)	-1.6 (NR)	Fremanezumab 675 mg	-5.08 (0.35)	-1.3 (NR)
Aurora 2010 (PREEMPT 1)[34]	24	Placebo	-6.10 (0.37)	Onabotulinum toxin A 155U	-7.60 (0.35)	-1.5 (-2.6, -0.6)			
Diener 2010 (PREEMPT 2)[35]	24	Placebo	-6.30 (0.35)	Onabotulinum toxin A 155U	-8.70 (0.36)	-2.4 (-3.3, -1.4)			
Silberstein 2007[32]	16	Placebo	-4.70 (0.49)	Topiramate 100 mg/day	-6.40 (0.47)	-1.7 (NR)			

*Results are for difference vs. placebo only.

CI: confidence interval, NR: not reported, Tx: treatment, SE: standard error

Table 3.2 presents the results from an NMA with random treatment effects. The first column is the difference in the change from baseline in monthly migraine days for each intervention versus placebo with corresponding 95% CrIs. Negative values indicate a larger reduction in monthly migraine days versus placebo. Note that in this analysis, the standard deviation of the random treatment effects (i.e., heterogeneity parameter) was not precise with an estimate and 95% CrI of 0.65 (0.03, 2.19), which led to wide Crls for the treatment effects. Consistent with the trial results, the NMA results suggest a larger reduction in monthly migraine days with CGRP inhibitors than placebo, although the NMA results are not statistically significant. Erenumab 70 mg and 140 mg had approximately 2.4 fewer migraine days per month than placebo, whereas fremanezumab quarterly and monthly had 1.3 and 1.7 fewer migraine days per month versus placebo, respectively. Onabotulinum toxin A had 2.0 fewer migraine days per month versus placebo which was statistically significant. Topiramate 100 mg per day had approximately 1.7 fewer migraine days per month versus placebo, which was not statistically significant. Results comparing active therapies were not statistically significant.

The estimated change from baseline in monthly migraine days for each active therapy is presented in the second column of Table 3.2, with the corresponding 95% CrIs. Here, the estimates for the CGRP inhibitors ranged from 5.3 fewer migraine days per month with fremanezumab quarterly to 6.4 fewer migraine days per month with erenumab 70 mg or 140 mg.

Table 3.2. NMA Results for Change from Baseline in Monthly Migraine Days in Chronic Migraine Patients

	Difference in Change From Baseline vs. Placebo Estimate (95% CrI)	Expected Change From Baseline Estimate (95% CrI)
Placebo	Reference	-4.0 (NA)
Erenumab 70 mg monthly	-2.4 (-4.8, 0.0)	-6.4 (-8.8, -4.0)
Erenumab 140 mg monthly	-2.4 (-4.8, 0.0)	-6.4 (-8.8, -4.0)
Fremanezumab 675 mg quarterly	-1.3 (-3.5, 0.9)	-5.3 (-7.5, -3.1)
Fremanezumab 675/225 mg monthly	-1.7 (-3.5, 0.1)	-5.7 (-7.5, -3.9)
Onabotulinum toxin A 155U quarterly	-2.0 (-3.6, -0.3)	-6.0 (-7.6, -4.3)
Topiramate 100 mg/day	-1.7 (-4.2, 0.8)	-5.7 (-8.2, -3.2)

Standard deviation for treatment effects: 0.65 (0.03, 2.19)

CrI: credible interval, NA: not applicable

For longer-term results, data were currently available for onabotulinum toxin A only. The pooled OLE data of PREEMPT 1 and 2 showed a continued reduction in monthly migraine days by 56 weeks that was statistically significant for those who received all five treatment cycles of onabotulinum toxin A (change from baseline -11.6 [95% CI -12.2, -11.0]) and those who were previously taking placebo and switched to onabotulinum toxin A during the open-label phase (change from baseline -10.7 [95% CI -11.3, -10.0]).[136]

We also reviewed data for the subpopulation of chronic migraine patients who experienced the failure of at least one preventive therapy prior to the start of the trial. Manufacturers of erenumab and fremanezumab submitted the data in confidence, which will be publicly reported here no later than December 2019, in line with ICER's data in confidence policy (https://icer-review.org/use-of-in-confidence-data/). Results for the difference in change from baseline with onabotulinum toxin A versus placebo were -2.0 (95% CI -3.2, -0.8) at week 12 based on pooled data from PREEMPT 1 and 2.[144]

50% Responders

Six trials reported the proportion of patients who experienced at least a 50% reduction in the number of migraine days (Tepper 2017, Bigal 2015a, HALO-CM, Silberstein 2007, Diener 2007) or number of migraine episodes (Freitag 2008). In addition, four trials defined 50% response as at least a 50% reduction in moderate-to-severe headache days (Bigal 2015a) or any headache days (HALO-CM, Silberstein 2007, Mathew 2009). Because of these differences in definitions, we were unable to conduct a quantitative analysis to indirectly compare treatment effects and describe reported results below.

In the erenumab trial, at 12 weeks, a greater proportion of the participants receiving erenumab 140 mg reduced their migraine days by 50% than those receiving placebo (41% vs. 23%, respectively; OR 2.3 [95% CI 1.6, 3.5]), as did patients receiving erenumab 70 mg vs. placebo (40% vs. 23%, respectively; OR 2.2 [95% CI 1.5, 3.3]).[90] For fremanezumab, 44% of patients on the monthly dose had a reduction in monthly migraine days of 50% or more during weeks 9-12, versus 34% of patients on placebo (OR 1.5).[130] In HALO-CM, a higher proportion of patients receiving fremanezumab monthly (33%) and quarterly (31%) had a reduction of monthly migraine days of 50% or more during the 12 week period than those on placebo (20%; OR 2.0 for monthly and 1.8 for quarterly).[145] Results from Diener 2007 showed a statistically significant greater proportion in participants receiving topiramate than placebo with a 50% reduction in migraine days by 16 weeks (29% vs 0%; OR 1.4).[33] Although not statistically significant, another topiramate trial (Silberstein 2007) reported a greater proportion of patients given topiramate with at least a 50% reduction in migraine days than in placebo (37% vs. 29%; OR 2.6) by week 16.[141]

In the Phase II fremanezumab trial (Bigal 2015a), a greater proportion of the participants receiving fremanezumab monthly (53%) experienced at least a 50% reduction in moderate-to-severe headaches than in the placebo group (31%) by week 12 (OR 2.4 [95% CI 1.3, 4.5]).[26] In addition, by 12 weeks, HALO-CM reported a greater proportion of patients with a reduction of at least 50% in headache days per month for both fremanezumab doses versus placebo (quarterly regimen, 38%; monthly regimen, 41%; placebo, 18%; OR 2.8 and 3.1, respectively)[28] as did one trial of topiramate (26% vs. 22% at 16 weeks OR 1.2)[141] and one trial of onabotulinum toxin A (58%) versus topiramate (32%) at 24 weeks (OR 2.9).[137]

Headache Days per Month

Eight trials reported the mean change in monthly headache days, including two trials of fremanezumab, four trials of onabotulinum toxin A, one trial of topiramate, and one head-to-head trial comparing onabotulinum toxin A and topiramate. Headache days were typically defined as the number of days in which pain lasted four or more continuous hours at any severity (duration of at least 30 minutes in Silberstein 2007). In the fremanezumab trials, a day involving the use of acute migraine-specific drugs was also classified as a headache-day. The analysis timepoint was the last four weeks of the randomization period for the two fremanezumab trials and two of the onabotulinum toxin A trials (Freitag 2008 and Cady 2014), whereas it was the full 24-week period for the two PREEMPT trials and the full 12-week period for the head-to-head onabotulinum toxin A and topiramate trial. Table 3.3 displays the data inputs for the NMA, which included the mean change from baseline and standard error for each arm of the trials. If these data were not reported, we included the reported change from baseline at endpoint. For the arm-level change from baseline, a negative value indicated a reduction in monthly headache days. Across the trials, the mean change from baseline with placebo was 3.3 to 8.0 fewer headache days per month. Greater reductions were reported in monthly headache days for all interventions versus placebo.

Table 3.3. Data for Change from Baseline in Monthly Headache Days in Chronic Migraine Patients

Trial	Week	Tx 1	Mean (SE)	Tx 2	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 3	Mean (SE)	Difference vs. Tx 1 (95% CI)
Bigal 2015a[26]	12	Placebo	NR	Fremanezumab 675/225 mg*	NR	-1.74 (-3.6, 0.1)			
Cohen 2018 (HALO-CM)[146]	12	Placebo	-3.31 (0.36)	Fremanezumab 675/225 mg	-5.21 (0.40)	-1.90 (NR)	Fremanezumab 675 mg quarterly	-4.80 (0.38)	-1.49 (NR)
Aurora 2010 (PREEMPT 1)[34]	24	Placebo	-6.40 (0.43)	Onabotulinum toxin A 155 U	-7.80 (0.33)	-1.4 (-2.4, -0.4)			
Diener 2010 (PREEMPT 2)[35]	24	Placebo	-6.70 (0.18)	Onabotulinum toxin A 155 U	-9.00 (0.18)	-2.3 (-3.3, -1.3)			
Cady 2014[38]	16	Placebo	18.0 (2.7)*	Onabotulinum toxin A 155 U	13.9 (2.0)*	-2.7 (NR)			
Freitag 2008[36]	16	Placebo	21.0 (1.22)*	Onabotulinum toxin A 100 U	19.0 (1.25)*	-2.0 (NR)			
Silberstein 2007[141]	16	Placebo	-4.70 (0.45)	Topiramate 100 mg/day	-5.80 (0.45)	-1.1 (NR)			
Cady 2011[39]	12	Onabotulinum toxin A 200 U	-8.0 (1.14)	Topiramate 200 mg/day	-8.1 (1.12)	-0.1 (NR)			

*Results are at timepoint, not change from baseline.

CI: confidence interval, NR: not reported, Tx: treatment, SE: standard error

Table 3.4 presents the results of the NMA with random treatment effects. The first column shows the difference in the change from baseline in monthly headache days for each intervention versus placebo with corresponding 95% CrIs. Negative values indicate a larger reduction in monthly headache days for active therapies versus placebo. Similar to the analysis of monthly migraine days, the standard deviation of the random treatment effects in this analysis was imprecise with an estimate and 95% CrI of 0.58 (0.03, 2.76), leading to wide CrIs for the treatment effects. Fremanezumab quarterly had approximately 1.5 fewer headache days per month than placebo, while fremanezumab monthly was statistically significant with approximately 1.8 fewer headache days per month than placebo. Onabotulinum toxin A had 2.1 fewer headache days per month than placebo and was statistically significant. The results for topiramate were not statistically significant with 1.1 fewer headache days per month for the 100 mg dose versus placebo and 2.1 fewer headache days per month for the 200-mg dose versus placebo.

The second column of Table 3.4 also shows the estimated change from baseline in monthly headache days for each active therapy with the corresponding 95% CrIs. The estimates for the fremanezumab ranged from 4.8 fewer headache days per month for the quarterly dose to 5.1 fewer headache days per month for the monthly dose.

Table 3.4. NMA Results for Change from Baseline in Monthly Headache Days in Chronic Migraine Patients

	Difference in Change From Baseline vs. Placebo Estimate (95% CrI)	Expected Change From Baseline Estimate (95% CrI)
Placebo	Reference	-3.3 (NA)
Fremanezumab 675 mg quarterly	-1.5 (-3.7, 0.8)	-4.8 (-7.0, -2.5)
Fremanezumab 675/225 mg monthly	-1.8 (-3.6, -0.1)	-5.1 (-6.9, -3.4)
Onabotulinum toxin A 100-200 U quarterly	-2.1 (-3.5, -0.6)	-5.4 (-6.8, -3.9)
Topiramate 100 mg/day	-1.1 (-3.6, 1.4)	-4.4 (-6.9, -1.9)
Topiramate 200 mg/day	-2.1 (-6.2, 1.9)	-5.4 (-9.5, -1.4)

Standard deviation for treatment effects: 0.58 (0.03, 2.76)
CrI: credible interval, NA: not applicable

Longer-term data consistent with the double-blind period were available for onabotulinum toxin A only. The pooled OLE data of the two PREEMPT trials showed a further reduction in monthly headache days by 56 weeks that was statistically significant for those who received all five treatment cycles of onabotulinum toxin A (change from baseline -12.0 [95% CI -12.6, -11.5]) and those who previously took placebo and subsequently received onabotulinum toxin A during the open-label phase (change from baseline -11.1 [95% CI -11.8, -10.5]).[136]

Days per Month of Acute Medication Use

Five placebo-controlled trials reported the change from baseline in days using acute medications – one trial assessing erenumab, two trials assessing fremanezumab, and two trials assessing topiramate. The data are presented in Table 3.5. The time point of the analysis was the last four weeks of the randomization period (9-12 weeks) for erenumab trials, 12 weeks for the fremanezumab trial, and 16 weeks for both topiramate trials. The data for the two fremanezumab and two topiramate trials were days of any acute medication. The data for the erenumab trial were days using migraine-specific acute medication as data on any acute medication were not reported. Across the trials, patients receiving placebo experienced an average of 0.7 to 3.4 fewer days per month using acute medications. Overall, the trials reported greater reductions from baseline in acute medication use with the active therapies than with placebo.

Table 3.6 presents the results of the random effects NMA in terms of the difference in change from baseline for each intervention versus placebo (first column). Imprecise estimates of the heterogeneity parameter of 0.70 (0.03, 2.31) contributed to wide intervals for the treatment effects. In the results table, the negative values indicate a larger reduction in days using acute medication versus placebo. Erenumab 140 mg and fremanezumab monthly dosing had the largest reduction versus placebo (2.5 and 2.2 fewer days per month, respectively), which were both statistically significant. Results for topiramate suggested a reduction of 1.3 days per month versus placebo, which was not statistically significant. No statistically significant results were found when comparing the CGRP inhibitors to each other or to other active therapies. The expected reduction in days per month using acute medication ranged from 3.4 days with fremanezumab quarterly to 4.5 days with erenumab 140 mg.

Table 3.5. Data for Change from Baseline in Days of Acute Medication Use per Month in Chronic Migraine Patients

Trial	Week	Tx 1	Mean (SE)	Tx 2	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 3	Mean (SE)	Difference vs. Tx 1 (95% CI)
Tepper 2017[90]	12	Placebo	-1.60 (0.20)	Erenumab 70 mg	-3.50 (0.30)	-1.9 (-2.6, -1.1)	Erenumab 140 mg	-4.1 (0.30)	-2.6 (-3.3, -1.8)
Bigal 2015a[26]	12	Placebo	NR	Fremanezumab 675/225 mg*	NR	-2.2 (-4.0, 0.3)			
Aycardi 2018 (HALO-CM)[147]	12	Placebo	-2.31 (0.33)	Fremanezumab 675/225 mg	-4.49 (0.35)	-2.2 (NR)	Fremanezumab 675 mg	-3.71 (0.38)	-1.4 (NR)
Silberstein 2007[141]	16	Placebo	-3.40 (0.43)	Topiramate 100 mg/day	-4.40 (0.47)	-1.0 (NR)			
Diener 2007[33]	16	Placebo	-0.70 (1.19)	Topiramate 100 mg/day	-3.00 (1.04)	-2.3 (NR)			

*Reported data are difference vs. placebo

NR: not reported, SE: standard error, Tx: therapy

Table 3.6. NMA Results for Days of Acute Medication Use in Chronic Migraine Patients

	Difference in Change From Baseline vs. Placebo Estimate (95% CrI)	Expected Change From Baseline Estimate (95% CrI)
Placebo	Reference	-2.0 (NA)
Erenumab 70 mg monthly	-1.9 (-4.3, 0.6)	-3.9 (-6.3, -1.4)
Erenumab 140 mg monthly	-2.5 (-4.9, 0.0)	-4.5 (-6.9, -2.0)
Fremanezumab 675 mg quarterly	-1.4 (-3.8, 1.0)	-3.4 (-5.8, -1.0)
Fremanezumab 675/225 mg monthly	-2.2 (-4.1, -0.3)	-4.2 (-6.1, -2.3)
Topiramate 100 mg/day	-1.3 (-3.5, 0.7)	-3.3 (-5.5, -1.3)

Standard deviation for treatment effects: 0.70 (0.03, 2.31)

CrI: credible interval, NA: not applicable

Quality of Life: MIDAS, HIT-6, MSQ

Three quality of life measures were infrequently assessed and reported in 11 trials. Due to limited data, results for each quality of life measure are presented below without further analysis. Reported data are presented in Appendix Table D11.

The MIDAS quality of life measure assesses overall disability based on the number of days that headaches interfered with daily routine/activities with a three-month recall. None of the CGRP inhibitor trials reported MIDAS total scores in chronic migraine populations. The erenumab trial[129] reported the mean change from baseline in MIDAS days of lost productivity, days due to absenteeism, and days due to presenteeism. The mean change in MIDAS days of lost productivity, days due to absenteeism, and days due to presenteeism by week 12 was statistically significant for both doses of erenumab versus placebo (erenumab 140 mg -19.8,-10.2, -9.9; erenumab 70 mg -19.4,-10.3, -9.3 vs. placebo -7.5,-5.2, -1.9; respectively).[129] Five trials of onabotulinum toxin A or topiramate also reported MIDAS, which also saw improvements in total MIDAS by weeks 12 to 26.[33,36,39,137,141]

Another quality of life measure, HIT-6, evaluates the burden and level of disability by showing the severity of the impact migraine has on patients, where a severe impact is a score of 60 or more. Seven trials reported HIT-6 data for erenumab, fremanezumab, onabotulinum toxin A, or topiramate, all of which had an average HIT-6 score above 60 at baseline.[28,34,35,39,129,137] Over the duration of the trials, the average HIT-6 scores decreased (improved) for all arms including placebo, although the improvement was greater with the active therapies. Across the studies, the average improvement in HIT-6 for patients on placebo ranged from 2.4 to 4.5, whereas the average improvement across all active therapies ranged from 3.5 to 10.4. Improvements in HIT-6 scores for erenumab, fremanezumab, and onabotulinum toxin A were similar, with improvements over placebo ranging from 2 to 2.5.

A third quality of life measure reported in some trials was the Migraine-Specific Quality of Life Questionnaire (MSQ), which reports a 100-point scale separated by three domains: role function-restrictive (RFR), role-function-preventive (RFP), and emotional function (EF). A positive change from baseline indicates improvement. One trial assessing erenumab,[129] one trial assessing fremanezumab,[132] and two topiramate trials [140,141] reported MSQ data. Across the four trials, there was an improvement in quality of life scores from baseline for all active therapies versus placebo in each of three domains by 12 to 16 weeks.

Overview of Observational Studies

In the chronic migraine population, we included two observational studies assessing onabotulinum toxin A conducted in general clinical practices throughout Europe, the United States, Australia, or Korea.[148-151] In three of the studies, a headache diary was used to record migraine days, headache

days, and acute pain medication use in patients for one to two years. Aicua-Rapan 2016 included 115 chronic migraine patients who could have other comorbidities such as anxiety, depression, fibromyalgia and other vascular conditions, those with medication overuse, and those for whom at least topiramate and a beta-blocker previously failed. In this study, mean number of days using acute pain medication decreased from 19.1 days per month to 8.6 days per month during the first year. In addition, 68.7% patients (79 of 115) had fewer than 15 headaches per month by the end of the first year. However, onabotulinum toxin A was discontinued after the first year in 15.7% of patients due to a lack of efficacy. In Negro 2016, 172 chronic migraine patients with acute medication overuse and for whom other preventive therapies had failed were given onabotulinum toxin A 195U for up to two years. In the 143 patients who completed two years of treatment, there was a statistically significant decrease in migraine days (pre: 21.6 days, post: -3.8 days) and in headache days (pre: 22.2 days, post: -4.1 days). The safety profile of this study was consistent with the trials on onabotulinum toxin A. In the COMPEL study, 716 patients with chronic migraine were allowed to take one oral preventive medication and any acute medication as needed. By 108 weeks, patients had a mean reduction of 10.7 headache days per month from baseline and a decrease in HIT-6 score of 7.1. Treatment-related adverse events were reported by 18% of patients. In the fourth study (Matharu 2017), investigators recorded onabotulinum toxin A utilization and safety information among 1,168 patients with chronic migraine. Treatment-related adverse events were reported by 25% of patients through 52 weeks. Overall, no additional long-term safety concerns were raised from these four observational studies.

Episodic Migraine

Overview of Trials Assessing CGRP Inhibitors

Nine of the CGRP inhibitor trials and one OLE we identified were conducted in patients with episodic migraine. We included one Phase II RCT of erenumab (NCT01952574, Sun 2016)[40] with its associated OLE,[152,153] two Phase III RCTs of erenumab (NCT02456740, STRIVE[41,154-157] and NCT02483585, ARISE[42]), one Phase II RCT of fremanezumab (NCT0202556, Bigal 2015b),[25,130], one Phase III RCT of fremanezumab (NCT02629861, HALO-EM)[43,158-160], two Phase II RCTs of galcanezumab (NCT01625988, Dodick 2014[27,161,162] and NCT02163993, Skljarevski 2018[44,163]), and two Phase III RCTs of galcanezumab (NCT02614183, EVOLVE-1[45,135] and NCT02614196, EVOLVE-2[46,135]).

Appendix Tables D3 and D6 contain the key study design and baseline characteristics of the trials. The CGRP inhibitor trials in episodic migraine were industry-funded and multi-centered, with locations predominately in North America and Europe. All trials included a four-week baseline period followed by a 12-week randomized, placebo-controlled treatment phase in which patients and investigators were blinded to treatment assignment. Patients were enrolled in the baseline phases of the trials if they had a diagnosis migraine based on ICHD (second or third edition, beta) or

self-reported history migraine, typically with four to 14 migraine days per month except for the fremanezumab trial (Bigal 2015b) which required patients to have eight to 14 migraine days per month. In all trials, patients who continued to meet these criteria during the baseline phase and who showed at least 80% compliance with an electronic headache diary continued to the randomized phase.

At the start of the randomization phase, more than 80% of participants were women with an average age of 40. Patients had been diagnosed with migraine for approximately 20 years. At baseline, the average number of migraine days per month was 8 to 9, except patients in Bigal 2015b (fremanezumab) experienced a higher frequency at baseline with approximately 12 migraine days per month. Across the trials, the average number of days using an acute migraine-specific medication at baseline was approximately 3 to 7 days per month, and the number of days using any acute medication was approximately 7 to 10. These data were not reported in two of the galcanezumab trials.

All CGRP inhibitor trials excluded patients who had experienced no therapeutic response to more than two classes of migraine preventive therapies. In Bigal 2015b, the patients could not have experienced the failure of more than two medication categories or more than three preventive medications across two categories. Proportions of patients with prior failures of at least one preventive therapy ranged from 35% to 40% in the erenumab trials and 30% in the fremanezumab trial (Bigal 2015b). Patients in five trials (Sun 2016, Dodick 2014, Skljarevski 2018, EVOLVE-1, EVOLVE-2) were required to discontinue any migraine preventive therapies at baseline, whereas patients in four trials (ARISE, STRIVE, HALO-EM, Bigal 2015b) were allowed stable doses of preventive migraine therapies. Bigal 2015b had the highest proportion of patients on concomitant preventive therapy (30%) whereas the proportion was 3% to 6% in the erenumab trials.

The primary efficacy outcomes for the three erenumab trials were either change in average monthly migraine days from baseline to last four weeks of treatment (Sun 2016, ARISE), or change in average monthly migraine days from baseline to the final three months of treatment (STRIVE). Patients on erenumab 70 mg experienced a larger reduction in monthly migraine days than those on placebo during weeks nine through 12 (difference vs. placebo -1.1 [95% CI -2.1, -0.2] in Sun 2016[40] and -1.0 [95% CI -1.6, -0.5] in ARISE[42]). During months three through six, patients on erenumab 140 mg and 70 mg also experienced a greater reduction in monthly migraine days than those on placebo (difference in erenumab 140 mg vs. placebo -1.9 [95% CI -2.3, -1.4], difference in erenumab 70 mg vs placebo -1.4 [95% CI -1.9, -0.9]).[41] In the fremanezumab trials, the primary outcome was the mean reduction (change) in migraine days from baseline to the last four weeks of the treatment phase (Bigal 2015b) or the full 12-week period (HALO-EM). Patients on fremanezumab 225 mg monthly experienced a greater reduction in monthly migraine days than those on placebo during weeks nine through 12 (difference in fremanezumab vs placebo -2.8 [95% CI -4.1, -1.6])[25] and during the full 12-week period (difference in fremanezumab monthly vs. placebo -1.5 [95% CI -2.0, -0.9] and fremanezumab quarterly vs. placebo -1.3 [95% CI -1.8, -0.7]).[43] For the

galcanezumab trials, the primary outcome was the mean change in migraine days from baseline to the last four weeks of the treatment phase (Skljarevski 2018, Dodick 2014) or the full 24-week treatment phase (EVOLVE-1, EVOLVE-2). Skljarevski 2018 measured this outcome based on the Bayesian posterior probability of a greater improvement in the number of migraine days being greater than 95%. The results in terms of the posterior probability were 99.6% with galcanezumab 120 mg monthly, which was greater than the prespecified threshold and suggested a greater reduction in migraine days with galcanezumab than with placebo during weeks nine through 12.[44] In Dodick 2014, patients on galcanezumab experienced a greater reduction in monthly migraine days than those on placebo during weeks nine through 12 (difference in galcanezumab 120 mg vs. placebo -1.2 [95% CI -1.9, -0.6]).[27] In EVOLVE-1 and EVOLVE-2, patients on 120 mg or 240 mg galcanezumab experienced a greater reduction in monthly migraine days than those on placebo during the 24-week period (difference in galcanezumab 120 mg vs placebo -1.9 [SE: 0.3] for EVOLVE-1 and -2.0 [95% CI: -2.6, -1.5] for EVOLVE-2 and galcanezumab 240 mg vs placebo -1.8 [SE: 0.3] for EVOLVE-1 and -1.9 [95% CI: -2.4, -1.4] for EVOLVE-2).

Overview of Trials Assessing Current Preventive Therapies in Episodic Migraine

Of the 24 trials assessing a comparator of interest in the episodic migraine population, we included 17 trials of an active therapy versus placebo (four RCTs assessed amitriptyline,[47,164-166] four RCTs[48,167-169] and one crossover of propranolol,[170] eight RCTs (10 publications) of topiramate[49-54,171-174]) and seven head-to-head studies (three RCTs of topiramate vs. propranolol,[55,175,176] one RCT of topiramate vs. amitriptyline,[56] one RCT of propranolol vs. amitriptyline,[177] one RCT of topiramate vs. amitriptyline vs. topiramate plus amitriptyline,[178] and one RCT of propranolol vs. amitriptyline vs. propranolol plus amitriptyline[179]).

Key study design and baseline patient characteristics are presented in the Appendix Tables D4 and D6. As with the CGRP inhibitor trials, most trials of the oral preventive therapies were industry funded. Ten of the trials were multi-centered whereas 10 other trials were single-centered and four were unclear. Where reported, the trials were conducted in the US and Europe, except for four conducted in Turkey and one in Singapore. Baseline phases were typically four weeks, followed by randomized phases of four weeks to 26 weeks. At baseline, the average number of migraine days ranged from 5 to 12 days per month. Most trials excluded patients who were currently taking other preventive therapies or and six trials excluded patients who had experienced the failure of more than two preventive therapies. No oral preventive therapy trials reported the percentage of patients who experienced prior failure of at least one preventive therapy.

Clinical Benefits

Of the 33 included trials that evaluated preventive therapies for episodic migraine patients, one galcanezumab Phase II trial (Dodick 2014) did not assess any doses of interest, so was not included in any analysis. Refer to Appendix D for the results data available from this trial. Of the remaining

32 trials, 18 trials reported outcome data on at least one of the efficacy endpoints described below (change from baseline in monthly migraine days, 50% responders, change from baseline in headache days, or change from baseline in days per month using acute medication). Sixteen of the trials were placebo-controlled and assessed erenumab (three trials), fremanezumab (two trials), galcanezumab (three trials), amitriptyline (one trial), propranolol (one trial), or topiramate (six trials) and two trials were head-to-head assessing amitriptyline versus topiramate (one trial) or topiramate versus propranolol (one trial). All trials except two topiramate trials (Mei 2004 and Storey 2001) were multi-centered. All trials were industry funded and conducted in the US and Europe, except Goncalves 2016 which was government sponsored in Brazil. The trials included a four-week baseline period followed by a 12- to 26-week randomized phase. Overall, these 18 trials were deemed sufficiently similar to include in the efficacy analyses below.

Migraine Days per Month

Fourteen of the 18 trials were included in the NMA of change from baseline in monthly migraine days. Twelve of the trials compared an active therapy to placebo only, while two trials compared topiramate with either amitriptyline or propranolol. Overall, the trials used similar definitions of migraine days: a day with migraine (with or without aura) or probable migraine (lacking one migraine feature) lasting at least 30 minutes (at least two hours in HALO-EM and at least four hours in Bigal 2015b). The erenumab and fremanezumab trials also considered a day taking acute migraine-specific medication as a migraine day. Table 3.7 presents the data inputs for the NMA, which included the mean change from baseline and standard error for each arm of the trials. If these data were not reported, we included the reported change from baseline at endpoint. For the arm-level change from baseline, a negative value indicated a reduction in monthly migraine days. Across the trials, patients receiving placebo experienced an average reduction from baseline of 1.1 to 5.3 migraine-days per month. Overall, trials reported greater reductions in monthly migraine days for all interventions versus placebo. The head-to-head trials reported greater reductions with topiramate than with amitriptyline (Dodick 2009) and greater reductions with propranolol than with topiramate (Diener 2004).

Table 3.8 presents the results from the NMA with random treatment effects. The first column shows the difference in the change from baseline for each intervention versus placebo, with the corresponding 95% CrIs. Negative values indicated a larger reduction in monthly migraine days versus placebo. Erenumab had an average of 1.3 (70 mg dose) and 1.9 (140 mg dose) fewer migraine days per month than placebo, fremanezumab had 1.2 (quarterly dose) or 1.6 (monthly dose) fewer migraine days per month than placebo, and galcanezumab had 1.8 (both 120 mg and 240 mg doses) fewer migraine days per month than those on placebo; these estimates were statistically significant. The oral preventive therapies (propranolol 160 mg, topiramate 100 mg, topiramate 200 mg, amitriptyline 25-100 mg) had an average of 1.0 to 1.2 fewer migraine days per month versus placebo, which were statistically significant except for amitriptyline. Results for erenumab 140 mg, galcanezumab 120 mg, erenumab 70 mg, and fremanezumab monthly versus

topiramate 50 mg were statistically significant. No other results comparing the CGRP inhibitors to active therapies were statistically significant.

The estimated change from baseline for each active preventive therapy is presented in the second column of Table 3.8 along with the corresponding 95% CrIs. Here, the estimates for the CGRP inhibitors ranged from 4.0 fewer migraine days per month with fremanezumab quarterly to 4.7 fewer migraine days per month with erenumab 140 mg.

For longer-term data, the OLE of the Phase II erenumab trial followed patients for one year. All patients were given 70 mg of erenumab. After one year, patients had an average of 5.0 fewer migraine days per month compared with 3.4 fewer migraine days per month at week 12 among the patients taking erenumab 70 mg during the double-blind phase.

Table 3.7. Data for Change from Baseline in Monthly Migraine Days in Episodic Migraine Patients

Trial	Week	Tx 1	Mean (SE)	Tx 2	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 3	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 4	Mean (SE)	Difference vs. Tx 1 (95% CI)
Sun 2016[40]	12	Placebo	-2.30 (0.30)	Erenumab 70 mg	-3.40 (0.40)	-1.1 (-2.1, -0.2)						
Goadsby 2017 (STRIVE)[41]	24	Placebo	-1.67 (0.21)	Erenumab 70 mg	-3.26 (0.21)	-1.6 (NR)	Erenumab 140 mg	-3.76 (0.21)	-2.09 (NR)			
Dodick 2018 (ARISE)[42]	12	Placebo	-1.80 (0.20)	Erenumab 70 mg	-2.90 (0.20)	-1.0 (-1.6, -0.5)						
Bigal 2015b[25]	12	Placebo	-3.46 (0.53)	Fremanezumab 225 mg	-6.27 (0.55)	-2.8 (-4.1, -1.6)						
Dodick, 2018 (HALO-EM)[43]	12	Placebo	-2.70 (0.28)	Fremanezumab 675 mg quarterly	-3.69 (0.31)	-1.0 (NR)	Fremanezumab 225 mg	-3.88 (0.29)	-1.2 (NR)			
Skljarevski 2018[44]	12	Placebo	-4.00 (0.31)	Galcanezumab 120 mg	-5.90 (0.41)	-1.9 (NR)						
Stauffer, 2018 EVOLVE-1[45]	24	Placebo	-3.34 (0.25)	Galcanezumab 120 mg	-5.15 (0.35)	-1.8 (NR)	Galcanezumab 240 mg	-5.30 (0.25)	-2.0 (NR)			
Skljarevski, 2018 EVOLVE-2[46]	24	Placebo	-2.84 (0.22)	Galcanezumab 120 mg	-4.56 (0.34)	-1.7 (NR)	Galcanezumab 240 mg	-4.53 (0.28)	-1.7 (NR)			
Goncalves 2016[47]	12	Placebo	-1.10 (0.73)	Amitriptyline 25 mg/day	-2.20 (0.73)	-1.1 (-1.5, -0.7)						
Lipton 2011 [49]	26	Placebo	-5.30 (0.28)	Topiramate 100 mg/day	-6.60 (0.28)	-1.3 (NR)						
Brandes 2004[50]	26	Placebo	-1.30 (0.32)	Topiramate 50 mg/day	-1.70 (0.52)	-0.4 (NR)	Topiramate 100 mg/day	-2.60 (0.31)	-1.3 (NR)	Topiramate 200 mg/day	-2.90 (0.32)	-1.6 (NR)
Silberstein 2004 [51]	26	Placebo	5.30 (0.34)*	Topiramate 50 mg/day	4.80 (0.37)*	-0.5 (NR)	Topiramate 100 mg/day	3.70 (0.30)*	-1.6 (NR)	Topiramate 200 mg/day	3.90 (0.32)*	-1.6 (NR)
Diener 2004[55]	26	Placebo	-1.10 (0.24)	Propranolol 160 mg/day	-1.90 (0.25)	-0.8 (NR)	Topiramate 100 mg/day	-1.80 (0.25)	-0.7 (NR)	Topiramate 200 mg/day	-1.30 (0.25)	-0.2 (NR)
Dodick 2009 [56]	26	Topiramate 100 mg/day	-3.20 (0.43)	Amitriptyline 100 mg/day	-3.10 (0.44)	-0.1 (-0.9, 0.7)						

* Results are at time point, not change from baseline

NR: not reported, SE: standard error, Tx: treatment

Table 3.8. NMA Results for Change from Baseline in Migraine Days in Episodic Migraine Patients

	Difference in Change From Baseline vs. Placebo Estimate (95% CrI)	Expected Change From Baseline Estimate (95% CrI)
Placebo	Reference	-2.8 (NA)
Erenumab 70 mg monthly	-1.3 (-1.8, -0.8)	-4.1 (-4.6, -3.6)
Erenumab 140 mg monthly	-1.9 (-2.7, -1.2)	-4.7 (-5.5, -4.0)
Fremanezumab 675 mg quarterly	-1.2 (-2.2, -0.3)	-4.0 (-5.0, -3.1)
Fremanezumab 225 mg monthly	-1.6 (-2.5, -0.8)	-4.4 (-5.3, -3.6)
Galcanezumab 120 mg monthly	-1.8 (-2.4, -1.2)	-4.6 (-5.2, -4.0)
Galcanezumab 240 mg monthly	-1.8 (-2.5, -1.2)	-4.6 (-5.3, -4.0)
Topiramate 50 mg/day	-0.2 (-1.0, 0.6)	-3.0 (-3.8, -2.2)
Topiramate 100 mg/day	-1.2 (-1.7, -0.7)	-4.0 (-4.5, -3.5)
Topiramate 200 mg/day	-1.0 (-1.5, -0.4)	-3.8 (-4.3, -3.2)
Amitriptyline 25-100 mg/day	-1.1 (-2.2, 0.1)	-3.9 (-5.0, -2.7)
Propranolol 160 mg/day	-1.2 (-2.0, -0.4)	-4.0 (-4.8, -3.2)

Standard deviation for treatment effects: 0.21 (0.01, 0.60)
CrI: credible interval, NA: not applicable

In addition, we reviewed data for the subpopulation of episodic migraine patients who experienced the failure of at least one preventive therapy prior to the start of the trial. Manufacturers of erenumab and fremanezumab submitted the data in confidence, which will be publicly reported here no later than December 2019, in line with ICER's data in confidence policy.

50% Responders

Eighteen trials reported on the proportion of patients who experienced a reduction of migraine frequency or migraine days by at least 50%, which we considered sufficiently similar to analyze. Table 3.9 provides the trial data included in the NMA, which are the sample size and the number of patients who met the 50% response definition. The number of responders for all CGRP inhibitor trials as well as one amitriptyline trial (Goncalves 2016), one topiramate trial (Lipton 2011), and one trial comparing topiramate versus amitriptyline (Dodick 2009) was the number of patients who experienced at least a 50% reduction in the number of migraine days. For the other seven trials, the number of responders is the number of patients who experienced at least a 50% reduction in migraine frequency. The trials assessed response between 12 and 26 weeks of treatment. Across the trials, between 10% to 62% of patients on placebo were responders. Overall, trials reported greater proportion of responders for all interventions versus placebo.

Table 3.10 presents the results of the NMA in terms of the odds ratio (OR) of 50% response for each intervention versus placebo. ORs above 1 indicate a higher odds of a 50% or higher response with the active intervention versus placebo. All CGRP inhibitors had statistically significant higher odds

of response versus placebo (erenumab 70 mg: 1.9, erenumab 140 mg: 2.2, fremanezumab quarterly: 1.7, fremanezumab monthly: 1.9, galcanezumab 120 mg: 2.5, galcanezumab 240 mg: 2.4). All oral preventive therapies were statistically significant versus placebo, with ORs ranging from 1.6 (topiramate 50 mg) to 2.7 (topiramate 100 mg and propranolol 120-160 mg). Results comparing the CGRP inhibitors to active therapies were not statistically significant.

The expected proportion of patients achieving 50% or higher response for the CGRP inhibitors was between 50-60%. The expected proportion of responders for the oral therapies ranged from 48% (topiramate 50 mg) to 61% (topiramate 100 mg and propranolol 120-160 mg).

For longer-term data, the OLE of the Phase II erenumab trial followed patients for one year. All patients were given 70 mg of erenumab. After 64 weeks, 65% of patients had experienced at least a 50% reduction in monthly migraine days from baseline, compared with 46% of patients taking erenumab during the 12-week double-blind phase.

Table 3.9. Data for 50% Responders in Episodic Migraine Patients

Trial	Week	Tx 1	r/n (%)	Tx 2	r/n (%)	OR (95% CI)	Tx 3	r/n (%)	OR (95% CI)	Tx 4	r/n (%)	OR (95% CI)
Sun 2016[40]	12	Placebo	43\144 (30%)	Erenumab 70 mg/month	46/99 (46%)	2.0 (1.2, 3.4)						
Goadsby 2017 (STRIVE)[41]	24	Placebo	93/316 (29%)	Erenumab 70 mg/month	147/312 (47%)	2.2 (NR)	Erenumab 140 mg/month	156/318 (49%)	2.4 (NR)			
Dodick 2018 (ARISE)[42]	12	Placebo	85/288 (30%)	Erenumab 70 mg/month	112/282 (40%)	1.6 (1.1, 2.2)						
Bigal 2015b[25]	12	Placebo	36/104 (35%)	Fremanezumab 225 mg/month	53/95 (56%)	2.4 (NR)						
Dodick 2018 (HALO-EM)[43]	12	Placebo	99/268 (37%)	Fremanezumab 675 mg/3 months	131/269 (49%)	1.6 (NR)	Fremanezumab 225 mg/month	134/263 (51%)	1.8 (NR)			
Skljarevski 2018[44]	12	Placebo	78/126 (62%)	Galcanezumab 120 mg/month	47/62 (76%)	1.9 (NR)						
Stauffer, 2018 EVOLVE-1[45]	24	Placebo	164/425 (39%)	Galcanezumab 120 mg/month	131/210 (62%)	2.6 (2.0, 3.4)	Galcanezumab 240 mg/month	127/208 (61%)	2.5 (1.9, 3.2)			
Skljarevski, 2018 EVOLVE-2[46]	24	Placebo	162/450 (36%)	Galcanezumab 120 mg/month	134/226 (59%)	2.6 (NR)	Galcanezumab 240 mg/month	124/220 (56%)	2.3 (NR)			
Goncalves 2016[47]	12	Placebo	12/59 (20%)	Amitriptyline 25 mg/day	23/59 (39%)	2.6 (NR)						
Diener 1996[48]	12	Placebo	17/55 (31%)	Propranolol 120 mg/day	33/78 (42%)	1.6 (NR)						
Lipton 2011[180]	26	Placebo	83/171 (49%)	Topiramate 100 mg/day	105/159 (66%)	2.1 (NR)						
Brandes 2004[50]	26	Placebo	26/114 (23%)	Topiramate 50 mg/day	45/116 (39%)	2.1 (NR)	Topiramate 100 mg/day	59/120 (49%)	3.2 (NR)	Topiramate 200 mg/day	55/117 (47%)	3.0 (NR)
Silberstein 2004 [51]	26	Placebo	26/115 (23%)	Topiramate 50 mg/day	42/117 (36%)	1.9 (NR)	Topiramate 100 mg/day	68/125 (54%)	3.9 (NR)	Topiramate 200 mg/day	59/112 (52%)	3.6 (NR)
Mei 2004[52]	16	Placebo	8/37 (22%)	Topiramate 100 mg/day	22/35 (63%)	6.1 (NR)						
Silberstein 2006[53]	20	Placebo	25/73 (34%)	Topiramate 200 mg/day	55/138 (40%)	1.3 (NR)						
Storey 2001[54]	16	Placebo	2/21 (10%)	Topiramate 200 mg/day	5/19 (26%)	3.2 (NR)						
Diener 2004[55]	26	Placebo	31/143 (22%)	Propranolol 160 mg/day	61/143 (43%)	2.7 (NR)	Topiramate 100 mg/day	51/139 (37%)	2.1 (NR)	Topiramate 200 mg/day	50/143 (35%)	1.9 (NR)
Dodick 2009 [56]	26	Topiramate 100 mg/day	96/172 (56%)	Amitriptyline 100 mg/day	73/159 (46%)	0.7 (NR)						

Data are the number of responders/sample size (percentage)

CI: confidence interval, NR: not reported, n: sample size; OR: odds ratio, r: responders, Tx: treatment

Table 3.10. NMA Results for 50% Response in Episodic Migraine Patients

	Odds Ratio vs. Placebo Estimate (95% CrI)	Expected Proportion of Responders Estimate (95% CrI)
Placebo	Reference	0.37 (NA)
Erenumab 70 mg monthly	1.9 (1.4, 2.5)	0.53 (0.45, 0.59)
Erenumab 140 mg monthly	2.2 (1.4, 3.3)	0.56 (0.45, 0.66)
Fremanezumab 675 mg quarterly	1.7 (1.1, 2.7)	0.50 (0.39, 0.61)
Fremanezumab 225 mg monthly	1.9 (1.4, 2.9)	0.53 (0.45, 0.63)
Galcanezumab 120 mg monthly	2.5 (1.9, 3.3)	0.60 (0.53, 0.66)
Galcanezumab 240 mg monthly	2.4 (1.7, 3.2)	0.58 (0.50, 0.65)
Topiramate 50 mg/day	1.6 (1.1, 2.3)	0.48 (0.39, 0.57)
Topiramate 100 mg/day	2.7 (2.1, 3.5)	0.61 (0.55, 0.67)
Topiramate 200 mg/day	2.3 (1.7, 3.1)	0.57 (0.50, 0.65)
Amitriptyline 25-150 mg/day	2.0 (1.2, 3.2)	0.53 (0.41, 0.65)
Propranolol 120-160 mg/day	2.7 (1.7, 4.1)	0.61 (0.50, 0.71)

Standard deviation for treatment effects: 0.10 (0.01, 0.33);
CrI: credible interval, NA: not applicable, OR: odds ratio

Headache Days per Month

Five trials reported results for monthly headache days, five of which assessed a CGRP inhibitor. The definition of headache day varied across the trials. Three trials defined headache day as a day with migraine or non-migraine headache that lasts for 30 minutes or longer.[40,49,56] In addition, two trials defined a headache day as a day in which headache pain lasted for four or more hours for any severity[25] or at least moderate severity.[159] Two of the trials also considered a day of treatment with an acute migraine-specific or headache medication as a headache day.[25,40] Due to the differences in definitions we were unable to conduct a quantitative analysis to indirectly compare the treatment effects. A summary of the reported trial results follows.

For monthly headache days defined as migraine or non-migraine days lasting 30 minute or longer, participants receiving erenumab 70 mg experienced fewer headache days per month than those receiving placebo (-3.5 vs. -2.4, respectively) at 12 weeks.[40] In another trial, patients receiving topiramate 100 mg had a statistically significant larger reduction headache days per month than placebo (-6.6 vs. -5.3, respectively) at 26 weeks.[49] A third trial comparing 100 mg daily dose each of topiramate and amitriptyline showed no difference in headache days between the two interventions (-3.6 for each arm).[56]

The two trials defining headache days as a day with headache lasting four or more hours showed larger reductions versus placebo. In the fremanezumab trial (Bigal 2015b), participants receiving fremanezumab 225 mg had slightly fewer headache days of any severity per month at 12 weeks

than those receiving fremanezumab 657 mg, with a larger reduction in the placebo arm (-6.14 vs. -6.10 vs. -3.52, respectively).[25] At 12 weeks in the HALO-EM trial, those receiving fremanezumab monthly experienced fewer headache days of at least moderate severity per month than those receiving fremanezumab quarterly or placebo (-3.15 vs. -3.0 vs. -1.95, respectively).[159]

Days per Month of Acute Medication Use

Twelve of the 14 trials reporting on the change from baseline in monthly migraine days also reported on the change in the number of days per month using acute medications during follow-up. Table 3.11 lists the data included in the NMA, which include the change from baseline in days per month using acute medications, where a negative value indicated a larger reduction. The data for nine of the trials were days of any acute medication. The data for the erenumab ARISE trial were days using migraine-specific acute medication and the data for the two galcanezumab EVOLVE 1&2 trials were migraine days using acute medication as data on days any acute medication were not reported in these trials. Across the trials, patients on placebo experienced an average reduction from baseline of 0.6 to 3.8 days using acute medications. The trials reported greater reductions with the active therapies versus placebo.

Table 3.12 provides the results from an NMA with random effects on the treatment parameters. Negative values indicate a larger reduction for the intervention versus placebo. Each dose of erenumab and fremanezumab had a statistically significant reduction in acute medication days per month (erenumab 70 mg: -0.9, erenumab 140 mg: -1.6, fremanezumab quarterly: -1.1, fremanezumab monthly: -1.2, galcanezumab 120 mg: -1.8, galcanezumab 240 mg: -1.7). For the oral preventives, the results for topiramate 100 mg, topiramate 200 mg, and propranolol 160 mg also were statistically significant and ranged from 0.7 (topiramate 200 mg) to 1.2 (amitriptyline 100 mg) fewer days per month using acute medications. Results comparing the CGRP inhibitors to active therapies were not statistically significant.

The expected reduction in days per month using acute medications with the CGRP inhibitors ranged from 2.7 (erenumab 70 mg) to 3.6 (galcanezumab 120 mg). The expected reduction using the oral therapies ranged from 2.2 (topiramate 50 mg) to 3.0 (amitriptyline 100 mg).

For longer-term data, the OLE of the Phase II erenumab trial followed patients for one year. All patients were given 70 mg of erenumab. After 64 weeks, patients had an average of 2.4 fewer days per month using acute migraine-specific medications compared with 1.2 fewer days per month at week 12 among the patients taking erenumab 70 mg during the double-blind phase.

Table 3.11. Data for Change from Baseline in Days of Acute Medication Use per Month in Episodic Migraine Patients

Trial	Week	Tx 1	Mean (SE)	Tx 2	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 3	Mean (SE)	Difference vs. Tx 1 (95% CI)	Tx 4	Mean (SE)	Difference vs. Tx 1 (95% CI)
Sun 2016[40]	12	Placebo	-1.40 (0.30)	Erenumab 70 mg	-2.50 (0.30)	-1.2 (-2.0, -0.3)						
Reuter 2018 (STRIVE)[155]	24	Placebo	-1.19 (0.17)	Erenumab 70 mg	-2.42 (0.20)	-1.2 (NR)	Erenumab 140 mg	-2.99 (0.16)	-1.8 (NR)			
Dodick 2018 (ARISE) [42]	12	Placebo	-0.60 (0.10)	Erenumab 70 mg	-1.20 (0.10)	-0.6 (-1.0, -0.2)						
Bigal 2015b[25]	12	Placebo	-3.10 (0.45)	Fremanezumab 225 mg	-4.86 (0.48)	-1.8 (-2.9, -0.7)						
Brandes 2018 (HALO-EM)[158]	12	Placebo	-1.99 (0.25)	Fremanezumab 675 mg quarterly	-3.00 (0.22)	-1.0 (NR)	Fremanezumab 225 mg	-2.99 (0.24)	-1.0 (NR)			
Stauffer, 2018 EVOLVE-1[45]	24	Placebo	-2.20 (0.21)	Galcanezumab 120 mg	-4.00 (0.30)	-1.8 (-2.3, -1.3)	Galcanezumab 240 mg	-3.80 (0.30)	-1.6 (-2.1, -1.1)			
Skljarevski, 2018 EVOLVE-2[46]	24	Placebo	-1.85 (0.20)	Galcanezumab 120 mg	-3.67 (0.20)	-1.8 (NR)	Galcanezumab 240 mg	-3.63 (0.20)	-1.8 (NR)			
Lipton 2011[180]	26	Placebo	-3.80 (0.28)	Topiramate 100 mg/day	-4.80 (0.28)	-1.0 (NR)						
Brandes 2004[50]	26	Placebo	-1.00 (0.29)	Topiramate 100 mg/day	-2.10 (0.29)	-1.1 (NR)	Topiramate 200 mg/day	-2.20 (0.29)	-1.4 (NR)			
Silberstein 2004[51]	26	Placebo	5.2 (0.31)*	Topiramate 50 mg/day	4.5 (0.29)*	-0.4 (NR)	Topiramate 100 mg/day	4.00 (0.30)*	-1.0 (NR)	Topiramate 200 mg/day	4.00 (0.26)*	-1.2 (NR)
Diener 2004[55]	26	Placebo	-0.80 (0.20)	Propranolol 160 mg/day	-1.60 (0.21)	-0.8 (NR)	Topiramate 100 mg/day	-1.50 (0.21)	-0.7 (NR)	Topiramate 200 mg/day	-0.90 (0.21)	-0.1 (NR)
Dodick 2009[56]	26	Topiramate 100 mg/day	-2.60 (0.33)	Amitriptyline 100 mg/day	-2.80 (0.35)	-0.2 (-0.9, 0.4)						

*Data are at time point, not change from baseline

NR: not reported, SE: standard error, Tx: treatment

Table 3.12. NMA Results for Days of Acute Medication Use in Episodic Migraine Patients

	Difference in Change From Baseline vs. Placebo Estimate (95% CrI)	Expected Change From Baseline Estimate (95% CrI)
Placebo	Reference	-1.8 (NA)
Erenumab 70 mg monthly	-0.9 (-1.4, -0.4)	-2.7 (-3.2, -2.2)
Erenumab 140 mg monthly	-1.6 (-2.4, -0.9)	-3.4 (-4.2, -2.7)
Fremanezumab 675 mg quarterly	-1.1 (-2.0, -0.3)	-2.9 (-3.8, -2.1)
Fremanezumab 225 mg monthly	-1.2 (-2.0, -0.4)	-3.0 (-3.8, -2.2)
Galcanezumab 120 mg monthly	-1.8 (-2.4, -1.2)	-3.6 (-4.2, -3.0)
Galcanezumab 240 mg monthly	-1.7 (-2.3, -1.1)	-3.5 (-4.1, -2.9)
Topiramate 50 mg/day	-0.4 (-1.3, 0.4)	-2.2 (-3.1, -1.4)
Topiramate 100 mg/day	-1.0 (-1.4, -0.5)	-2.8 (-3.2, -2.3)
Topiramate 200 mg/day	-0.7 (-1.3, -0.2)	-2.5 (-3.1, -2.0)
Amitriptyline 100 mg/day	-1.2 (-2.4, 0.1)	-3.0 (-4.2, -1.7)
Propranolol 160 mg/day	-1.1 (-1.9, -0.3)	-2.9 (-3.7, -2.1)

Standard deviation for treatment effects: 0.26 (0.02, 0.64)
CrI: credible interval, NA: not applicable

Quality of Life: MIDAS, HIT-6, MSQ

Three quality of life measures were infrequently assessed and reported in ten trials. Due to limited data, results for each quality of life measure are summarized below without further analysis. Reported data are presented in Appendix Table D12.

For the change from baseline in total MIDAS using a three-month recall, scores were assessed over 12 weeks for erenumab, fremanezumab, and galcanezumab, with one erenumab study reporting results from 13 through 24 weeks. Overall, there were greater reductions with the CGRP inhibitors than placebo, which was statistically significant in the fremanezumab trials (Bigal 2015b and HALO-EM), one erenumab trial (Sun 2016) and two galcanezumab trials (EVOLVE-1 and EVOLVE-2). Although not statistically significant, one trial reported an improvement with topiramate versus placebo over 26 weeks,[49] and another trial reported an improvement with amitriptyline over topiramate in 26 weeks.[56]

HIT-6 data were reported in three erenumab trials (Sun 2016, STRIVE, ARISE) and one galcanezumab trial (Skljarevski 2018). At baseline, participants had values near the most severe impact category (severe impact ≥ 60). Reductions in scores with erenumab or galcanezumab did not substantially differ from placebo through 12 weeks (difference versus placebo ranged from 2 to 2.7).

With higher scores indicating improvement in MSQ, a positive change in scores from baseline was generally seen in all domains with the CGRP inhibitors (EF, range: 2-35; RFR, range: 2-33; RFP,

range: 10-21). The comparator trials (topiramate and amitriptyline only) also reported larger improvements in scores for up to 26 weeks.

In one OLE, participants on open-label erenumab 70 mg maintained improvements in MIDAS total score, HIT-6, and each MSQ domain throughout the one-year observation period.

Overview of Observational Studies

In the episodic migraine population, we included three non-randomized studies[181-183] that were conducted in a general practice or community setting in Germany. The studies assessed topiramate and allowed patients to concomitantly take acute pain medications as needed. One of the studies (Nelles 2009) gave 185 patients a flexible dose of topiramate where the titration rate was guided by the patient's clinical response to treatment (mean: 25 mg, range: 12-100 mg/day) for 24 weeks with an optional follow-up to 48 weeks. Mean monthly migraine days decreased from 6.2 at baseline to 3.9 by 24 weeks, with 51% of patients reporting having experienced a reduction of at least 50% in migraine days by 24 weeks. Patients' quality of life improved, with a reduction from 92.4% strongly impaired at baseline to 34.3% by week 24. By 48 weeks, monthly migraine days decreased further to 3.1 with 60% of patients reporting a 50% or more reduction in monthly migraine days. Another study (Nelles 2010) used the same flexible dosing procedure and reported findings in 336 patients receiving topiramate for six months (optional follow-up of 12 months). Mean monthly migraine days decreased from 6.9 days at baseline to 2.4 days at six months with 76% of patients reporting a reduction of at least 50% in monthly migraine days. At 12 months, the mean monthly migraine days reduced to 1.6 days with 79% of patients reporting at least a 50% reduction in monthly migraine days. The third study (Malessa 2010) followed 360 patients for 24 weeks (optional endpoint up to 48 weeks) with a dose titration of 25 mg/day up to an average dose of 90 mg/day. By 24 weeks, mean monthly migraine days decreased from 8.3 days at baseline to 5.7 days and 42% experienced a reduction from baseline in migraine days by at least 50%. Along with the decrease in migraine days, days using acute medication decreased with an average of 3.6 days compared to 6.9 at baseline. By 48 weeks, migraine days continued to decrease to 4.5 days and 57% experienced a 50% reduction in migraine days. Across the three studies, adverse events were generally similar to those reported in the clinical trials. The most commonly reported adverse events were paresthesia, fatigue, nausea, dizziness, taste perversion, and weight decrease.

Tolerability and Harms

Tolerability and harms assessed include all-cause discontinuations, discontinuations due to AEs, SAEs, and any AE reported by at least 5% of a trial arm. We reported results for all-cause discontinuations separately for chronic and episodic migraine trials, as there may be differential discontinuations related to efficacy between these groups. All other outcomes are presented jointly for chronic and episodic migraine trials.

All-Cause Discontinuations

Thirty-nine trials reported on the number of patients who discontinued treatment for any reason. The data from the 13 trials reporting on chronic migraine are reported in Appendix Table D13. Discontinuations among patients on placebo ranged from 0% to 48% between eight and 24 weeks. Discontinuations among patients on a CGRP inhibitor ranged from 4% to 18% by 12 weeks. Discontinuations among patients on other preventive therapies ranged from 7% to 50% between eight and 36 weeks. Results from the NMA in Table 3.13 are expressed as ORs, where values greater than one indicate a higher odds of discontinuation for the active therapy versus placebo. Note that because of sparse data and zero counts, results for topiramate 50 mg were not able to be estimated. No results were statistically significant, although the point estimates for erenumab 70 mg, erenumab 140 mg, fremanezumab quarterly, and topiramate 100 mg indicated lower odds of discontinuation. All other interventions had point estimates indicating a higher odds of discontinuation. The expected proportion of patients discontinuing CGRP inhibitor by the end of trial ranged from 6% (erenumab 140 mg) to 12% (fremanezumab monthly).

For the episodic population, Appendix Table D14 presents the data available from 26 trials. Discontinuations among patients on placebo ranged from 0% to 54% between four and 26 weeks. Discontinuations among patients on a CGRP inhibitor ranged from 5% to 17% between 12 and 24 weeks. Discontinuations among patients on other preventive therapies ranged from 0% to 62% between four and 26 weeks. As with the chronic migraine population, the results from an NMA were not statistically significant (Table 3.14). The point estimates for erenumab (70 mg and 140 mg), galcanezumab (120 mg and 240 mg), and propranolol (60-160 mg) indicate a lower odds of discontinuation, whereas the point estimates for all other interventions indicate a higher odds. The expected proportion of patients discontinuing CGRP inhibitor by the end of trial ranged from 8% (erenumab 140 mg) to 16% (fremanezumab monthly).

Results from the erenumab OLE reported 28% (107/383) of patients discontinued therapy after one year.

Table 3.13. NMA Results for All-Cause Discontinuations in Chronic Migraine

	Odds Ratio vs. Placebo Estimate (95% CrI)	Expected Proportion Discontinuing Estimate (95% CrI)
Placebo	Reference	0.10 (NA)
Erenumab 70 mg monthly	0.7 (0.2, 2.1)	0.07 (0.02, 0.19)
Erenumab 140 mg monthly	0.6 (0.2, 1.7)	0.06 (0.02, 0.16)
Fremanezumab 675 mg quarterly	0.8 (0.4, 2.0)	0.09 (0.04, 0.18)
Fremanezumab 675/225 mg monthly	1.2 (0.6, 2.4)	0.12 (0.06, 0.21)
Onabotulinum toxin A 100-200 U quarterly	1.1 (0.6, 1.7)	0.11 (0.06, 0.16)
Topiramate 50 mg/day	NE	NE
Topiramate 100 mg/day	0.9 (0.5, 1.6)	0.09 (0.05, 0.15)
Topiramate 200 mg/day	1.3 (0.3, 5.5)	0.12 (0.03, 0.38)

Standard deviation for treatment effects: 0.23 (0.01, 0.83)
CrI: credible interval, NA: not applicable, NE: not able to be estimated

Table 3.14. NMA Results for All-Cause Discontinuations in Episodic Migraine

	Odds Ratio vs. Placebo Estimate (95% CrI)	Expected Proportion Discontinuing Estimate (95% CrI)
Placebo	Reference	0.12 (NA)
Erenumab 70 mg monthly	0.7 (0.3, 1.3)	0.09 (0.04, 0.15)
Erenumab 140 mg monthly	0.6 (0.3, 1.4)	0.08 (0.04, 0.16)
Fremanezumab 675 mg quarterly	1.1 (0.5, 2.6)	0.13 (0.06, 0.26)
Fremanezumab 225 mg monthly	1.4 (0.7, 2.9)	0.16 (0.09, 0.28)
Galcanezumab 120 mg monthly	0.9 (0.5, 1.5)	0.11 (0.06, 0.17)
Galcanezumab 240 mg monthly	0.8 (0.5, 1.5)	0.10 (0.06, 0.17)
Topiramate 50 mg/day	1.1 (0.6, 1.8)	0.13 (0.08, 0.20)
Topiramate 100 mg/day	1.0 (0.7, 1.4)	0.12 (0.09, 0.16)
Topiramate 200 mg/day	1.7 (1.1, 2.5)	0.19 (0.13, 0.25)
Amitriptyline 25-150 mg/day	1.1 (0.7, 1.7)	0.12 (0.09, 0.19)
Propranolol 60-160 mg/day	0.9 (0.6, 1.6)	0.11 (0.08, 0.18)

Standard deviation for treatment effects: 0.31 (0.08, 0.59);
CrI: credible interval, NA: not applicable

Discontinuations from Adverse Events

Appendix Table D15 contains the data available from 33 trials reporting discontinuations due to AEs. Discontinuations due to AEs among patients on placebo ranged from 0% to 30% between four and 26 weeks. Discontinuations due to AEs among patients on a CGRP inhibitor ranged from 0% to 5% between 12 and 24 weeks. Discontinuations due to AEs among patients on other preventive

therapies ranged from 0% to 49%. The results from a random effects NMA are expressed in terms of an OR for each intervention versus placebo (Table 3.15). Values above 1 indicate a higher odds of discontinuation with the active therapy. The NMA results were statistically significant for topiramate 100 mg, topiramate 200 mg, and amitriptyline 75-150 mg, all of which had a higher odds of discontinuation due to AEs versus placebo. The results for all other interventions versus placebo were not significant and suggested a higher odds of discontinuation. The expected proportion of patients discontinuing CGRP inhibitor due to AEs by the end of trial ranged from 2% to 4%.

In the OLE of erenumab, 4% (14/383) of patients with episodic migraine on erenumab reported discontinuing treatment due to AEs after a year of follow-up.

Table 3.15. NMA Results for Discontinuations from Adverse Events in Chronic or Episodic Migraine

	Odds Ratio vs. Placebo Estimate (95% CrI)	Expected Proportion Discontinuing From Adverse Events Estimate (95% CrI)
Placebo	Reference	0.02 (NA)
Erenumab 70 mg monthly	1.4 (0.5, 3.5)	0.03 (0.01, 0.07)
Erenumab 140 mg monthly	1.4 (0.4, 4.5)	0.03 (0.01, 0.08)
Fremanezumab 675 mg quarterly	1.0 (0.4, 3.0)	0.02 (0.01, 0.06)
Fremanezumab 675/225 mg monthly	1.7 (0.7, 4.2)	0.03 (0.01, 0.08)
Galcanezumab 120 mg monthly	1.6 (0.6, 4.2)	0.03 (0.01, 0.08)
Galcanezumab 240 mg monthly	1.9 (0.7, 4.9)	0.04 (0.01, 0.09)
Onabotulinum toxin A 100-200 U quarterly	2.6 (1.1, 6.2)	0.05 (0.02, 0.11)
Topiramate 50 mg/day	1.6 (0.8, 3.1)	0.03 (0.02, 0.06)
Topiramate 100 mg/day	2.5 (1.7, 4.0)	0.05 (0.03, 0.08)
Topiramate 200 mg/day	3.7 (2.1, 6.3)	0.07 (0.04, 0.11)
Amitriptyline 75-150 mg/day	2.8 (1.4, 5.7)	0.05 (0.03, 0.10)
Propranolol 120-160 mg/day	1.4 (0.7, 2.9)	0.03 (0.01, 0.06)

Standard deviation for treatment effects: 0.44 (0.13, 0.83)

CrI: credible interval, NA: not applicable

Serious Adverse Events

SAEs were reported by 19 trials as listed in Appendix Table D16. Overall, SAEs were rare. SAEs with placebo ranged from 0% to 5% between 12 and 26 weeks. SAEs with a CGRP inhibitor ranged from 0% to 3% between 12 and 24 weeks. SAEs with other preventive therapies ranged from 1% to 15%. The results of the NMA are expressed as ORs (Table 3.16), with values above one indicating higher odds of SAEs with the active therapy versus placebo. Amitriptyline had a statistically-significant higher odds of SAEs versus placebo, whereas all other results were not significant. The point estimates favored the erenumab 140 mg and both fremanezumab doses versus placebo, whereas

all other interventions had a higher odds of SAEs. The expected proportion of patients experiencing a SAE with a CGRP inhibitor by the end of trial was less than 1%.

In the OLE of erenumab, 5% (21/383) of patients with episodic migraine on erenumab experienced a SAE after a year of follow-up. In patients with chronic migraine who entered the OLE for onabotulinum toxin A (PREEMPT 1 and 2), 7.4% (38/515) of patients who took five cycles of onabotulinum toxin A experienced a SAE after a year of treatment. 4.9% (24/490) of patients who took placebo during the randomized portion experienced a SAE after three cycles onabotulinum toxin A by one year.

Table 3.16. NMA Results for Serious Adverse Events in Chronic or Episodic Migraine

	Odds Ratio vs. Placebo Estimate (95% CrI)	Expected Proportion Experiencing SAEs Estimate (95% CrI)
Placebo	Reference	0.01 (NA)
Erenumab 70 mg monthly	1.1 (0.5, 2.6)	0.01 (0.01, 0.03)
Erenumab 140 mg monthly	0.6 (0.2, 1.8)	0.01 (0.00, 0.02)
Fremanezumab 675 mg quarterly	0.5 (0.1, 1.6)	0.00 (0.00, 0.02)
Fremanezumab 675/225 mg monthly	0.8 (0.3, 2.2)	0.01 (0.00, 0.02)
Galcanezumab 120 mg monthly	2.6 (0.9, 7.8)	0.03 (0.01, 0.07)
Galcanezumab 240 mg monthly	1.4 (0.4, 4.3)	0.01 (0.00, 0.04)
Onabotulinum toxin A 155 U quarterly	2.1 (0.9, 5.3)	0.02 (0.01, 0.05)
Topiramate 100 mg/day	1.1 (0.3, 3.3)	0.01 (0.00, 0.03)
Topiramate 200 mg/day	1.2 (0.1, 11.1)	0.01 (0.00, 0.10)
Amitriptyline 100 mg/day	3.1 (1.1, 8.4)	0.03 (0.01, 0.08)

Standard deviation for treatment effects: 0.28 (0.01, 1.05)

CrI: credible interval, NA: not applicable, NE: not able to be estimated, SAE: serious adverse event

Adverse Events ≥ 5%

AEs reported in ≥ 5% of patients in each arm of the CGRP inhibitor trials are presented in Appendix Table D17. The most commonly reported AEs involved injection-related issues (injection pain and injection-site reactions including erythema, induration, and pruritis), nasopharyngitis, and upper respiratory tract infection by 12 or 24 weeks. Two erenumab trials reported injection-site pain or reactions in ≤ 6% of patients taking erenumab. In the fremanezumab trials, 18-25% of patients reported specific injection-site reactions (18-21%, erythema; 20-25%) and up to 30% reported injection-site pain. For the galcanezumab trials, 5-8% of patients reported an injection-site reaction and 8-21% of patients reported injection-site pain. Nasopharyngitis and upper respiratory tract infection were reported in less than 12% of patients in erenumab, fremanezumab, and galcanezumab trials. Across the CGRP inhibitor trials, paresthesia, sinusitis, and dizziness were reported in ≤ 5% of patients.

In the trials of other preventive therapies, patients taking an active therapy generally reported more AEs and at a higher frequency than those on placebo (see Appendix Table D18). In these trials, the most commonly reported AEs were fatigue, cognitive symptoms (including cognitive difficulties, difficulty with memory, concentration, language), paresthesia, taste perversion, and weight change. Cognitive symptoms, paresthesia, taste perversion, and weight change were more frequently reported in topiramate trials. Common only to amitriptyline trials were constipation (gastrointestinal symptoms) and dry mouth.

In the OLE of erenumab in episodic migraine, commonly reported AEs by one year included nasopharyngitis (17%), upper respiratory tract infection (11%), back pain (7%), and influenza (7%). In addition, arteriosclerosis, myocardial ischemia, and occurrences of electrocardiogram T-wave inversion were present in three patients after a year of follow-up. In patients with chronic migraine who continued to the OLE with onabotulinum toxin A (PREEMPT 1 and 2), the authors reported that no additional safety or tolerability issue emerged by one year.

Controversies and Uncertainties

The currently available trials of erenumab, fremanezumab, and galcanezumab show treatment benefits with few harms. However, these trials assessed outcomes by 12 or 24 weeks, and there remains uncertainty in any durability of effects and AEs from prolonged use. These interventions are the first in the CGRP inhibitor class, and some concerns exist about the long-term effects of continuous blocking of CGRP or its receptor due to CGRP's cardiovascular protective role.[57-59] If patients, particularly chronic migraine patients, are expected to take CGRP inhibitors for a long duration (> 1 year), studies with longer follow-up are needed.[59] Limited data exist from one OLE on erenumab in the episodic migraine population,[152] and longer-term studies are currently ongoing (NCT01952574, NCT02638103, NCT03303105, NCT02614287, NCT02959190). In its review of erenumab, the FDA specifically requested postmarketing surveillance data for liver toxicity, myocardial infarction, and stroke among patients receiving erenumab.[24]

In addition, there is a paucity of evidence on optimal duration of preventive treatments, both for the existing preventives and for the CGRP inhibitors. Although patients may discontinue treatment due to poor tolerability or lack of efficacy, patients may also discontinue treatment if treatment has improved their condition. This "positive" stopping rule was not reported in the trials, and data on specific reasons for discontinuation were limited. Although benefits from treatment may continue after discontinuation, such data were not reported in the trials.

We understand that there remains a gap between those outcomes reported in the trials and the outcomes that patients seek. Patients expressed their desire for an improvement in their disability by reducing the burden of their condition on their daily life activities. Furthermore, chronic migraine tends to be more burdensome due to the sheer number of symptoms experienced from the higher average monthly migraine days.[60] However, quality of life measures were infrequently

reported across the trials. When reported, the follow-up periods were short. MIDAS, one of the quality of life measures reported in trials, was evaluated no longer than three months (12 weeks). As a result, it was difficult to definitively ascertain an improvement of a long-term outcome with a short-term follow-up period.

The designs of the CGRP inhibitor trials also raise concerns about generalizability of the results to clinical practice. First, the four-week baseline period used in the CGRP inhibitor trials required patients to comply with a headache diary. It is unclear how the efficacy results from these trials would apply to those who did not comply with a headache diary. For example, if the non-compliers were different from the compliers who initiated the randomized phase and these differences affect the treatment effect estimates, then the trial results cannot be generalized.

Second, the efficacy and safety of CGRP inhibitors in migraine patients who are pregnant and those with comorbidities, particularly cardiovascular diseases, have not been evaluated. Topiramate use in pregnant woman is associated with fetal harm (oral clefts).[184] The FDA is requiring prospective pregnancy registries to compare the maternal, fetal, and infant outcomes of women with migraine exposed to erenumab.[24] As migraine is associated with a higher prevalence of comorbidities including cardiovascular disease than in the general population, data on these patients are of interest.[61] In particular and, in part, due to CGRP's cardiovascular protective role, studies should assess the long-term effects of blocking CGRP or its receptor in patients with preexisting cardiovascular conditions.[57,58]

Finally, from the current evidence base, we have limited subgroup data on patients for whom prior preventive treatments have failed. The CGRP inhibitor trials excluded those patients who experienced failures from as few as two or three previous treatments. However, these patients are the most in need of an effective and tolerable preventive therapy and are most likely to receive a CGRP inhibitor in practice. Full results from trials assessing patients with two to four prior failures are anticipated (NCT03096834, NCT03308968).

3.4 Summary and Comment

Results from clinical trials and from our NMAs suggest that preventive treatment with the CGRP inhibitors erenumab and fremanezumab provide some clinical benefit in patients with chronic or episodic migraine. Few harms were seen in these short-term trials. Below, we provide a summary of the evidence for each CGRP inhibitor.

Erenumab (70 mg or 140 mg, monthly)

- **Number of trials:** In the chronic migraine population, we included one Phase II, 12-week trial. In the episodic migraine population, we included one Phase II 12-week trial along with

its OLE at one-year, one Phase III 12-week trial, and one Phase III 24-week trial. All trials were placebo-controlled.

- **Efficacy:** Results suggest a modest reduction in monthly migraine days (1.0-2.5 fewer migraine days per month), a modest reduction in days using acute medications (0.6-2.6 fewer days per month), and a greater proportion of patients experiencing a reduction in migraine days by at least 50% (OR 1.6-2.4) with erenumab compared with placebo.
- **Safety:** Erenumab was generally well tolerated during the 12-week or 26-week trials, with fewer proportions of patients discontinuing for any cause than with placebo, and small proportions discontinuing due to adverse events or experiencing a SAE. The most commonly-reported AEs pertained to injection-site pain or reactions. Nasopharyngitis and upper respiratory tract infections were also reported by < 10% of patients in the randomized trials, which were also reported during the one-year open-label extension of one trial.

Fremanezumab (675 mg quarterly or 225 mg monthly)

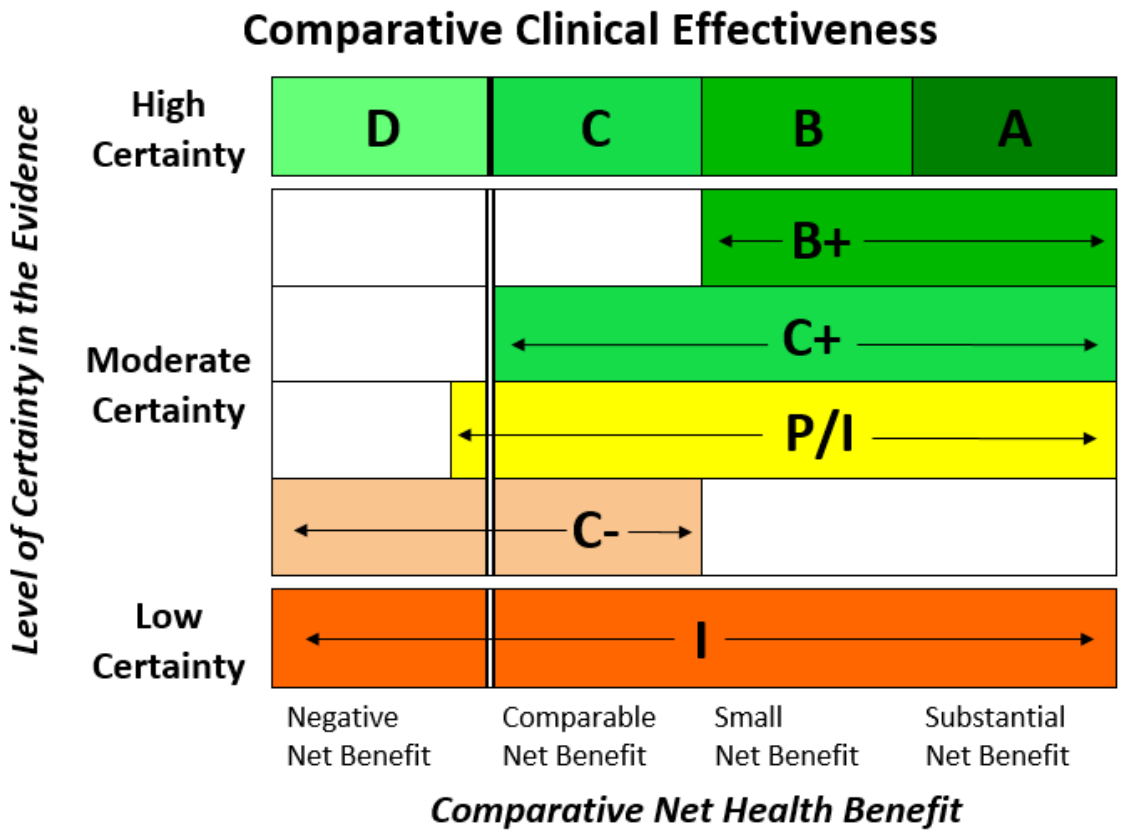
- **Number of trials:** In the chronic migraine population, we included one Phase II 12-week trial and one Phase III 12-week trial. In the episodic migraine population, we included one Phase II 12-week trial and one Phase III 12-week trial. All trials were placebo-controlled.
- **Efficacy:** Results suggest a modest reduction in monthly migraine days (1.0-2.8 fewer migraine days) and modest reduction in days using acute medications (1.0-2.2 fewer days). Results also suggest a greater proportion of patients experiencing a reduction in migraine days by at least 50% versus placebo (OR 1.6-2.4 in episodic migraine) or a reduction in moderate-to-severe headache days by at least 50% versus placebo (OR 2.4 in chronic migraine).
- **Safety:** Fremanezumab was generally well tolerated during the 12-week trials, with small proportions of patients discontinuing for any cause, discontinuing due to AEs, or experiencing a SAE. The most commonly-reported AEs pertained to injection-site pain or reactions. Sinusitis and upper respiratory tract infections were also reported by ≤ 5% of patients.

Galcanezumab (120 mg or 240 mg, monthly)

- **Number of trials:** In the chronic migraine population, we did not identify any published trials. In the episodic migraine population, we included one Phase II 12-week trial and two Phase III 24-week trials of galcanezumab. All trials were placebo-controlled.
- **Efficacy:** Results in episodic migraine suggest a modest reduction in monthly migraine days (1.7-2.0 fewer days per month) and modest reduction in days using acute medications (1.6-1.8 fewer days). Results also suggest a greater proportion of patients experiencing a reduction in migraine days by at least 50% versus placebo (OR 1.9-2.6).

- **Safety:** Galcanezumab was generally well tolerated during the 12-week or 24-week trials, with small proportions of patients discontinuing for any cause, discontinuing due to AEs, or experiencing a SAE. The most commonly-reported AEs pertained to injection-site pain or reactions. In addition, nasopharyngitis was reported by <10% of patients and upper respiratory tract infections were reported by <20% of patients.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

In terms of limitations of this evidence base, the trials compared CGRP inhibitors to placebo, restricted the patient population to those for whom no more than two or three other preventive therapies had failed, and were short-term in duration. The generalizability of the results is limited

and may not apply to many of the patients who would likely be treated with CGRP inhibitors, such as those who have tried more than three preventive therapies and those with comorbidities. In addition, the short-term trials limit our certainty about the safety of these agents with a novel mechanism of action, particularly related to AEs that may manifest after a longer duration of treatment such as cardiovascular AEs. Hence, we rated the evidence as follows:

- Among patients with chronic migraine who are eligible to receive preventive therapy, we rated the evidence on the net benefit of erenumab and fremanezumab as insufficient ("I") compared to oral agents or to onabotulinum toxin A. Among patients with chronic migraine for whom prior preventive therapy has failed, we rated the net benefit of erenumab and fremanezumab as comparable or better ("C+") compared to no treatment, weighing uncertainties about potential harms of CGRP inhibitors against the need for therapy in patients with frequent migraine and no other preventive treatment options.
- Among patients with episodic migraine who are eligible to receive preventive therapy, we rated the evidence on the net benefit of erenumab, fremanezumab, and galcanezumab as insufficient ("I") compared to oral agents. Among patients with episodic migraine for whom oral preventive therapies have failed, we rated the net benefit of erenumab and fremanezumab as promising but inconclusive ("P/I") compared to no treatment, again weighing uncertainties about potential harms of CGRP inhibitors against the need for therapy in patients without other preventive treatment options but with less frequent migraine than in the chronic migraine population.
- Given the limited amount of data currently available, we rated the evidence on net benefit of galcanezumab as insufficient ("I") for all other populations and comparisons.
- We rated the evidence on net benefit of erenumab versus fremanezumab as insufficient ("I") for all populations and comparisons due to the lack of direct evidence and weighing uncertainties about potential longer-term benefits and harms of each intervention.

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the incremental cost-effectiveness of two CGRP inhibitors, erenumab and fremanezumab, compared to no preventive treatment in people with chronic and episodic migraine for whom previous preventive therapy had failed. Erenumab and fremanezumab were included in the economic modeling based on available evidence. We did not model galcanezumab given the lack of currently available data in the subpopulation of patients for whom prior preventive therapy had failed.

For erenumab and fremanezumab, we built separate semi-Markov models for chronic and episodic migraine that were similar in structure to recent models in migraine treatment.[185-188] The base-case analyses were performed from a health system perspective (i.e., focus on direct medical care costs only) and were based on monthly cycles over a two-year time horizon. The outcomes included in the model were quality adjusted life years (QALYs), reduction in migraine days and total costs for interventions and comparators. We used these outcomes to generate incremental cost-effectiveness ratios of cost per QALY gained and cost per migraine day avoided, comparing CGRP inhibitors to the comparators. Both costs and QALYs were discounted at a rate of 3% per annum. We also conducted several scenario analyses that evaluated the impact of productivity losses, the cost-effectiveness relative to other preventive treatments, longer time horizons, titration of CGRP inhibitors after a period of treatment success, and using alternative assumptions about long-term discontinuation rates. The general model framework for this analysis is shown in Figures 4.1 and 4.2. The models were developed in Microsoft Excel 2013 (Redmond, WA).

4.2 Methods

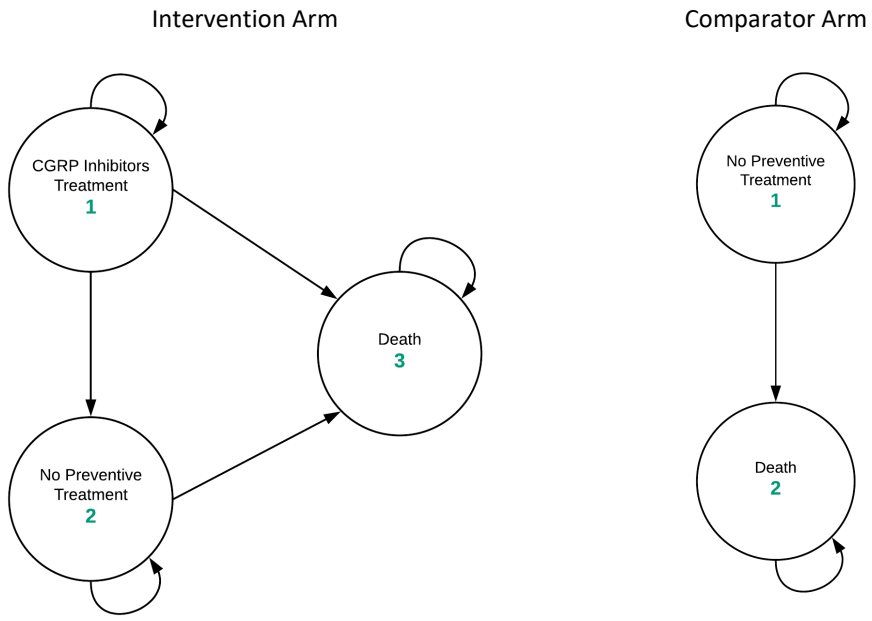
Model Structure

We developed separate semi-Markov models to assess the cost-effectiveness of erenumab and fremanezumab compared to no preventive treatment in both chronic and episodic migraine patients for whom a previous preventive therapy had failed. More specifically, patients had at least one but not more than three prior preventive treatments result in failure. This subset of patients was selected as the base-case population to estimate outcomes in patients for whom other preventive therapies are no longer an option, which aligns with input from stakeholder groups about the anticipated place in therapy of the CGRP inhibitors (use among patients who experienced the failure of at least some oral preventive therapies). Hence, in the base case models, we evaluated the cost-effectiveness of the CGRP inhibitors in the following specific clinical scenarios:

1. **Chronic migraine:** CGRP inhibitor versus no preventive treatment (Figure 4.1). The intervention arm of the model includes three health states: 1) CGRP inhibitor treatment, 2) no preventive treatment, and 3) death. The comparator arm includes two health states: 1) no preventive treatment and 2) death. The treatment effects for the CGRP inhibitors were estimated from the results of an NMA and were characterized in terms of reduction in migraine days per month on the subset of patients for whom a previous therapy for chronic migraine had failed.
2. **Episodic migraine:** CGRP inhibitor versus no preventive treatment (Figure 4.1). The intervention arm of the model includes three health states: 1) CGRP inhibitor treatment, 2) no preventive treatment, and 3) death. The comparator arm includes two health states: 1) no preventive treatment and 2) death. The treatment effects for the CGRP inhibitors were estimated in terms of migraine days per month and were based on results from an NMA using the subset of patients for whom a previous therapy for episodic migraines had failed.

Patients moved through the health states in the model in monthly cycles. In the models, in each of the arms (see Figure 4.1 below), patients start in an initial health state numbered "1" in the figure and can either remain in that state or transition to other connected health states. Once patients transitioned out of the initial health state, they could not re-enter that health state. Patients in the intervention arm could discontinue and entered a no preventive treatment state. Patients in any non-death health state could transition to the death health state based on age- and gender-specific mortality rates. All of the analyses followed cohorts of patients over a two-year period. The two-year period was selected to be consistent with previous migraine models and because there is a lack of data on the long-term use of preventive medications for management of migraine.[185-191] The semi-Markov models included time-dependent measures of treatment effects and mortality estimates. Each of the health states included estimates of the number of migraine days per month. Note that where necessary, clinical trial data used in the model that were based on periods of four weeks were adjusted to reflect a 30-day period. The models included estimates of the daily costs of acute migraine treatments and other health care services used to treat migraines as well as AEs from the underlying treatments in each of the health states. Utilities, described in more detail below, were a function of migraine severity for each migraine day along with non-migraine days each month across the health states along with disutility from adverse events.

Figure 4.1. Model Framework for CGRP Inhibitors versus No Preventive Treatment (Chronic and Episodic Migraine)



Target Population

The populations of interest were the prevalent cohort of individuals in the US currently experiencing either chronic or episodic migraine for whom previous treatments with preventive therapies had failed. As noted above, this population was selected based on the anticipated place in therapy of the CGRP inhibitors in response to feedback from stakeholders. The general characteristics of the population in each model reflected the average patient who experiences chronic or episodic migraine in the US. We were unable to further identify specific characteristics of the population for whom previous therapy had failed and therefore we used information on the general migraine population. The mean age, gender distribution, ethnicity, and mean migraine days per month along with the relevant sources for episodic and chronic migraines are provided in Table 4.1. The mean number of migraine days per month used for the populations in the chronic and episodic migraine models were based on the mean number of migraines in the clinical trial populations that were used in the NMAs.

Table 4.1. Base-Case Model Cohort Characteristics

Migraine Type	Characteristics	Value	Primary Source
Chronic Migraine	Mean age	39.2 years	Ford et al. 2017[6]
	Female	80.5%	Lipton et al. 2016[192]
	Race/Ethnicity	88.6% - white 11.4% - non-white	Lipton et al. 2016[192]
	Mean Migraine Days per Month	17.7	RCT Population in Network Meta-analysis
Episodic Migraine	Mean age	39.9 years	Ford et al. 2017[6]
	Female	76.4%	Lipton et al. 2016[192]
	Race/Ethnicity	85.0% - white 15.0% - non-white	Lipton et al 2016[192]
	Mean Migraine Days per Month	8.0	RCT Population in NMA

Treatment Strategies

As described above, each of the CGRP inhibitors was compared with no preventive treatment in chronic and episodic migraine patients, separately.

Key Model Characteristics and Assumptions

Key model assumptions are outlined in Table 4.2. For the base-case models, we used a health care system third-party payer perspective in which only direct medical care costs were included. As noted above, a two-year timeframe was selected for the base case because of a lack of data on the long-term use of preventive migraine treatments and because it was consistent with previous cost-effectiveness related migraine models.[185-188] We used a cycle length of one month as that seemed the most consistent with treatment patterns as well as with available data on costs and patient outcomes. Costs and QALYs were discounted by 3% per annum.

Table 4.2. Key Model Assumptions

Assumption	Rationale
For the base-case scenario, we used the CGRP inhibitor dose with the largest treatment effect for each respective indication at the 12-week measurement point adjusted to reflect one-month (30 day) cycles.	Given little information on which dose would be used predominantly in the market, we chose the dose most in favor of the CGRP inhibitors.
Regardless of migraine intensity and/or type, migraine treatment does not have a direct effect on mortality, outcomes, or cost of treating underlying conditions other than migraines.	There are currently insufficient data to demonstrate that the CGRP inhibitors directly improve mortality compared to current treatment or placebo. More generally, there are insufficient data regarding the mortality of those with migraine vs. those without migraine for the effect of migraine treatment on mortality to be a feature in the model. Further, although there are sufficient data showing that patients with migraines are at higher risk for cardiovascular complications than those who are migraine-free, there are inadequate data to demonstrate if any preventive migraine medication reduces these cardiovascular events.
For the treatment effects and discontinuation rates, we assumed the values from the network meta-analyses were constant over the entire model time horizon.	The treatment effects tend to be stable in the trials after three months and there are no other data on which to base long-term treatment effects. Similarly, we did not have data on long-term discontinuation rates for all of the treatments of interest.
The effect of migraine days on utilities was based on published disutility weights for mild, moderate, and severe migraine days. Estimates for the distribution of severity across migraine days was based on a representative sample of the US population with migraine.	We consistently projected treatment related gains in quality adjusted life years proportional to treatment effects on migraine days as this is the best proxy for treatment effect that we have across all the drugs.
We modeled the cost offsets related to health care utilization from reduced migraine days using the average number of hospitalizations, emergency department (ED) visits, and physician office visits per migraine day observed in the literature.	Health care utilization costs were not reported in the clinical trials. However, we expected a reduction in migraine days would result in a proportional reduction in migraine-related health care utilization.

Assumption	Rationale
To estimate the impact on acute migraine medication use, we assumed that patients in the treatment arm were using a set of migraine medications similar to current patients with episodic and chronic migraine.[64] Reduction in the number of days of acute medication use were determined from the literature based on an NMA. The number of days reduced was combined with an estimated cost per day of acute medication use based on the literature.[64]	The NMA for the migraine day reduction covered all acute medications and was conducted over all available evidence on preventive medications.
For AE costs, we used the cost of one primary care physician's office visit (CPT 99213).[193]	A variety of AEs were associated with the treatments in the model and relatively little information exists regarding the severity and duration of those events. In addition, clinical trials for the medications in the model did not report utilization such as those being hospitalized vs. those who saw a physician. Overall, given the types of AEs associated with these treatments, hospitalization was likely rare, so we assumed all AEs would only involve a physician office visit.
For the disutility of AEs, we assumed a small constant disutility of 0.05.	Again, severity and duration of AEs were not generally reported. However, there is likely at least a small utility impact associated with most of them and there are differences in the rates of AEs across treatments. Therefore, we assumed a small constant disutility and explored the impact of changing the score in sensitivity analyses.

Model Inputs

Clinical Inputs

The populations considered in each of the chronic and episodic migraine models included an estimate of the number of migraine days per month and the distribution of headache severity on days with migraine (Table 4.3).[67] The distribution of migraine severity was based on data from the American Migraine Prevalence and Prevention study, which was a mailed survey to 120,000 US households. Among those identified with migraine, information on the frequency of migraines and the severity of the migraine was reported. Data for those with more than four migraines per month up to 14 migraines per month were used to determine the severity distribution for the episodic migraine population where the categories of no impairment, some impairment, and severe impairment were summarized as mild, moderate, and severe. We selected this population for the distribution of headache severity as it was the population that was indicated as eligible for treatment in the paper. The same distribution was applied to the chronic migraine population.

These distributions were similar to pooled estimates of migraine severity provided by manufacturers, which was based on PREEMPT 1 and 2 and eptinezumab Phase II and III data.[26,194-197] These distributions were mild at 10.3%, moderate at 38.6% and severe at 51.1%.

Table 4.3. Clinical Characteristics of the Patients in the Chronic and Episodic Models

Characteristics		Chronic Model	Episodic Model	Source
Migraine Days		17.7	8.0	RCT Population in NMA
Headache Severity (%)	Mild	7.1%	7.1%	Lipton 2007[1]
	Moderate	41.0%	41.0%	Lipton 2007[1]
	Severe	51.9%	51.9%	Lipton 2007[1]

Treatment Effects - Reduction in Migraine Days

The treatment effects for each of the medications used in the base-case analyses are listed in Tables 4.4 and 4.5. The treatment effects for the CGRP inhibitors are redacted in the tables and text since they were submitted as academic-in-confidence data to ICER by the respective manufacturers. The treatment effect estimates reflect the reduction in migraine days associated with each medication compared to no preventive treatment among the subset of patients that failed at least one prior preventive therapy.

Table 4.4. Treatment Effects for CGRP Inhibitors in Chronic Migraine Among Those for Whom Previous Therapy Failed

Treatment	Mean Reduction in Migraine Days (95% CI)		
	Week 4	Week 8	Week 12
Erenumab 140 mg monthly	[redacted]	[redacted]	[redacted]
Fremanezumab 675/225 mg monthly	[redacted]	[redacted]	[redacted]

Note: These inputs were provided by the drug manufacturers as "academic in confidence" data and are redacted as such. They will be unmasked no later than December 2019 per ICER's data in confidence policy.
CI: confidence interval

Table 4.5. Treatment Effects for CGRP Inhibitors in Episodic Migraine Among Those for Whom Previous Therapy Failed

Treatment	Mean Reduction in Migraine Days (95% CI)		
	Week 4	Week 8	Week 12
Erenumab 140 mg monthly	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg monthly	[redacted]	[redacted]	[redacted]

Note: These inputs were provided by the drug manufacturers as "academic in confidence" data and are redacted as such. They will be unmasked no later than December 2019 per ICER's data in confidence policy.
CI: confidence interval

Acute Treatment Use

Average acute migraine treatment days per month was based on an estimate from a web-based survey of individuals in the United States with either chronic or episodic migraine (Table 4.6).[64]

Table 4.6. Average Acute Migraine Treatment Days per Month

	Chronic Migraine	Episodic Migraine	Source
Total Acute Treatments (Days Per Month)	7.62	2.97	Messali et al. 2016[64]

In addition to direct treatment effects, results from an NMA on the reductions in days per month with acute treatments were used to determine the reduction in acute treatments associated with each of the preventive treatments. The reductions in acute treatments per 30 days are listed below (Table 4.7).

Table 4.7. Reduction in Days per Month of Acute Treatments for CGRP Inhibitors

Treatment	Chronic Migraine: Mean Reduction in Acute Treatment Days per Month (95% CI)	Episodic Migraine: Mean Reduction in Acute Treatment Days per Month (95% CI)
Erenumab 140 mg monthly	-2.67 (-5.30, -0.01)	-1.76 (-2.71, -0.85)
Fremanezumab 225 mg monthly	-2.33 (-4.34, -0.30)	-1.31 (-2.27, -0.42)

CI: confidence interval

Discontinuation Rates

In each of the models, patients transitioned from the "CGRP Inhibitor Treatment" health state based on the proportion of patients who discontinued treatment for any cause from the clinical trials. Specifically, the rate of discontinuation for each of the treatments were based on results of a NMA. Odds of discontinuation at 12 weeks for the placebo arm among the studies included in the NMA were used along with the ORs found from the NMA for the treatments. The odds were then converted to monthly rates and used in the model (Table 4.8).

Table 4.8. Monthly Discontinuation Rates for CGRP Inhibitors

Treatment	Chronic Migraine: Discontinuation Rate (95% CI)	Episodic Migraine: Discontinuation Rate (95% CI)
Erenumab 140 mg monthly	0.031 (0.010, 0.084)	0.041 (0.017,0.090)
Fremanezumab 225 mg monthly	0.062 (0.034, 0.114)	0.084 (0.044,0.160)

CI: confidence interval

Mortality

As noted in Table 4.2 we assumed the treatments had no impact on mortality rates. Therefore, for the transition to death from any non-death health state, we used age and gender-specific death rates from the US life tables from the Centers for Disease Control and Prevention (CDC) for both chronic and episodic migraine populations.[198]

Severity Distribution and Utilities

For the health state utilities, we weighted the utilities for chronic and episodic migraine days based on the severity distribution for migraines shown in Table 4.3. The distribution of mild, moderate, and severe migraines was shifted by a monthly rate based on the severity distribution at the end of a three-month trial for fremanezumab (Table 4.9). The change in distribution from fremanezumab data was applied to the erenumab model because there were no publicly-available data for erenumab. At the end of three months, the severity distribution remained the same throughout the time horizon of the model. We used trial-specific data on the change in distribution of migraine-severity due to treatment effect since we no real-world data on this currently exists for the CGRP inhibitors. Table 4.10 shows the utility values used for a severe, moderate, mild, and migraine-free day. The utility weights were estimated using the EQ-5D in a population of adults in the United States who were in good physical health and had experienced migraine in the two months preceding enrollment.[65] Stratified estimates of utility based on the self-reported severity of migraine were determined. We combined the distribution of migraine severity and the utility weights to determine the utilities associated with a migraine day. In addition, we incorporated a disutility score based on the proportion of patients with an AE where those with an AE had a disutility score of 0.05 per month.

Table 4.9. Migraine Severity Distribution at Three Months in Patients in the Chronic and Episodic Models

		Chronic Model	Episodic Model	Source
Migraine Severity (%)	Mild	[redacted]	[redacted]	Teva data on file[199]
	Moderate	[redacted]	[redacted]	Teva data on file[199]
	Severe	[redacted]	[redacted]	Teva data on file[199]

Note: These inputs were provided by the drug manufacturer as "academic in confidence" data and are redacted as such. They will be unmasked no later than December 2019 per ICER's data in confidence policy.

Table 4.10. Utility Values Based on Severity of Migraine

	Utility Value			Source
	Mean Value	95% CI	Method	
Severe Migraine Day	0.440	(0.374, 0.502)	EQ-5D	Xu et al 2011[65]
Moderate Migraine Day	0.773	(0.755, 0.789)	EQ-5D	Xu et al 2011[65]
Mild Migraine Day	0.835	(0.790, 0.883)	EQ-5D	Xu et al 2011[65]
Migraine-Free Day	0.959	(0.896, 0.967)	EQ-5D	Xu et al 2011[65]

CI: confidence interval

Adverse Events

The AEs in the clinical trials of the CGRP inhibitors were heterogeneous and relatively mild. To estimate the impact of these events on resource use, we assumed AEs were associated with a physician office visit (Current Procedural Terminology [CPT] Code 99213) and a small decrement in utility. The overall rate of AEs in the clinical trial was converted to monthly proportions for each of the medications. The proportion of patients experiencing an AE during a monthly cycle for each of the treatments included in the models are shown in Table 4.11.

Table 4.11. Proportion of Patients Experiencing an Adverse Event Each Cycle

Treatment	Chronic Migraine: AE Rate	Source	Episodic Migraine: AE Rate	Source
Erenumab 140 mg monthly	2.7%	Tepper et al. 2017[90]	5.6%	Goadsby et al. 2017[41]
Fremanezumab 225 mg monthly	11.5%	Silberstein et al. 2017[28]	6.6%	Bigal et al. 2015[26]

AE: adverse event, NA: not applicable

Economic Inputs

All costs included in the model were adjusted to 2017 US dollars using the medical care component of the Consumer Price Index.[200]

Drug Acquisition Costs

The wholesale acquisition cost (WAC) for erenumab is $6,900 per year.[62] There were conflicting reports on whether discounts will be offered and the magnitude of the discounts. Therefore, the industry-wide average discount rate of 27% was applied to the annual WAC for a rounded annual cost of $5,000 which was used for both CGRP inhibitors (Table 4.12).[63]

Table 4.12. Preventive Drug Cost Inputs

Drug	Administration	Unit	Annual WAC	Annual Net Drug Cost
Erenumab 140 mg monthly	SQ	mg	$6,900	$5,000
Fremanezumab 225 mg monthly	SQ	mg	NA	$5,000

SQ: subcutaneous

Administration and Monitoring Costs

For administration costs, we used the costs of a physician office visit (CPT Code 99213; 2017 national non-facility price = $73.93) during the first month of administration for the CGRP inhibitors.

Health Care Utilization Costs

For the medications used for acute treatment of migraine, we determined daily medication costs based on cost estimates and days of use as reported by Messali et al.[64] The cost per day for acute treatments was $25 for chronic migraine patients and $21 for episodic migraine patients.

To determine the cost of a migraine-related ED visit, the monthly rate of ED visits reported in the paper from Messali et al. for both episodic and chronic migraines was used. An estimate of the cost for an ED visit for migraine was based on an analysis of the MarketScan Commercial Claims and Encounters Database where the ED cost was $775 per visit ($949 when inflated to 2017 dollars).[64,201] These numbers were multiplied to obtain the monthly cost of ED visits of $16. For the costs of hospitalizations, data from Lucado et al., which was an analysis of the costs associated with headache using data from the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project (HCUP) were used.[202] The rate of migraine hospitalizations based on the HCUP data was 16.8 hospitalizations per 100,000 person-years for the US population. To convert this rate to migraine hospitalizations among patients with migraines, we divided the rate by the estimated prevalence of migraines in the US (16%).[203] This hospitalization rate was converted to a monthly rate and multiplied by the costs of a hospitalization reported in the analysis of the MarketScan Commercial Claims and Encounters Database of $7,317 (or $8,996 in 2017).[201] For the costs of a primary care visit, nurse practitioner visit, neurologists, and other specialists, monthly rates were estimated using the data from Messali et al. and the costs from the analysis of the MarketScan Commercial Claims and Encounters database ($140 [$152 in 2017]).[64,201] For transcutaneous nerve simulator, occipital nerve block, imaging, and blood tests, we used the cost estimates from the Messali et al. paper.[64]

Adverse Event Costs

The monthly costs of AEs were calculated as the monthly rate of the event multiplied by the costs of a level 3 office visit (CPT Code 99213; 2017 national non-facility price = $73.93).

Sensitivity Analyses

We conducted deterministic one-way sensitivity analyses to identify the key drivers of model outcomes using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section. The ranges of values used in the one-way sensitivity analyses are not presented in this report to avoid the disclosure of confidential data. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 10,000 simulations and calculating 95% credible range estimates for each model outcome based on the results. In the probabilistic sensitivity analyses we used log-normal distributions for costs, beta distributions for utilities and the discount rate, Dirichlet distributions for multivariate distributions, and normal distributions for migraine day reduction and abortive migraine and headache medication reduction. Baseline counts of migraine days and acute medication use days were varied in addition to the other inputs based on gamma distributions. Additionally, we performed a threshold analysis by systematically altering the price of the CGRP inhibitors to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds.

Scenario Analyses

We conducted several scenario analyses to evaluate the impact on the incremental cost-effectiveness ratios. These scenario analyses are described briefly in the following list:

1. CGRP Inhibitors Compared to Current Preventive Treatments

The first scenario analysis evaluated the cost-effectiveness of CGRP inhibitors compared to onabotulinum toxin A for patients with chronic migraine for whom a previous preventive treatment had failed. In the comparative effectiveness section of the report, we have rated the evidence comparing erenumab and fremanezumab to onabotulinum toxin A as insufficient ("I"). Therefore, we have excluded onabotulinum toxin A as a comparator in the base-case analysis of chronic migraine patients for whom previous preventive therapy had failed and included it as a scenario analysis. In this scenario analysis, the administration of onabotulinum toxin A is based on a quarterly cost of administration prorated to the monthly cycles in the model (CPT Code 64615; 2017 national non-facility price = $149.30).[193] A separate model was created to evaluate the cost-effectiveness of the CGRP inhibitors versus a mix of current preventive treatments for all patients with chronic or episodic migraine who are eligible for preventive therapy.

1. **Chronic migraine:** CGRP inhibitor versus onabotulinum toxin A (Figure 4.2). In this comparison, CGRP inhibitors were compared directly to onabotulinum toxin A in patients with chronic migraine. The intervention arm of the model included three health states: 1) CGRP inhibitor treatment, 2) no preventive treatment, and 3) death. The comparator arm also included three health states: 1) onabotulinum toxin A treatment, 2) no preventive treatment, and 3) death. The treatment effects for both the CGRP inhibitors and

onabotulinum toxin A were characterized in terms of the reduction in migraine days per month and were based on results from an NMA.

2. CGRP inhibitor versus active preventive treatments in chronic migraine (Figure 4.3). In this comparison, CGRP inhibitors were compared to active preventive treatments for chronic migraine, including amitriptyline, propranolol, topiramate, and onabotulinum toxin A. The intervention arm of the model included three health states: 1) CGRP inhibitor treatment, 2) prevalent treatment mix, and 3) death. The prevalent treatment mix reflected the entire mix of preventive treatment patterns of patients with chronic migraine and included the comparator medications along with no treatment. The rates of use for the prevalent treatment mix in chronic patients were based on contemporary estimates of the use of preventive migraine treatments in chronic migraine.[6] The comparator arm included three health states: 1) preventive treatments; 2) prevalent treatment mix; and 3) death. The rates of use for the prevalent treatment mix in chronic migraine patients were the same as in the CGRP arm, again based on contemporary estimates of the use of all preventive migraine treatments in chronic migraine including no treatment.[6] The treatment effects for both the CGRP inhibitors and the comparator treatments were estimated from an NMA and characterized as the reduction in migraine days per month. Those who discontinued either the CGRP inhibitor treatment or the comparator treatments were assumed to have the same migraine days, costs, and outcomes as the prevalent treatment mix health state.
3. CGRP inhibitor versus active preventive treatment in episodic migraine (Figure 4.3). In this comparison, CGRP inhibitors including galcanezumab, were compared to active treatments for episodic migraine, including amitriptyline, propranolol, and topiramate. The intervention arm of the model included three health states: 1) CGRP inhibitor treatment, 2) prevalent treatment mix, and 3) death. The prevalent treatment mix reflected the use of all preventive treatment strategies seen in patients with episodic migraine and included the comparator medications along with no treatment. The rates of use for the prevalent treatment mix in episodic migraine patients were based on contemporary estimates of the use of preventive migraine treatments in episodic migraine.[6] The comparator arm also included three health states: 1) preventive treatment, 2) prevalent treatment mix, and 3) death. The rates of use for the prevalent treatment mix in episodic migraine patients were the same as in the CGRP inhibitor arm again based on contemporary estimates of the use of preventive migraine treatments in episodic migraine as well as no treatment.[6] The treatment effects for both the CGRP inhibitors and the comparator treatments were estimated based on the reduction in number of migraine days per month and were based on results from a network meta-analysis. Those who discontinued either the CGRP inhibitor treatment or the active preventive treatments were assumed to have the same migraine days, costs, and outcomes as the prevalent treatment mix health state.

Figure 4.2. Model Framework for CGRP Inhibitors versus Onabotulinum Toxin A (Chronic Migraine)

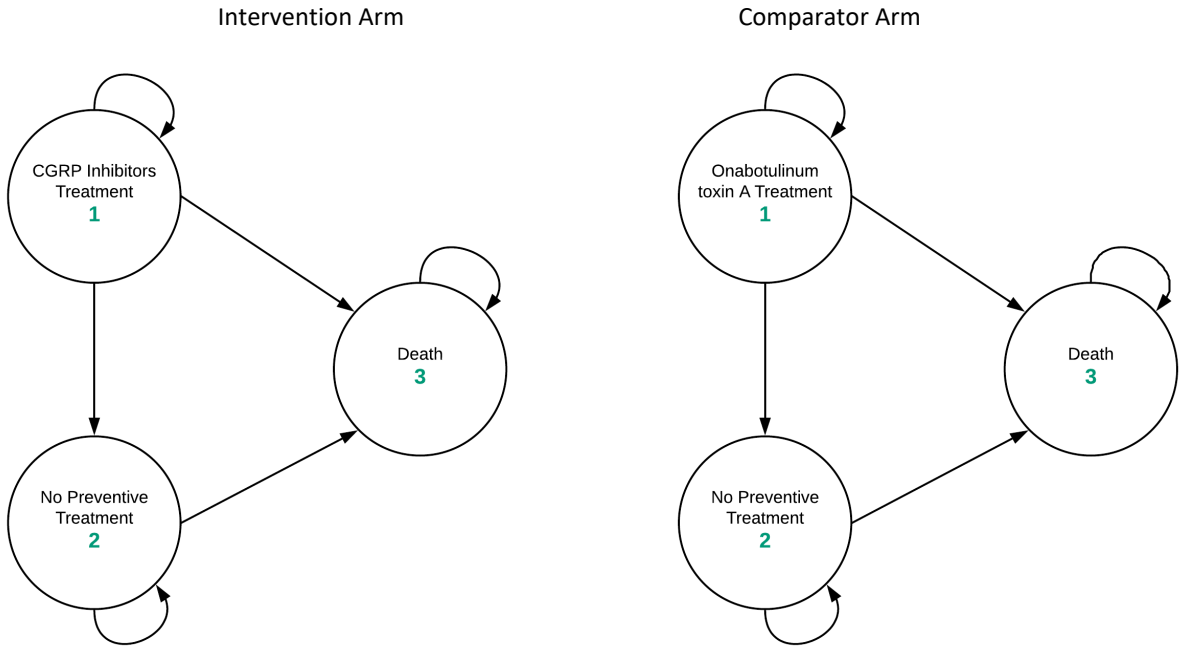
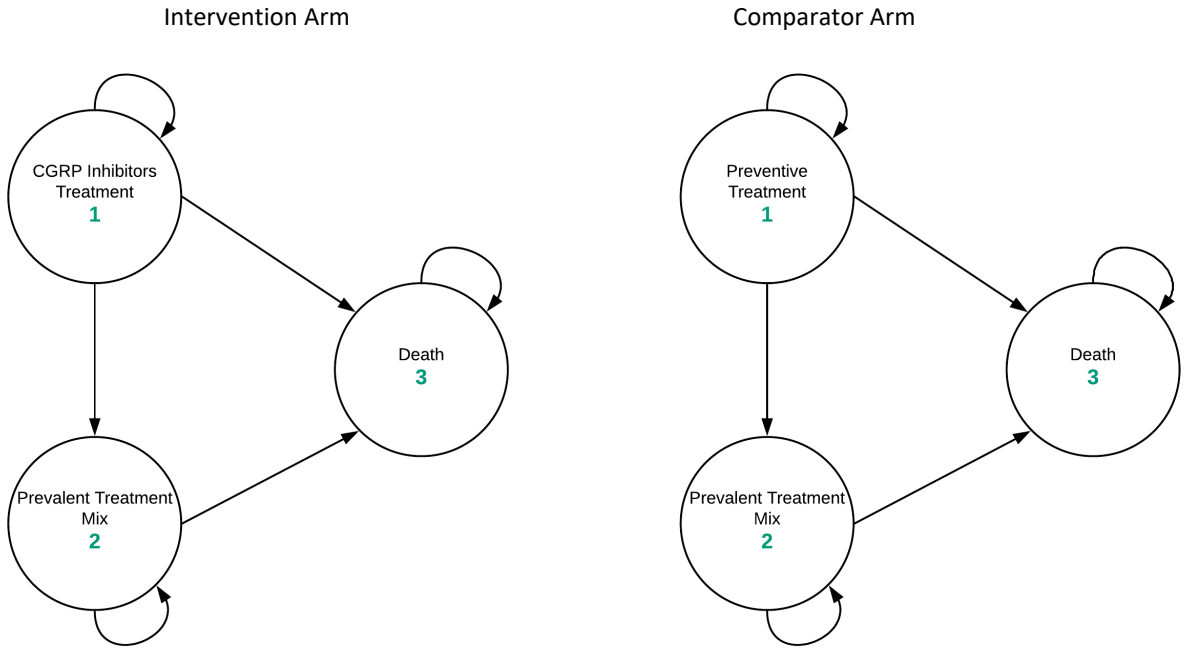


Figure 4.3. Model Framework for CGRP Inhibitors versus Active Preventive Treatment



2. Modified Societal Perspective

Here we conducted a scenario analysis that incorporated the impact of treatment on productivity in the economic evaluation. The costs of lost productivity were based on data from the American Migraine Prevalence and Prevention study, in which nearly 200,000 participants reported estimates of lost productivity time.[204] Specifically, patients with migraine reported the average number of hours of productivity lost in the last two weeks. Data on the number of migraines experienced in the last three months and the amount of lost productivity was used to estimate the number of hours lost per migraine day. To estimate the cost, the median income rate in the US was used.[205]

3. Longer Time Horizons

The base-case model used a two-year time horizon. We conducted scenario analyses that expanded the time horizon to five and ten years, as well as lifetime. In the lifetime model, we assumed that patients remain on the CGRP inhibitors based on discontinuation rates consistent with rates from the NMA and ran the model until 99.9% of patients were in the death state.

4. Persistence of Treatment Effect Following Discontinuation

This scenario allowed a proportion of patients, based on those that had a greater than 50% reduction in migraine days, to discontinue treatment after one year and maintain the treatment effect during the second year. Beginning in the second year, patients on treatment transitioned to a state where they had no drug costs but maintained the treatment effects. The rate of transition was set up so that over the course of the second year, the total proportion of patients that ended up in that state would equal the proportion with greater than 50% reduction seen in the trials. Hence, some patients would be in that state for 12 months and some only one month. While there are no data to support such an effect, clinical experts suggested this may occur in practice among responders. We made assumptions in the model to give some level of persistent effect to the proportion of patients with greater than 50% reduction but capped that effect at 12 months and required patients to experience at least a year of treatment response before discontinuing.

5. Impact of CGRP Inhibitors on Depression

To evaluate the potential effects of CGRP inhibitors on depression, we included an improvement in QALYs for the subset of patients treated with CGRP inhibitors with moderate to severe depression. We assumed that about 20% of patients with migraine would have moderate to severe depression. For this subset of patients, we assumed a utility gain of 0.05 which is approximately equal to a two-point change on the Patient Health Questionnaire (PHQ-9).[206]

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs. Model validation was also conducted in terms of comparisons to other model findings.

4.3 Results

Below we present the results of the cost-effectiveness analyses. In order to preserve the confidential data used in the generation of these results, several tables have been redacted. In addition, incremental cost-effectiveness ratios have been rounded to the nearest $10,000 when confidential data were used or when the ratios exceeded one million dollars per QALY gained, and to the nearest $1,000 when only publicly-available data were used. Willingness-to-pay threshold prices have been rounded to two significant digits. Cost per migraine-free day gained results have been rounded to the nearest $10.

Base-Case Results

Treatment with CGRP inhibitors resulted in higher total costs, more migraine-free days, and increased QALYs compared to no preventive treatment in both chronic and episodic migraine among patients for whom at least one but not more than three previous preventive therapies had failed (Table 4.13 and 4.14). In both comparisons for the CGRP inhibitors, the drug costs were responsible for the majority of the total costs over the two-year period. The drug costs and total costs were lower in the fremanezumab treated group because of higher discontinuation rates when compared to erenumab.

Table 4.13. Discounted Costs and Effects for the Base Case for CGRP Inhibitors Compared to No Preventive Treatment in Chronic Migraine*

Treatment	Drug Cost	Total Cost	Migraine-Free Days Gained	QALYs
CGRP Inhibitors vs. No Preventive Treatment				
Erenumab 140 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 625/225 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
No Preventive Treatment	$0	[redacted]	0	[redacted]

Results in this table are redacted to preserve the confidentiality of certain data inputs used in their generation

Table 4.14. Discounted Costs and Effects for the Base Case for CGRP Inhibitors Compared to No Preventive Treatment in Episodic Migraine*

Treatment	Drug Cost	Total Cost	Migraine-Free Days Gained	QALYs
CGRP Inhibitors vs. No Preventive Treatment				
Erenumab 140 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
No Preventive Treatment	$0	[redacted]	0	[redacted]

Results in this table are redacted to preserve the confidentiality of certain data inputs used in their generation

The base case incremental cost-effectiveness ratios for erenumab in chronic migraine for patients among whom prior preventive therapy failed was approximately $90,000 per QALY gained compared to no preventive treatment (Table 4.15). The comparable results for fremanezumab were approximately $120,000 per QALY gained compared to no preventive treatment. For patients with episodic migraine among whom prior preventive therapy failed, the incremental cost-effectiveness ratios for the CGRP inhibitors compared to no preventive treatment were approximately $150,000 per QALY gained for erenumab and for fremanezumab.

Table 4.15. Incremental Cost-Effectiveness Ratios for the Base Case*

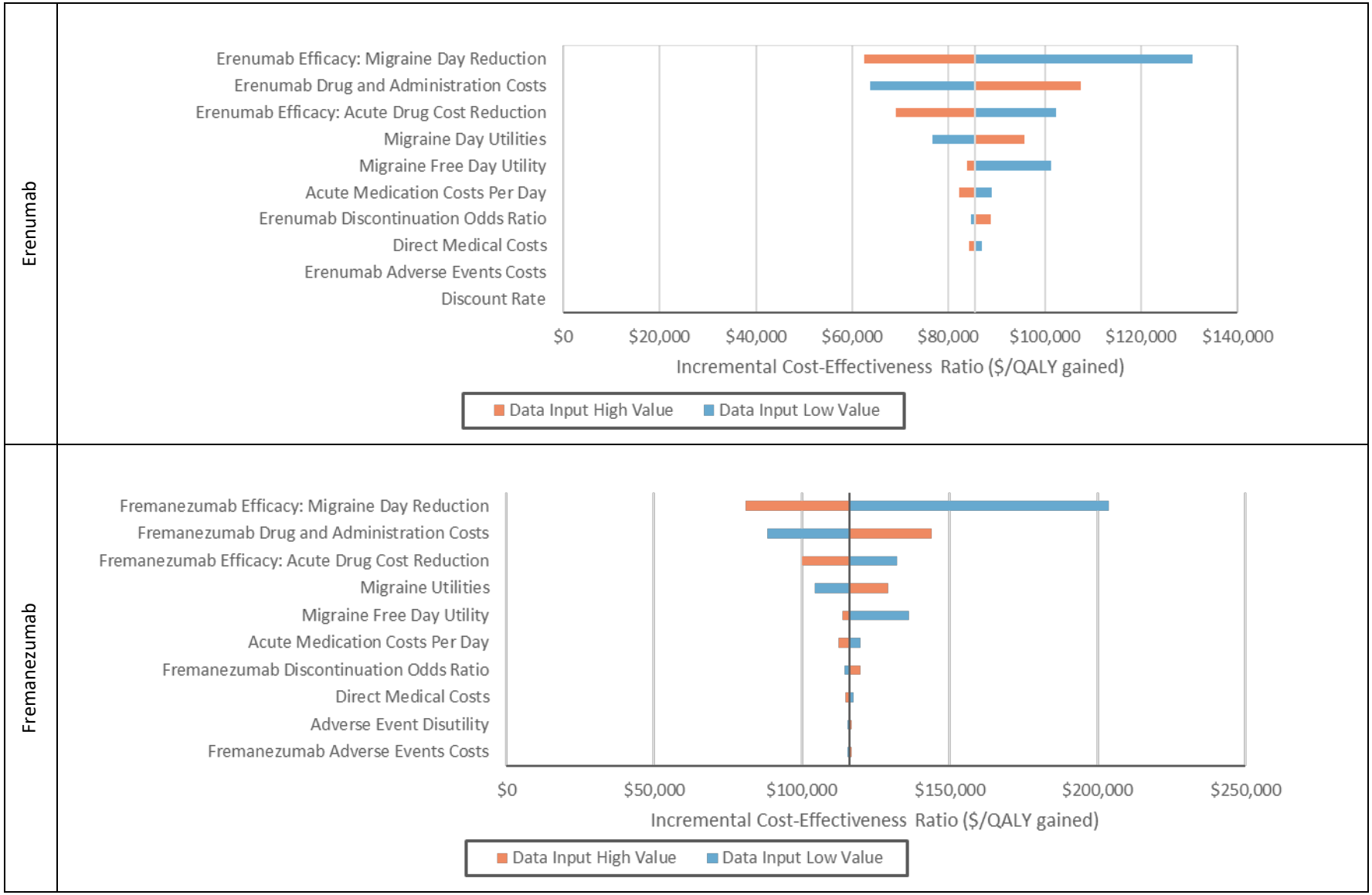
Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-free Day Gained
Chronic Migraine			
Erenumab 140mg monthly	No Preventive Treatment	$90,000	$100
Fremanezumab 625/225mg monthly	No Preventive Treatment	$120,000	$140
Episodic Migraine			
Erenumab 140mg monthly	No Preventive Treatment	$150,000	$160
Fremanezumab 225mg monthly	No Preventive Treatment	$150,000	$150

*To ensure the confidentiality of the data used to generate the results, are rounded to the nearest $10,000 for cost per QALY gained and to the nearest $10 for cost per migraine-free day gained

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for each of the relevant inputs in the model. The key drivers of variability/uncertainty are shown in the tornado diagrams below (Figure 4.4).

Figure 4.4. Tornado Diagrams for One-Way Sensitivity Analyses of CGRP Inhibitors versus No Preventive Treatment in Chronic Migraine



Migraine day reduction associated with the treatments was the most influential variable, followed by drug and administrative costs associated with the treatments, the impact of treatments on use of acute medications, migraine day utilities and migraine free day utilities. Variation in other inputs had negligible impact.

Figure 4.5 below shows the tornado diagram results from the base case model for CGRP inhibitors relative to no preventive treatment in episodic migraine. The findings are similar in terms of the variables that influence the incremental cost effectiveness ratios from the models for episodic migraine.

Figure 4.5. Tornado Diagrams for One-Way Sensitivity Analyses of CGRP Inhibitors versus No Preventive Treatment in Episodic Migraine

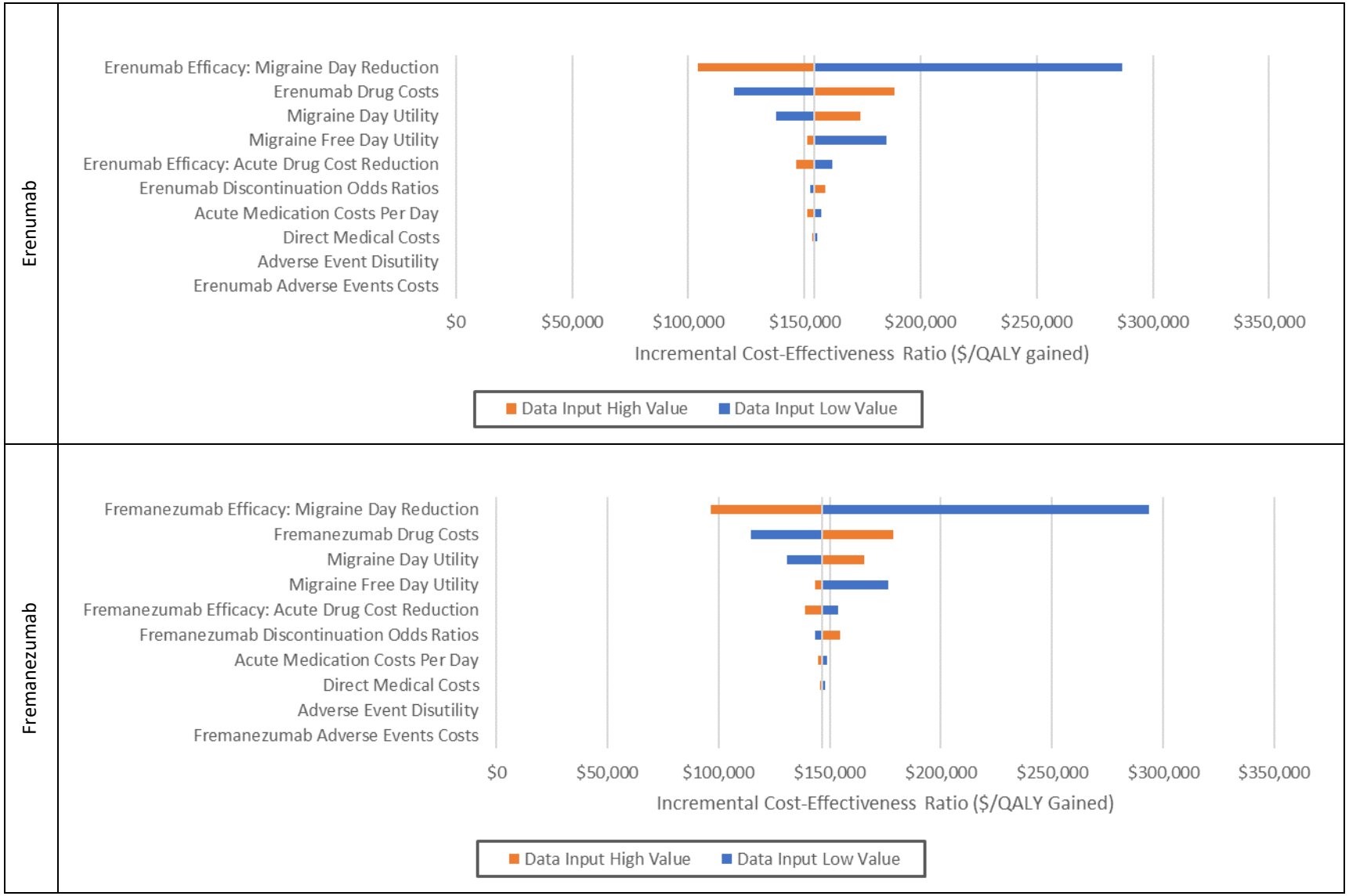


Table 4.16 summarizes the probabilistic sensitivity analyses (see Appendix E including Figures E1-E6 for more details). In chronic migraine, in the simulations reflecting potential variance in the model inputs, erenumab had a very small proportion result in an incremental cost effectiveness ratio below $50,000 per QALY gained (1.2%), but was associated with an incremental cost effectiveness ratio less than $100,000 per QALY gained more than two-thirds of the time (66.8%) and less than $150,000 per QALY gained, 95.7% of the time. Fremanezumab was below $50,000 in less than 1% of the simulations, was below $100,000 per QALY gained less than one-quarter of the time (23.3%) and was below $150,000 per QALY gained more than three-quarters of the time (79.2%)in chronic migraine relative to no preventive treatment. In addition, both treatments were rarely (less than 3.5%) associated with in incremental cost effectiveness ratio less than $100,000 per QALY gained in episodic migraine relative to no preventive treatment and were associated with incremental cost effectiveness ratios below $150,000 per QALY gained 33.5% of the time for erenumab and 44.2% of the time for fremanezumab.

Table 4.16. Probabilistic Sensitivity Analysis Results: CGRP Inhibitors versus No Treatment

Treatment	Comparator	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY
Chronic Migraine				
Erenumab 140 mg monthly	No preventive treatment	1.2%	66.8%	95.7%
Fremanezumab 625/225 mg monthly	No preventive treatment	<1.0%	23.3%	79.2%
Episodic Migraine				
Erenumab 140 mg monthly	No preventive treatment	0%	1.5%	33.5%
Fremanezumab 225 mg monthly	No preventive treatment	0%	3.3%	44.2%

Scenario Analyses Results

CGRP Inhibitors versus Current Preventive Treatments

The inputs and detailed results of the scenario analysis comparing CGRP inhibitors to current preventive treatments for all patients (i.e., not conditional on prior treatment failure) is included in Appendix E Tables E2-E15 and Figures E7-E12. The comparison of the CGRP inhibitors to onabotulinum toxin A in the population for whom prior preventive treatments have failed is also included in Appendix E. In the chronic migraine population, erenumab 140 mg monthly had an incremental cost-effectiveness ratio of approximately $345,000 per QALY gained while fremanezumab had an incremental cost-effectiveness ratio of approximately $12.78 million per QALY gained (Table 4.17). In episodic migraine, erenumab 140 mg monthly had an incremental cost-effectiveness ratio of approximately $395,000 per QALY gained, fremanezumab 225 mg monthly had an incremental cost-effectiveness ratio of approximately $1.02 million per QALY

gained, and galcanezumab 240 mg monthly had an incremental cost-effectiveness ratio of approximately $389,000 per QALY gained.

Table 4.17. Incremental Cost-Effectiveness Ratios for CGRP Inhibitors Compared to Other Preventive Treatments

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-Free Day Gained
Chronic Migraine			
Erenumab 140 mg monthly	Preventive treatment	$345,000	$334
Fremanezumab 625/225 mg monthly	Preventive treatment	$12,780,000	$2,593
Episodic Migraine			
Erenumab 140 mg monthly	Preventive treatment	$395,000	$381
Fremanezumab 225 mg monthly	Preventive treatment	$1,016,000	$874
Galcanezumab 240 mg monthly	Preventive treatment	$389,000	$356

Modified Societal Perspective

In scenarios that employed a modified societal perspective to the base case model and included the impact of reduced migraine days on productivity, lower (i.e., more favorable) incremental cost effectiveness ratios were found in all the comparisons. In particular, the incremental cost of erenumab was slightly below $50,000 per QALY gained for chronic patients relative to no preventive treatment, and the incremental cost of fremanezumab relative to no preventive treatment in chronic patients was below $100,000 per QALY gained (Table 4.18).

Table 4.18. Incremental Cost-Effectiveness Ratios Incorporating Impact on Productivity*

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-Free Day Gained
Chronic Migraine			
Erenumab 140 mg monthly	No preventive treatment	$50,000	$50
Fremanezumab 625/225 mg monthly	No preventive treatment	$80,000	$90
Episodic Migraine			
Erenumab 140 mg monthly	No preventive treatment	$110,000	$120
Fremanezumab 225 mg monthly	No preventive treatment	$110,000	$110

*To ensure the confidentiality of the data used to generate the results, are rounded to the nearest $10,000 for cost per QALY gained and to the nearest $10 for cost per migraine-free day gained

Longer Time Horizons

Scenarios employing different time horizons to the base case models are shown in Table 4.19. Only small differences were found in the incremental cost effectiveness ratios across different time horizons.

Table 4.19. Incremental Cost-Effectiveness Ratios Across Various Time Horizons*

Treatment	Comparator	5 years	10 years	Lifetime
Chronic Migraine				
Erenumab 140 mg monthly	No preventive treatment	$80,000	$80,000	$80,000
Fremanezumab 625/225 mg monthly	No preventive treatment	$110,000	$110,000	$110,000
Episodic Migraine				
Erenumab 140 mg monthly	No preventive treatment	$150,000	$150,000	$150,000
Fremanezumab 225 mg monthly	No preventive treatment	$150,000	$150,000	$150,000

*To ensure the confidentiality of the data used to generate the results, are rounded to the nearest $10,000 for cost per QALY gained

Persistence of Treatment Effect Following Discontinuation

Results from allowing a persistent treatment effect among patients with more than a 50% reduction in migraine days are shown in Table 4.20. Lower cost-effectiveness ratios are found in general, although not substantially different from the base case results.

Table 4.20. Incremental Cost-Effectiveness Ratios Incorporating Persistent Treatment Effect in Year Two*

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-Free Day Gained
Chronic Migraine			
Erenumab 140 mg monthly	No preventive treatment	$70,000	$80
Fremanezumab 625/225mg monthly	No preventive treatment	$100,000	$120
Episodic Migraine			
Erenumab 140 mg monthly	No preventive treatment	$130,000	$140
Fremanezumab 225 mg monthly	No preventive treatment	$130,000	$140

*To ensure the confidentiality of the data used to generate the results, are rounded to the nearest $10,000 for cost per QALY gained and to the nearest $10 for cost per migraine-free day gained

Impact of CGRP Inhibitors on Depression

The incorporation of the impact of CGRP inhibitors on depression had little impact on the ICERs when compared to the base case.

Table 4.21. Incremental Cost-Effectiveness Ratios Incorporating Impact of CGRP Inhibitors on Depression*

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-Free Day Gained
Chronic Migraine			
Erenumab 140 mg monthly	No preventive treatment	$80,000	$100
Fremanezumab 625/225mg monthly	No preventive treatment	$110,000	$140
Episodic Migraine			
Erenumab 140 mg monthly	No preventive treatment	$150,000	$160
Fremanezumab 225 mg monthly	No preventive treatment	$150,000	$150

*To ensure the confidentiality of the data used to generate the results, are rounded to the nearest $10,000 for cost per QALY gained and to the nearest $10 for cost per migraine-free day gained

Threshold Analyses Results

Table 4.22 shows unit drug prices, separately for chronic and episodic migraine, associated with various cost-effectiveness thresholds based on the base case model results.

Table 4.22. Threshold Analysis Results

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Chronic Migraine			
Erenumab 140 mg vs. No Preventive Treatment	$3,300	$5,600	$7,900
Fremanezumab 625/225 mg vs. No Preventive Treatment	$2,600	$4,400	$6,200
Episodic Migraine			
Erenumab 140 mg vs. No Preventive Treatment	$1,900	$3,400	$4,800
Fremanezumab 225 mg vs. No Preventive Treatment	$1,900	$3,500	$5,100

Model Validation

All mathematical functions in the model were consistent with the report (and supplemental Appendix materials). The model produced findings consistent with expectations when testing individual functions. Sensitivity analyses with null input values ensured the model was producing

findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model, as well as specific inputs and corresponding outputs.

We searched the literature to identify models that were similar to our analysis and found only one economic evaluation that compared a CGRP inhibitor to no preventive therapy in migraine patients for whom other preventive therapy had failed.[207] Other published economic evaluations included only non-CGRP inhibitor treatments. Our review of all other non-CGRP inhibitor models thus focused on comparing modeling methodologies and not on results between our and other models. We reviewed only those models that included current preventive and active drug treatments, were developed in the last 10 years, and were similar to our model from a setting, and population perspective.

A manufacturer-funded cost-effectiveness analysis by Lipton et al. compared erenumab 140 mg administered subcutaneously every four weeks to standard of care (no active preventive therapy) in a US-specific migraine population for whom prior preventive therapy had failed.[207] Both the ICER and Lipton et al. models had similar structures and were developed for a US setting, although the base-case analysis in Lipton et al.'s evaluation was from a societal perspective, while the ICER model employs this perspective only in a scenario analysis. Both models reported outcomes in terms of total costs, total QALYs, and monthly migraine days. Both models estimated higher costs, QALYs, and reductions in monthly migraine days for erenumab relative to no preventive treatment.

Results in the two models were most similar when comparing our base-case model to scenario two in the Lipton et al. paper, which assumed a health system perspective and excluded the added placebo effect from treatment benefit in the CGRP inhibitor arm. However, their scenario analysis employed a 10-year time horizon versus the two-year horizon in the ICER analysis. Lipton et al. presented value-based annual prices for erenumab at the $100,000 per QALY gained threshold, which were higher compared to the corresponding threshold price for the weighted migraine population in the ICER analysis.

All other analyses, including the primary analysis, conducted by Lipton et al. differed from ICER's in two key ways. Lipton et al. included the placebo effect in their estimates of erenumab's efficacy, while the ICER model did not. The approach by Lipton et al. likely overestimates the treatment effect of erenumab, thus resulting in the higher value-based prices their analysis, which ranged from approximately $14,200 to $24,000 annually at the $100,000 and $200,000 per QALY thresholds, respectively. Furthermore, Lipton et al. used a 10-year time horizon while the ICER model used a two-year time horizon. We used a two-year horizon due to the uncertainty in long-term treatment effect and AE rates, as well as uncertainty regarding potential stopping rules. We heard from clinical experts that the CGRP inhibitors are likely to be cycled in practice based on patient response, but the details of such practices and their impact on clinical efficacy is unknown.

In addition, there are several other differences between the two models:

1. Lipton et al. derived a discontinuation rate ratio for erenumab relative to onabotulinum toxin A from an NMA of clinical studies in chronic migraine patients. They applied this rate ratio to the onabotulinum toxin A real-world persistence rates, which were based on a claims analysis, to derive erenumab-specific discontinuation rates. This approach likely underrepresents the discontinuation of erenumab seen in episodic migraine since the rate ratio derived from the NMA is specific to chronic migraine patients. Additionally, it is unclear whether the NMA used for deriving erenumab discontinuation rates included "all comers" or a sub-population of patients for whom preventive therapy has failed. The ICER model derives erenumab discontinuation rates based on all-cause discontinuation data output from an NMA of relevant clinical trials in the prior failed treatment population.
2. Lipton et al. use a blended target population in their model, with 67% of patients being those with chronic migraine and the remaining with episodic migraine. The ICER model includes separate analyses for chronic and episodic migraine populations.
3. In the absence of a list price for erenumab at the time of publication, Lipton et al. calculate a value-based price for thresholds between $100,000 and $200,000 per QALY gained, whereas the ICER model uses an annual net price of $5,000 based on estimated discounted WAC price, in addition to calculating prices for erenumab at thresholds of $50,000, $100,000, and $150,000 per QALY gained. In their scenario analysis versus onabotulinum toxin A, Lipton et al. use the list price of onabotulinum toxin A while ICER's corresponding analysis used a discounted price as published in the Federal Supply Schedule.[208]
4. Both models estimated utility as a function of migraine days, with Lipton et al. estimating this based on migraine frequency each month, while the ICER model estimated utility based on a distribution of migraine severity. Lipton et al. derived utility estimates from the International Burden of Migraine Study that included participants from 10 countries, whereas the ICER model used a US-specific dataset. Additionally, Lipton et al. derived utility measures that are different across placebo and treatment, such that patients had 1) a utility gain associated with the treatment that was independent of migraine day reduction, and 2) a utility gain directly related to migraine day reduction. Furthermore, the ICER model applied a disutility of 0.05 for adverse events experienced, which the Lipton et al. model did not include.
5. Both models included a modified societal perspective that accounted for productivity loss due to migraine. Lipton et al. awarded costs to an eight-hour work day based on hourly wages as reported by the US Bureau of Labor Statistics. On presenteeism days, they assumed 50% productivity, which was then applied to the number of monthly migraine days experienced by patients, irrespective of severity of migraine. This likely overestimated the productivity loss, particularly for presenteeism. The ICER model included productivity loss costs. The costs of lost productivity were based on data from the American Migraine Prevalence and Prevention study, in which nearly 200,000 participants reported estimates of lost productivity time.[204]

A model by Yu et al.[188] measured the cost-effectiveness of existing preventive therapies, (propranolol, timolol, divalproex sodium, amitriptyline and topiramate) compared to no preventive therapy in patients with acute migraine in the US. Patients in both the intervention(s) and comparator arms were assumed to be treated with abortive medications, as in the ICER model. The model time horizon used was one year with 365 daily cycles, unlike the ICER model, which employed a two-year time horizon with 24 monthly cycles in the base-case analysis. Yu et al. measured the cost-effectiveness of each individual existing preventive therapy, while the corresponding scenario analysis in the ICER model used a market basket of preventive treatments, weighting their costs and efficacy by usage in the US. Some of the preventive treatments modeled by Yu et al. were included in the current treatment mix in the ICER model. While both models included AEs arising from existing preventive therapies, Yu et al. did not associate costs with the treatment of AEs while the ICER model awarded costs to treating AEs in the form of a physician's office visit. Yu et al. included health states defined by "feeling well" (i.e., without migraine), and for migraine episodes with and without AEs resulting from preventive or abortive medication use. The ICER model included health states representing positive treatment effect using the CGRP inhibitors and patients could move to the market basket treatment upon CGRP inhibitor failure (i.e., recurrence of base-line migraine days per month). Another key difference between both models is that Yu et al. modeled daily health states and transition probabilities based on migraine frequency while the ICER model used a fixed number of migraine days in each monthly health state. AE data for preventive therapy in the Yu et al. model was sourced from respective trial data, as in the ICER model, where we sourced AE data for CGRP inhibitors from the clinical trials. Both models made assumptions around AE-related disutility, with Yu et al. assuming a 20% reduction from current health state utility, while the ICER model assumed a fixed 0.05 disutility. Overall migraine-related utilities used were higher in the ICER models (using EQ-5D) than in Yu et al.'s model (using Health Utility Index Mark 3).

A model by Batty et al.[185] compared prophylactic use of onabotulinum toxin A versus placebo in adults with chronic migraine in the UK. The model employed a two-year time horizon, as in ICER model, but had longer cycle lengths of 12 weeks unlike the ICER model which used one-month cycles. Onabotulinum toxin A's efficacy was sourced from the PREEMPT trials in the UK model, while the ICER model sources these estimates from an NMA which included the PREEMPT trial data. Both models included patients for whom prior preventive therapy had failed for chronic migraine, although the UK model also include a population superset that included all migraine patients in the UK. The UK model comprised 13 health states corresponding to different frequency rates of headache days in a 28-day cycle, of which six were consistent with chronic migraine, both "on" and "off" treatment, and six were episodic migraine states, that also included "on" and "off" treatment states. The ICER model evaluated chronic and episodic migraine separately and did not allow for patients to enter episodic migraine state(s) from the chronic population. The UK model used transition probabilities beyond cycle one that comprise aggregate probabilities from week 12 to 56 as per the PREEMPT trial data for the intervention, while the ICER model assumed the same

transition probabilities seen in the CGRP inhibitor trials to extend beyond the trial duration in the model, due to lack of robust real-world data on this estimate. Further, the UK model adopted a negative stopping rule if headache days did not decrease by 30% within the first two model cycles, while the ICER model included all-cause discontinuation through the entire time horizon of the model. Also, we did not include a positive stopping rule since we heard from clinical experts that positive stopping rules are individualized at the patient and physician level and can vary substantially. Quality of life utility estimates in the UK model were based on the frequency of migraine days in each state; the ICER model uses EQ-5D-derived utility estimates based on migraine severity, distribution of severity across migraine days that is then varied based on treatment efficacy at three months after which it remains constant. Utilities associated with a migraine day did not differ by treatment in the ICER model but did so in the UK model. Both models included non-drug health care costs such as those associated with ED visits, office visits, hospitalizations, and both models were built from a health system perspective.

4.4 Summary and Comment

Relative to no preventive treatment, CGRP inhibitors are predicted to positively impact the health of patients with chronic or episodic migraine for whom prior preventive therapy had failed. In the base-case analyses, where results from patients for whom one to three prior preventive treatments had failed were used to estimate outcomes in patients for whom other preventive therapies are no longer an option, both erenumab and fremanezumab were under the $150,000 per QALY gained threshold compared to no preventive treatment in those with chronic migraine. In the episodic migraine population, erenumab and fremanezumab's cost-effectiveness ratios were approximately $150,000 per QALY gained. Importantly, the analyses were sensitive to a number of parameters including the costs of the medication and to scenarios that took a societal perspective.

Limitations

The models were based on clinical trial results that may not hold true for longer time horizons or in particular patient populations different from those seen in the trials. Discontinuation rates may be lower in the clinical trials than would be seen in a general patient population. The price estimates for the drugs may not reflect actual market prices.

Costs and disutilities of the AEs were crude estimates. However, they did not substantially impact the estimated cost-effectiveness ratios. The available estimates for the severity distribution of migraines may not reflect the actual patient population.

Conclusions

CGRP inhibitors are projected to have positive impact on migraine days and associated QALYs for episodic and chronic migraine patients. For patients with chronic migraine for whom other

preventive treatments have failed, at a price of $5,000 per year, the cost-effectiveness of CGRP inhibitors is below the upper bound of commonly accepted thresholds. In patients with episodic migraine for whom other preventive treatments have failed, cost-effectiveness is near the upper bound of commonly accepted thresholds. In patients with chronic or episodic migraine who have other treatment options available, cost-effectiveness will likely exceed commonly accepted thresholds.

5. Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of the CGRP inhibitors to commonly-used oral migraine preventive therapies, onabotulinum toxin A (in chronic migraine), and no preventive therapy.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “the comparator,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

As described in Section 1.4, many aspects of patients' lives are affected by migraine including work, school, housework, and social activities. Migraine typically recurs over many years and represents a long-term burden for patients and their families, friends, and colleagues. For example, patients may perform their job duties less productively while experiencing migraine (presenteeism), regularly stop showing up for work (absenteeism), or leave the workforce or drop out of college.

Furthermore, migraine is associated with high prevalence of other comorbidities, including mental disorders and cardiovascular conditions. If patients on CGRP inhibitors experience fewer migraines, there may be additional indirect benefits arising from improvements in other co-conditions. These long-term burdens and impacts on quality of life are not captured in the trials with only 12-26 weeks of follow-up. Our model estimates may not fully reflect the improvements in quality of life or work productivity with the CGRP inhibitors.

In addition, a monthly (or quarterly) rather than daily, administration may ease the burden of living with migraine for some patients. And, with a more tolerable short-term safety profile, patients may be less likely to discontinue CGRP inhibitors due to tolerability. However, a subcutaneous injection rather than oral ingestion may add complexity, particularly if the injection would be administered by a medical professional. Additional data from open-label extensions and other observational studies may provide additional insights on long-term adverse events, treatment discontinuations, and treatment satisfaction.

Many patients are not receiving the care and treatment needed to prevent migraines. When they do experience a migraine attack, patients can take acute medications as described in Section 1. However, despite guidelines recommending against opioids as a first line acute treatment, many migraine patients are frequently prescribed opioids. Patients and patient advocacy groups expressed concern about the opioid epidemic and its associated health and cost consequences in the migraine population. Although data are lacking on the long-term impact of CGRP inhibitors on opioid use and addiction, preventive migraine therapies that reduce the number of migraines and acute medication use may also reduce opioid dependence in this population.

Erenumab, fremanezumab, and galcanezumab are the first monoclonal antibodies targeting the CGRP pathway for migraine prevention. For some patients, existing preventive therapies have not provided enough relief or have otherwise not been tolerable. The CGRP inhibitors could be a treatment option for patients for whom other therapies have failed. Currently, the evidence on CGRP inhibitors in this subgroup of patients is limited to those for whom up to three prior preventive therapies have failed. Additional evidence in patients for whom more than three preventive therapies have failed is needed.

6. Value-Based Price Benchmarks

The value-based benchmark prices for erenumab and fremanezumab are presented in Table 6.1. The value-based prices were calculated using a blended population of patients with chronic and episodic migraine. Specifically, it was assumed that the proportion of those eligible for treatment with the CGRP inhibitors in the United States would be comprised of 19.4% with chronic migraine and 80.6% with episodic migraine. We calculated the single value drug price such that the weighted sum of the outputs from the chronic and episodic populations equaled the threshold value.

Table 6.1. Value-Based Benchmark Prices for Erenumab and Fremanezumab*

	Annual WAC	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY	Discount from WAC Required to Achieve Threshold Prices
Erenumab 140 mg	$6,900	$3,700	$5,300	23% to 46%
Fremanezumab 625/225 mg	$6,900	$3,700	$5,200	25% to 46%

*Annual prices are rounded to the nearest $100 in order to ensure the confidentiality of the data used to generate the results

7. Potential Budget Impact

7.1 Overview

We used the results from the cost-effectiveness model to estimate the potential total budgetary impact of erenumab and fremanezumab separately in patients in the US with chronic migraine or episodic migraine for whom at least one preventive treatment has failed. We used the same estimated net price (based on a 27% discount from the WAC price of erenumab) used in the cost-effectiveness analyses, the WAC, and the three threshold prices for each CGRP inhibitor in our estimates of potential budget impact.

7.2 Methods

Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate populations eligible for treatment: adults with chronic or episodic migraine for whom at least one preventive therapy had failed. To estimate the size of the potential candidate populations for treatment, we first estimated the size of the US adult population by gender for years 2018 to 2022 using population projection data published by the US Census Bureau.[66] The age-range-specific prevalence of chronic and episodic migraine was estimated from a two-year longitudinal, population-based study, in which individuals completed a self-administered questionnaire that was mailed to a sample of 120,000 US households. Screening for the study was performed in 2004.[67,72] Chronic and episodic migraine were defined as ≥ 15 and 1-14 headache days per month, respectively, based on the ICHD (second edition) criteria. Detailed prevalence estimates by gender and age ranges are available in Appendix E Tables E16-E17.

Applying these estimates to the projected US population resulted in approximately 2.4 million people with chronic migraine and approximately 26 million people with episodic migraine. We considered all chronic migraine patients eligible for treatment with active preventive therapy. In the episodic migraine population, Lipton et al. estimated that a total 38.8% of this patient population could be offered or were considered for treatment with active preventive therapy, based on criteria for preventive treatment as defined by an expert panel, in their American Migraine Prevalence and Prevention (AMPP) study.[67] Applying this estimate to the prevalent episodic migraine population resulted in approximately 10.1 million people with episodic migraine

eligible for preventive therapy. A MarketScan claims database analysis by Burrell et al., 2018 found that 45% of all patients with migraine who were on preventive therapy failed at least one line of preventive therapy.[68] Applying this percentage to the calculated total population with chronic and episodic migraine and on preventive therapy in the US, we estimated our target population to be approximately 4.5 million people with episodic migraine and approximately 1.1 million people with chronic migraine who were eligible to be treated with CGRP inhibitors. Our calculations may overestimate the population size since we also consider those patients who are not currently seeking preventive therapy but might do so now that at least one CGRP inhibitor is available in the market. Other estimates by independent analysts (submitted through Amgen's public comment on the draft version of this report) estimate the population eligible for treatment with CGRP inhibitors to be approximately 2% of the US population, which closely aligns with the size of the eligible population we estimated.[209]

When using a prevalent population under ICER's standard methodology for estimating potential budget impact, the entire population is split equally over five years with 20% uptake occurring each year to reach 100% over five years. However, since people with migraine tend to cycle through several preventive therapies and since we have no long-term data on CGRP usage, we assumed that each sub-cohort (i.e., 20% of the prevalent cohort) remained in the model for two years, and a new cohort entered the model every year, resulting in larger patient populations for years two through five. We thus used only year one and two undiscounted costs for interventions and no preventive treatment.

ICER's methods for estimating potential budget impact are described in detail elsewhere (https://icer-review.org/final-vaf-2017-2019/) and have recently been updated – note that because this review commenced in 2017, the analyses within use the potential budget impact threshold for 2017-2018, rather than the updated range for 2018-2019. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug(s) that would take market share from one or more drugs or existing standard of care and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that CGRP inhibitors would replace no preventive treatment since patients had already experienced the failure of other preventive therapy. While some patients may switch to CGRP inhibitors from other preventive therapies, others may add CGRP inhibitor treatment to existing therapy. In the absence of data on relevant rates, we were not able to estimate any cost-offsets associated with discontinuing other preventive therapy when starting treatment with a CGRP inhibitor.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in

ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015-2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.3 Results

We assessed the budget impact of CGRP inhibitors jointly in chronic and episodic migraine. Results presented here used CGRP inhibitor prices (WAC, estimated net price, and the three WTP threshold prices) weighted by the size of the prevalent population.

The combined annual average potential budget impact per patient for erenumab at its WAC ($6,900 annually) and estimated net price ($5,000 annually, assuming an approximate 27% discount from WAC) were approximately $4,200 and $2,100 respectively, versus no current preventive treatment. The per-patient annual budget impact ranged from approximately $1,000 using the price to reach

$50,000 per QALY (~$2,200 annually) to approximately $3,200 using the price to reach $150,000 per QALY (~$5,300) threshold (Table 7.2). The total potential annual budget impact across the entire eligible migraine populations when using erenumab at its assumed net price relative to no active preventive treatment was estimated at approximately $5.9 billion. At other prices of erenumab, the total population annual budget impact ranged from approximately $2.1 billion using the price to reach the $50,000 per QALY threshold (~$2,200 annually) to approximately $8.4 billion using the WAC ($6,900 annually). As shown in Figure 7.1, approximately 11% and 16% of the total annual eligible migraine population could be treated with erenumab at its WAC and assumed net price without crossing the ICER annual budget impact threshold of $915 million. At the annual prices to reach the cost-effectiveness thresholds between $150,000 and $50,000 per QALY, between 15% and 44% of the entire eligible migraine population could be treated annually.

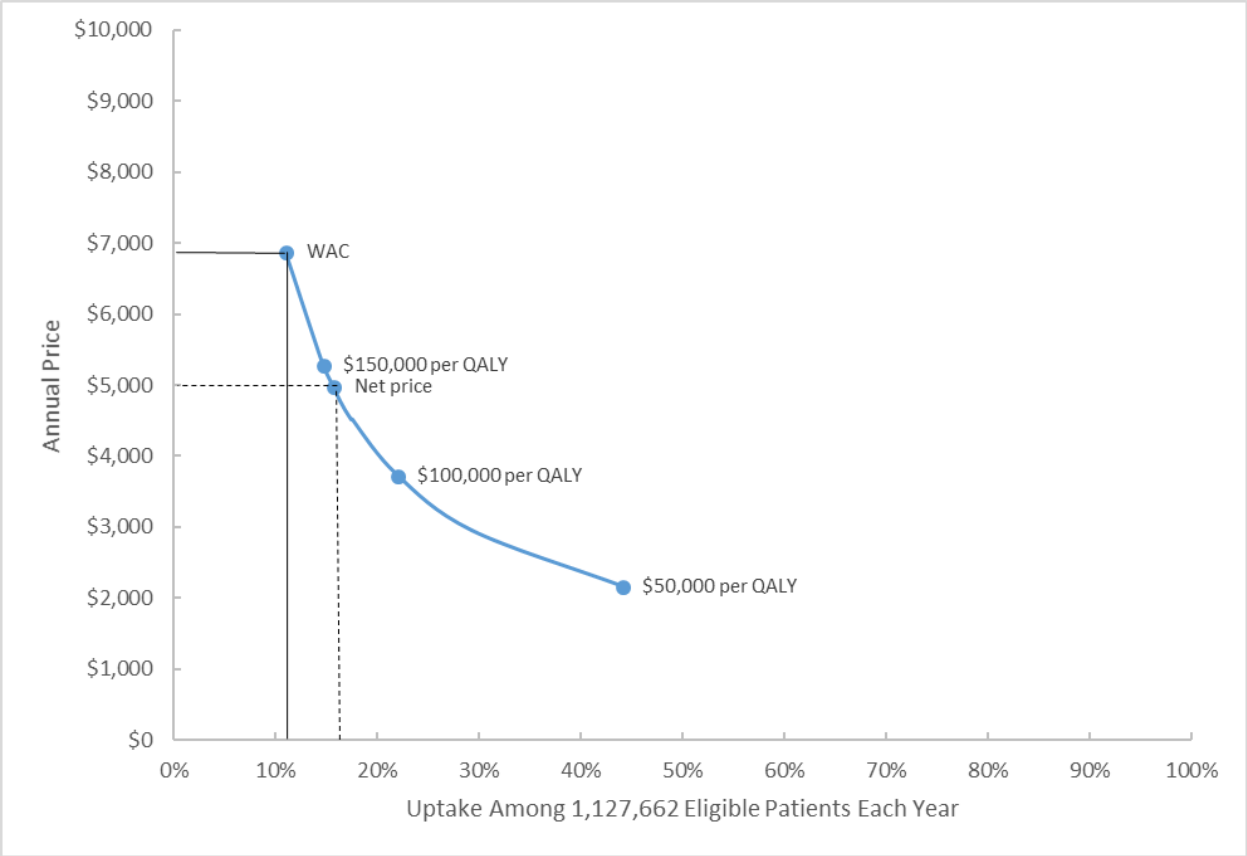
Table 7.2. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Erenumab in Migraine Patients for Whom At Least One Previous Preventive Therapy Has Failed

	Average Annual Per Patient Budget Impact				
	WAC	Assumed Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$6,041	$3,432	$4,961	$3,906	$2,851
No Active Preventive Treatment	$1,803				
Difference	$4,238	$2,147	$3,159	$2,103	$1,048

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Budget impact weighted by predicted prevalent populations of chronic and episodic migraine

Figure 7.1. Potential Budget Impact Scenarios at Different Prices of Erenumab in Migraine Population Eligible for Preventive Treatment for Whom At Least One Previous Preventive Therapy Has Failed



The combined annual average potential budget impact per patient for fremanezumab at its estimated WAC ($6,900 annually) and estimated net price ($5,000 annually, assuming an approximate 27% discount from estimated WAC) were approximately $3,000 and $2,100 respectively, relative to no current preventive treatment. The per patient annual budget impact ranged from approximately $800 using the price to reach $50,000 per QALY (~$2,100 annually) to approximately $2,200 using the price to reach $150,000 per QALY (~$5,200 annually) threshold (Table 7.3). The total potential annual budget impact across the entire eligible migraine populations when using fremanezumab at its estimated net price relative to no active preventive treatment was estimated at approximately $4.2 billion. At other prices of fremanezumab, this total population annual budget impact ranged from approximately $1.5 billion using the price to reach the $50,000 per QALY threshold ($2,100 annually) to approximately $5.9 billion using the estimated WAC ($6,900 annually). The lower per-patient and population potential budget impact of treatment with fremanezumab as compared to erenumab was primarily driven by the higher discontinuation rate of fremanezumab. As shown in Figure 7.2, approximately 15% and 22% of the total annual eligible migraine population could be treated with fremanezumab at its estimated WAC and estimated net price without crossing the ICER annual budget impact threshold of $915 million.

At the annual prices to reach the cost-effectiveness thresholds between $150,000 and $50,000 per QALY, between 21% and 62% of the entire eligible migraine population could be treated annually.

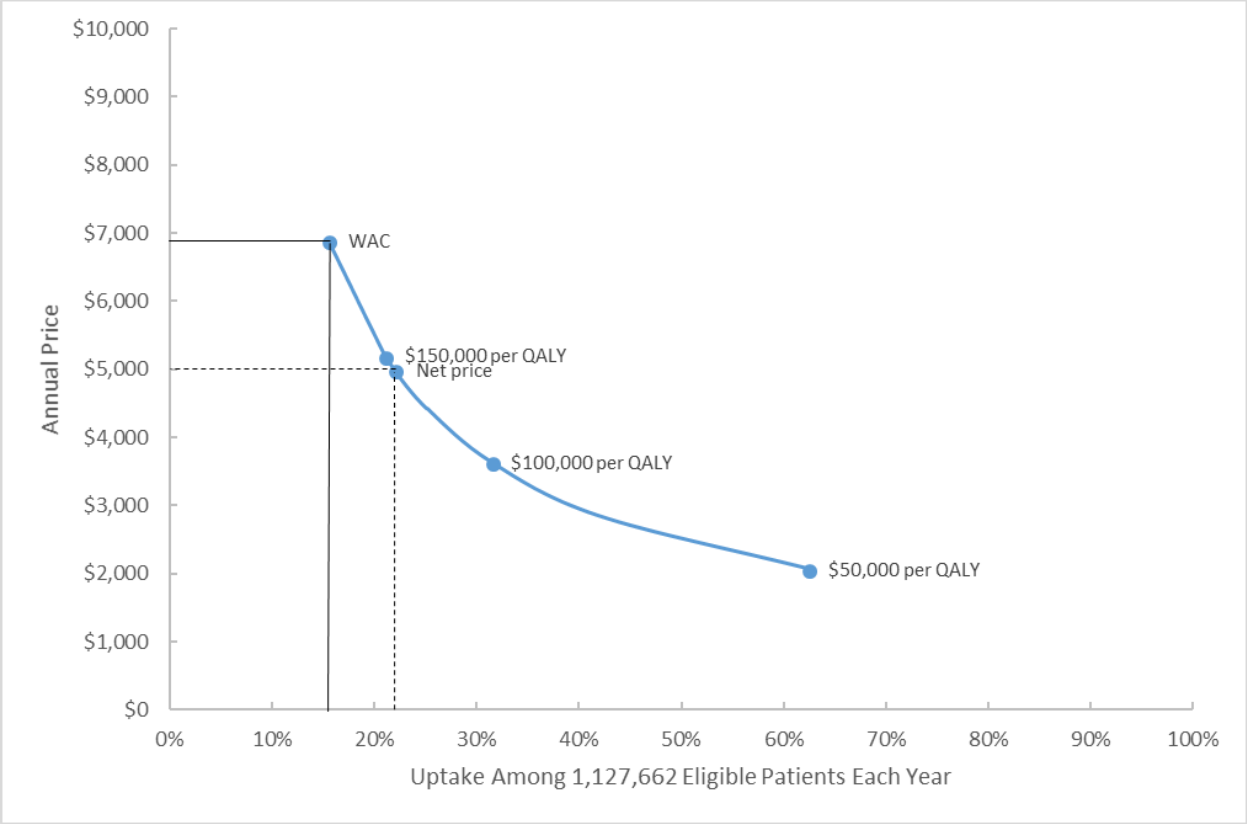
Table 7.3. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Fremanezumab in Migraine Patients for Whom At Least One Previous Preventive Therapy Has Failed

	Average Annual Per Patient Budget Impact				
	Estimated WAC	Estimated Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Fremanezumab	$4,842	$3,942	$4,038	$3,296	$2,555
No Active Preventive Treatment	$1,803				
Difference	$3,040	$2,140	$2,235	$1,494	$752

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Budget impact weighted by predicted prevalent populations of chronic and episodic migraine

Figure 7.2. Potential Budget Impact Scenarios at Different Prices of Fremanezumab in Migraine Population Eligible for Preventive Treatment for Whom At Least One Previous Preventive Therapy Has Failed



In summary, the annual budget impact of using either erenumab or fremanezumab at their assumed/estimated net price, in the eligible migraine population relative to no preventive therapy resulted in an additional approximately $2,100 in costs per patient to the health system. At this assumed net price, only 14% of the eligible migraine population could be treated using erenumab before total costs exceed the ICER potential budget impact threshold. At the same estimated net price, only 20% of the eligible migraine population could be treated with fremanezumab before total costs exceed the ICER potential budget impact threshold.

7.4 Access and Affordability

As illustrated in these analyses, treating the entire patient population eligible for treatment with CGRP inhibitors would have a substantial budget impact. However, at the June 14 public meeting, clinical experts indicated that uptake is unlikely to exceed levels that would threaten access and affordability, as CGRP inhibitors use a novel mechanism of action with an unknown long-term safety profile, are injectable, and patients who do not benefit from therapy are likely to discontinue treatment. As such, ICER is not issuing an access and affordability alert at this time. However, given the budget impact potential, all stakeholders should closely monitor the use of CGRP inhibitors in the event that actual uptake exceeds expectations.

8. Summary of the Votes and Considerations for Policy

8.1 About the CTAF Process

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the June 14, 2018 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of CGRP inhibitors for the preventive treatment of patients with chronic or episodic migraine. Following the evidence presentation and public comments (public comments from the meeting can be accessed at https://youtu.be/rEzVgZahSsI?t=1h19m55s, starting at minute 1:19:55), the CTAF Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and other benefits and contextual considerations related to CGRP inhibitors for patients with migraine. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and votes related to value, the CTAF Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

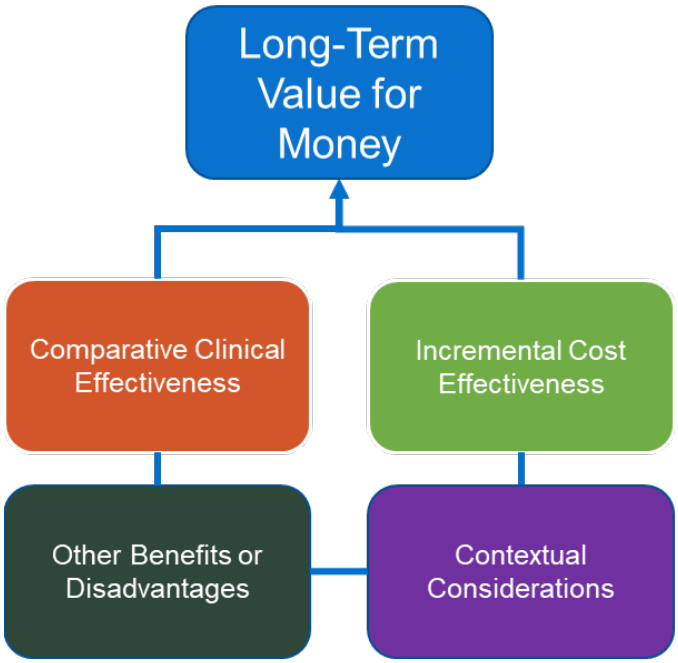
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the CTAF voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

Patient population for questions 1-4: Adult patients with 15 or more headache days per month (i.e., chronic migraine).

1) Is the evidence adequate to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab?

Yes: 0 votes	***No: 13 votes***

Comments: The Panel unanimously voted that the available evidence was inadequate to distinguish the net health benefits among the three CGRP inhibitors. The majority of Panelists emphasized the lack of comparative trials, that the results of these comparisons in the ICER NMAs were not statistically significant, and the lack of published trials of galcanezumab in the chronic migraine population. Additionally, Panelists noted that, due to the short-term nature of the available evidence, they were unable to draw conclusions regarding the long-term benefits and risks of therapy with CGRP inhibitors. These concerns were more pronounced because the CGRP inhibitors represent a new mechanism of action that affects a pathway present throughout the body.

2) Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies (e.g., amitriptyline, topiramate, or propranolol)?

Yes: 0 votes	***No: 13[ii] votes***

Comment: The Panel unanimously judged that there was insufficient evidence to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies. Panel members highlighted the lack of comparative trials among CGRP inhibitors and oral preventive therapies and the lack of statistically-significant NMA results. As in their responses to the previous question, a majority of Panelists underscored the uncertainty regarding the long-term benefits and risks of treatment with CGRP inhibitors versus the known benefits and risks of treatment with oral preventive therapies.

3) Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and onabotulinum toxin A (Botox®, Allergan)?

Yes: 0 votes	***No: 13 votes***

Comment: The Panel unanimously judged that there was inadequate evidence to distinguish the net health benefit between treatment with CGRP inhibitors and onabotulinum toxin A. As in other votes, the Panel underscored the lack of comparative trials between CGRP inhibitors and onabotulinum toxin A, the absence of statistically-significant results from the NMA, and uncertainty regarding the long-term risks and harms of using CGRP inhibitors.

4) For patients who have no other options for preventive therapy, is the evidence adequate to demonstrate a net health benefit for treatment with CGRP inhibitors compared with no treatment?

Yes: 10 votes	No: 3 votes

Comment: Members of the Panel who voted in the affirmative judged the evidence adequate to demonstrate that CGRP inhibitors provide "comparable or better" net health benefits than no treatment. However, of the Panelists who voted "yes," a majority expressed concern regarding the benefits and harms of long-term use or the existence of rare side effects. Conversely, those that voted in the negative stated that the evidence is currently insufficient. The Panelists who voted "no" noted the absence of data regarding long-term harms of CGRP inhibitors as their primary rationale. Some Panelists who voted "no" also argued that the population referenced in the question did not match the population studied in the clinical trials, which excluded patients who had been failed by three or more treatments, thus decreasing their certainty regarding the generalizability of the trial results.

[ii] One Panelist's vote was not recorded during the meeting and was provided after the session concluded.

Patient population for questions 5-7: Adult patients with 14 or fewer migraine days per month

5) Is the evidence adequate to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab?

Yes: 1 votes	***No: 12 votes***

Comment: A majority of the Panel judged that there was inadequate evidence to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab. The majority's rationale followed closely with their responses to question one.

6) Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies (e.g., amitriptyline, topiramate, or propranolol)?

Yes: 0 votes	***No: 13 votes***

Comment: The Panel unanimously judged that the evidence was insufficient to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies. The Panelists reiterated their concerns about the lack of comparative trials between CGRP inhibitors and oral preventive therapies. The Panel also noted that the NMA results comparing treatment outcomes between CGRP inhibitors and oral preventive therapies were not statistically significant.

7) For patients who have no other options for preventive therapy, is the evidence adequate to demonstrate a net health benefit for treatment with CGRP inhibitors compared with no treatment?

Yes: 4 votes	***No:9 votes***

Comment: The majority of Panel members judged that, for patients without other options for preventive therapy, the evidence was inadequate to demonstrate a net health benefit for treatment of CGRP inhibitors compared with no treatment. These Panel members considered the evidence to demonstrate "promising but inconclusive" net health benefits and judged that the potential for long-term harms and rare side effects raised uncertainties about the net benefit for patients with episodic migraine, whose burden of disease is, in general, lower than that of patients with chronic migraine. Two Panelists who voted in the negative reiterated their concerns that the population referenced in the question did not match the population studied in the clinical trial. Conversely, one Panelist who voted in the affirmative argued that the evidence supporting positive treatment outcomes with CGRP inhibitors is too substantial to ignore. Another Panelist who voted "yes" argued that the disease burden faced by episodic migraine patients is substantial enough to outweigh the potential risks of treatment with CGRP inhibitors.

Patient population for questions 8-9: Adult patients with migraine for whom other preventive treatments have failed.

8) Does treating patients with CGRP inhibitors offer one or more of the following "other benefits?" (select all that apply)

Reduced complexity	4/13
Reduce important health disparities	2/13
Reduce caregiver/family burden	12/13
Novel mechanism of action or approach	13/13
Significant impact on improving return to work/overall productivity	13/13
Other important benefits or disadvantages	3/13

Comment: The Panel unanimously recognized that the novel mechanism of action and the impact on overall productivity are important "other benefits" offered by treatment with CGRP inhibitors. Similarly, a majority of Panelists argued that treatment with CGRP inhibitors would allow patients to recover lost income, contribute to child care, and fulfill familial obligations, which would substantially reduce caregiver or family burden. Four Panelists noted that CGRP inhibitors are administered via subcutaneous injection, offering reduced complexity compared to multiple daily oral treatments. Conversely, other Panelists noted that the method of administration could instead introduce complexity for some patients. Three members of the Panel emphasized other important benefits that CGRP inhibitors may offer, including a reduction in the stigma felt by many migraine patients, positive impact on the opioid epidemic, and avoidance of the sometimes intolerable side effects that accompany other treatment options.

9) Are any of the following contextual considerations important in assessing CGRP inhibitors' long-term value for money? (select all that apply)

Care of individuals with condition of high severity	11/13
Care of individuals with condition with high lifetime burden of illness	9/13
First to offer any improvement	1/13
Compared to comparator, there is significant uncertainty about long-term risk of serious side effects	11/13
Compared to the comparator, significant uncertainty about magnitude or durability of the long-term benefits of this intervention	12/13
Other important contextual considerations.	6/13

Comment: Some Panelists in the majority emphasized the differential severity between chronic and episodic migraine patients, while other Panelists argued that the severity and burden of disease can be equally debilitating in both patient groups. Overall, the Panel emphasized the lack of data on the effects of modulating the CGRP pathway as a key contextual consideration. One Panelist offered a further contextual consideration and

questioned whether the results from the clinical trials are generalizable to patients for whom three or more treatments had failed.

Patient population for question 10: Adult patients with 15 or more headache days per month (i.e., chronic migraine) for whom other preventive therapies have failed.

10) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with erenumab versus no treatment?

Low: 0 votes	***Intermediate: 12 votes***	High: 1 votes

Comment: The majority of the Panel judged the long-term value for money to be "intermediate" for treatment with erenumab versus no treatment in chronic migraine patients. Panelists who voted "intermediate" cited concerns regarding potential long-term harms, the absence of data on the long-term efficacy of erenumab, and the lack of direct comparative evidence. Several voted "intermediate" because the clinical trials of erenumab excluded the patient population that had been failed by more than three treatments, which represents a substantial proportion of the target population for CGRP inhibitors. However, the majority also noted that the evidence suggests that treatment with erenumab may improve quality of life and the ability to return to work in many migraine patients and that treatment with erenumab met commonly-accepted cost-effectiveness thresholds in this population. The one Panelist who voted "high" was persuaded to vote for a more favorable long-term value for money by the presence of substantial other benefits and contextual considerations, such as the reduction of caregiver or family burden, the novel mechanism of action offered by erenumab, and the potential increase in overall productivity and likelihood of returning to work. Three Panelists echoed these sentiments but judged that the lack of data on long-term safety and efficacy and the absence of evidence on the patient population that were failed by three or more treatments to preclude a "high" value vote.

Patient population for question 11: Adult patients with 14 or fewer migraine days per month for whom other preventive therapies have failed.

11) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with erenumab versus no treatment?

Low: 6 votes	***Intermediate: 7 votes***	High: 0 votes

Comment: A slight majority of the Panel judged the long-term value for money to be "intermediate" for treatment with erenumab versus no treatment in episodic migraine patients. Although these Panelists voiced concerns regarding the long-term safety and

efficacy of treatment with erenumab, they also emphasized the substantial potential other benefits and contextual considerations that may be associated with treatment with erenumab. In addition, several Panelists in the majority again emphasized that the severity of disease and burden of illness were considerable in many patients with episodic migraine. The six Panelists that judged the long-term value of money to be "low" reiterated the uncertainty regarding long-term risks and rare side effects. Although some of these Panelists acknowledged the contextual considerations and other benefits, they argued that these considerations were outweighed by the potential for harm in the episodic migraine population.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on CGRP inhibitors' use in chronic and episodic migraine to policy and practice. The policy roundtable members included two patient advocates, two clinicians, representatives from Amgen and Teva, a pharmacy benefit manager, and a representative from a large public purchaser. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 8.1 Policy Roundtable Members

Name	Title and Affiliation
Amy Benavente, BA	Executive Director, Reimbursement, Access, and Value, Neuroscience, Amgen
Jill Dehlin, RN, MA, MPH, CHES	Migraine Patient, Former President of American Headache and Migraine Association
Aaron Deves, BS	Global Disease Lead, Migraine and Headache, Teva Pharmaceuticals
Kevin Lenaburg, MA	Executive Director, Coalition for Headache and Migraine Patients (CHAMP), Caregiver for Person With Migraine
Everett Neville, RPh	Executive Vice President, Strategy, Supply Chain, and Specialty, Express Scripts
Sonja Potrebic, MD, PhD	Residency Program Director, Headache Specialist, and Co-Assistant Chief of Neurology, Southern California Permanente Medical Group, Kaiser Permanente
Richard KP Sun, MD, MPH	Medical Consultant and Chief, Clinical Programs and Appeals Section, Health Plan Administration Division, California Public Employees' Retirement System (CalPERS)
Yvette Yeung, MD	Neurologist, Clinical Pod Lead, HealthCare Partners Medical Group

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

1. Given that CGRP inhibitors have a new mechanism of action, are entering clinical use without long-term safety and efficacy data, and were labeled by the FDA using language that could suggest that all patients with migraine are eligible for treatment, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments.

2. When responsible pricing is accomplished, and the net price of CGRP inhibitors aligns with the estimated added benefit for patients, prior authorization criteria should be relatively streamlined and allow documentation of eligibility through clinician attestation rather than requiring extensive submission of clinical documents.

3. Payers should negotiate discounts to seek the best value for patients and the health system by bringing the net price into traditional cost-effectiveness ranges. Adequate discounts may require preferential formulary placement for one particular CGRP inhibitor, but payers should maintain options for clinicians and patients to seek coverage for more than one CGRP inhibitor.

The CTAF panel voted that the current evidence base was inadequate to distinguish the clinical benefits among the three CGRP inhibitors erenumab, fremanezumab, and galcanezumab. Clinicians and patients may therefore feel that any of these options is a reasonable first choice for patients starting CGRP inhibitor therapy. Payers are likely to judge that the evidence supports the option to negotiate discounts on the basis of preferential formulary placement for a single drug. However, given the different targets of the agents (i.e., erenumab binds to the CGRP receptor whereas fremanezumab and galcanezumab bind to the CGRP ligand), it is possible that some patients may respond better to one agent than another. To balance affordability with access, payers should consider ways to maintain coverage for multiple CGRP inhibitors for patients who have tried and not received adequate response from the preferred agent.

4. Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Potential patient eligibility criteria

a. Adults with migraine with four or more headache days per month.

- "Adults with migraine"
  Although it can at times be difficult to make the clinical distinction between migraine

headache and other forms of headache, there was no sense among the policy roundtable members that insurance coverage should try to provide specific criteria, leaving the clinical diagnosis of migraine to the treating clinician.

- "four or more headache days per month"
  Although the CTAF panel's value vote differed between chronic and episodic migraine, experts on the roundtable highlighted that patients with 10-14 headache days per month often suffer functional disability at levels equal to those of patients with chronic migraine. Although some insurers may consider separate coverage criteria for episodic and chronic migraine, members of the policy roundtable suggested that this distinction would be clinically difficult to justify. Previous clinical consensus statements have suggested that patients with a minimum of four headache days per month are generally thought of as candidates for preventive therapy, and therefore a minimum of four headache days per month may be viewed by many payers as a reasonable threshold for coverage.

b. Patients with inadequate response to treatment with or intolerance of two to three other migraine preventive medications and a reasonable trial of triptan medications.

Despite concerns that step therapy can sometimes present inappropriate barriers to care, in the case of CGRP inhibitors the policy roundtable concurred with the manufacturer position that step therapy was reasonable. Many patients with migraine have not tried other preventive treatment options, and several of these other options (primarily tricyclic antidepressants, beta-blockers, and certain anti-seizure medications) have well-established and generally acceptable safety profiles. Triptan medications for acute relief can also be very effective for many patients, limiting the potential added benefit of preventive therapy. All these options are also far less expensive that CGRP inhibitors, and therefore patients themselves stand to benefit if they can be successfully treated with one of them.

Payers are likely to differ on the number of other preventive treatments patients will be required to have tried without adequate success prior to receiving coverage for a CGRP inhibitor. Given the varying mechanisms of action of these other options the policy roundtable discussed coverage criteria requiring either two or three be tried before starting a CGRP inhibitor. Similarly, payers may differ in how they define an "adequate" trial of triptans. As noted above, when pricing meets reasonable value-based thresholds, clinician attestation should be considered adequate to demonstrate that other treatments have been tried without adequate success. Attestation may be particularly important in this case because of the long-term course of migraine for many patients, resulting in clinical and pharmacy records that may not capture trials of treatment from previous years or when paid for out of pocket by patients. For some payers, it may be reasonable to ask the clinician to summarize the prior treatment history and reason for discontinuations, which would enhance the likelihood that only appropriate patients receive treatment. Nevertheless, such a summary should not require medical record submissions, which would be overly burdensome as noted above.

Potential provider criteria

a. CGRP inhibitors can be covered if prescribed by any clinician – or – CGRP inhibitors may be covered only if prescribed by a specialist clinician with formal training in neurology or pain management.

Most migraine is cared for by clinicians who are not specialists in neurology or pain management, and access to these specialists can be quite limited in rural areas. Thus, to maximize access to CGRP inhibitors for appropriate patients, payers should consider allowing all clinicians to prescribe them. On the other hand, these medications have a new mechanism of action, have very limited safety data, and are given as a self-administered injection, which will require patients to be taught how to properly store and administer the treatment. Insurance coverage for most other treatments with these characteristics, when first introduced, have required specialist prescribing. Clinical experts on the roundtable suggested that within integrated delivery systems it may well prove feasible to provide adequate access while limiting prescribing to headache specialists.

Payers may consider both coverage options, but the policy roundtable members suggested that allowing broad prescribing is more appropriate in this case given important concerns that access would be too limited if restricted to specialists. If payers do choose to limit prescribing to specialists at the outset, it is incumbent on them to evaluate for potential access problems and to revisit this restriction early on as clinical experience evolves.

Potential limitations on initial length of coverage

a. Ongoing coverage may require that clinicians attest to clinical improvement after some pre-specified length of treatment (e.g. three to six months) – or – no limitation on length of coverage may be required for CGRP inhibitors.

Coverage for expensive therapies is frequently limited in duration at the outset in order to assure that clinicians and patients discuss the initial outcomes of treatment and can affirm that the clinical benefit gained is worth continuing treatment. Currently, however, there are no guidelines on how long an initial trial of a preventive therapy should last before determining that the treatment is ineffective. CGRP inhibitors may have an earlier onset than current preventive options, but it is unknown how long it will take for some patients to begin to see benefits. Roundtable members expressed the view that patients typically stop taking preventive therapy if it is not tolerable or ineffective, reducing the risk that CGRP inhibitors would be used for an extended time while providing no clinical benefit.

Manufacturers

1. Following the example set by the launch of the first CGRP inhibitor, manufacturers should continue to exercise restraint in pricing and price negotiation with payers so that net prices align reasonably with the added benefits for patients. Consideration of price increases in future years should be transparently justified by new clinical evidence of superior performance.

Many considerations inform manufacturers' pricing decisions, including value-based price ranges for target populations, potential positions on formularies, and responses from the patient and healthcare communities. The launch price for the first CGRP inhibitor, erenumab, was reportedly selected in part to ensure the agent would be placed on formularies with patients being responsible for a copayment rather than coinsurance. In addition, the assumed discounted price aligned with clinical value in the target patient population despite the availability of many generic options, which should lead to less restrictive coverage policies from insurers. Manufacturers should continue to consider patient access and affordability in future pricing decisions.

2. Manufacturers should exercise restraint in marketing CGRP inhibitors to incorporate the reality that patients will be required to have tried other preventive options first. Promotional material for patients and for clinicians should refrain from building unrealistic expectations of a cure.

Many patients with migraine have tried extensive lists of preventive therapies which have failed due to lack of efficacy of tolerability. Patients and patient groups are hopeful about the CGRP inhibitors, in part because they have been studied specifically for migraine. Nevertheless, given the clinical trial results, manufacturers should be clear in their marketing messages that these new agents are not a cure and may not reduce migraine frequency for some patients. Manufacturers, clinicians, and patient representatives agreed that these agents are appropriate for patients for whom existing preventive therapies have failed. Manufacturers should also clearly specify that this is the target population in their marketing materials.

3. Manufacturers and researchers should support studies that evaluate the efficacy of CGRP inhibitors in the patients most likely to receive them: those for whom more than three prior preventive therapies have failed.

For patients who have no other options for preventive therapy, the CTAF panel voted that there was adequate evidence to demonstrate a positive net health benefit with the CGRP inhibitors in patients with chronic migraine but not in episodic migraine. However, there were some concerns that the patients most likely to receive these agents first were not represented in the clinical trial populations (e.g., those for whom more than three preventive therapies have failed). Patients may also use a CGRP inhibitor in combination with existing prevention rather than as monotherapy, and currently there is no evidence on the benefits and risks comparing these approaches.

4. Manufacturers and researchers should conduct studies directly comparing CGRP inhibitors and other treatment options using standardized research protocols and outcome assessments to permit real-world, long-term outcome assessment.

For patients with chronic or episodic migraine, the CTAF panel voted that there was inadequate evidence to distinguish the net health benefit between the CGRP inhibitors or with other treatment options in part because of the short-term duration of the trials. Although the short-term trials showed clinical benefits, there is considerable uncertainty about the long-term safety and efficacy of these interventions with a novel mechanism of action. Furthermore, manufacturers, the research community, and regulators should collaboratively develop standard approaches for trial recruitment, entry criteria, study duration, and measurement of key outcomes (e.g., 50% responders, days using acute medications) to facilitate comparisons across trials.

Patient Advocacy Organizations

1. Patient groups should advocate early during trial development to ensure evidence on the outcomes most important to patients is available at the time of product launch.

The primary outcomes in the clinical trials were typically migraine-related events (e.g., migraine days), which does not accurately capture the impact of migraine on work or daily activities that are important outcomes to patients. Across the clinical trials, quality of life outcomes were inconsistently reported which precluded any formal indirect comparisons between interventions. Patients and patient groups should participate in discussions of core outcome measures to ensure patient-relevant outcomes assessed in clinical trials and that such outcomes can be compared across trials. In addition, patient groups should work with manufacturers to collaboratively develop standard approaches for trial recruitment and entry criteria to ensure those patients most likely to receive these agents in the real world are represented in the trials.

Providers

1. Clinicians should be aware of the uncertainties in long-term efficacy and potential harms when prescribing CGRP inhibitors.

As with any new mechanism of action, limitations and uncertainties in the evidence base influence decision-making. For the CGRP inhibitors, due to the limitations in terms of populations studied and short-term trial duration described above, clinicians may reasonably exercise restraint in prescribing so as to allow more safety data to unfold. The FDA is requiring additional post-marketing studies of erenumab in pregnant women to identify potential maternal, fetal, and infant serious adverse events. Post-marketing surveillance for liver toxicity, myocardial infarction, and stroke after exposure to erenumab is also requested. In addition, clinicians should have extensive conversations with patients to convey the uncertainties about the new interventions and to understand patient preferences.

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This is the first ICER review of CGRP inhibitors for chronic or episodic migraine.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials via Ovid, May 2, 2018.

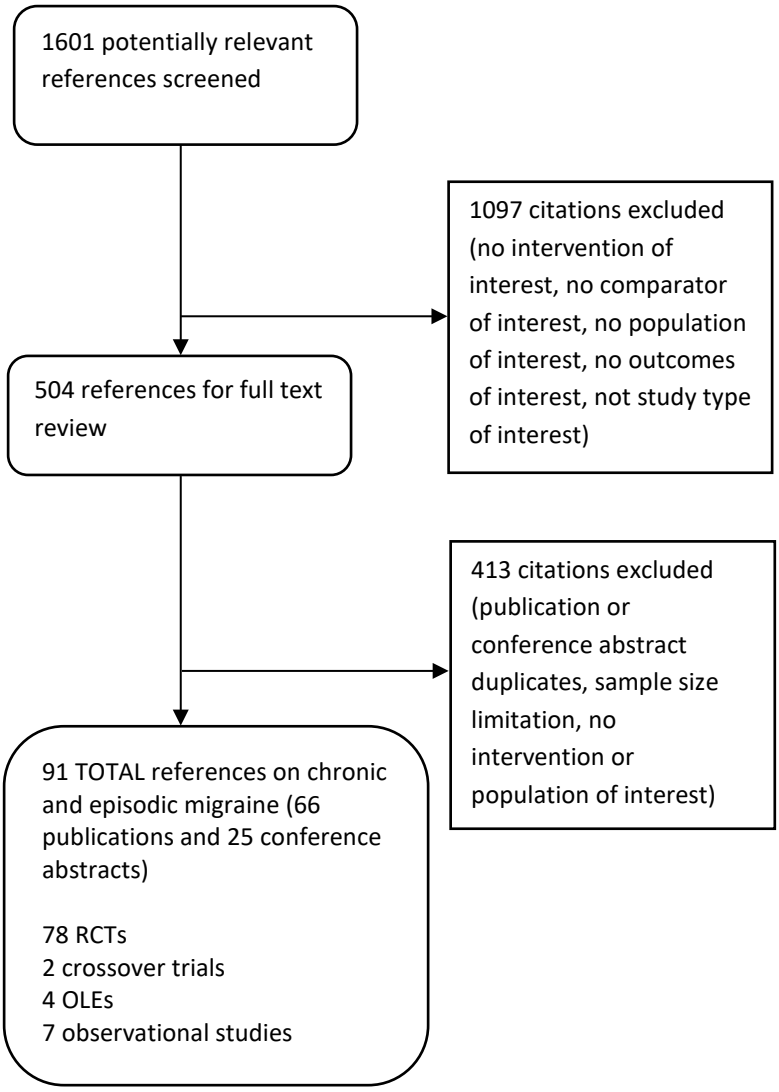
#	Search Terms
1	exp migraine/
2	(migrain* or headache* or cephalgi* or cephalalgi*).ti,ab.
3	(migrain* disorder* or headache disorder*).mp.
4	1 or 2 or 3
5	(AMG-334 or AMG 334 or AMG334 or erenumab).mp.
6	(TEV-48125 or TEV 48125 or TEV48125 or fremanezumab).mp.
7	(LY2951742 or LY 2951742 or galcanezumab).mp.
8	calcitonin gene-related peptide or (CGRP).mp.
9	5 or 6 or 7 or 8
10	topiramate or Topamax.mp.
11	propranolol.mp.
12	onabotulinum toxin A or Botox.mp.
13	amitriptyline.mp.
14	10 or 11 or 12 or 13
15	9 or 14
16	4 and 15
17	clinical trial.pt. or clinical trial, phase I.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or multicenter study.pt. or randomized controlled trial.pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or (4 arm or four arm).ti,ab,kw.
18	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. or case-control studies/ or control groups/ or matched-pair analysis/ or retrospective studies/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab,kw.
19	17 or 18
20	16 and 19
21	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt.

22	20 not 21
23	(animals not (humans and animals)).sh.
24	22 not 23
25	limit 24 to english language
26	remove duplicates from 25

Table A3. Embase Search Strategy, May 2, 2018.

#	Search Terms
#1	'migraine'/exp
#2	(migrain* or headache* or cephalgi* or cephalalgi*):ab,ti
#3	('migrain* disorder*' or 'headache disorder*'):ab,ti
#4	#1 or #2 or #3
#5	('AMG-334' or 'AMG 334' or 'AMG334' or erenumab):ab,ti
#6	('TEV-48125' or 'TEV 48125' or 'TEV48125' or fremanezumab):ab,ti
#7	('LY2951742' or 'LY 2951742' or galcanezumab):ti,ab
#8	(calcitonin gene-related peptide or (CGRP)):ti,ab
#9	#5 or #6 or #7 or #8
#10	('topiramate' or 'Topamax'):ti,ab
#11	propanolol:ti,ab
#12	onabotulinum toxin A or Botox:ti,ab
#13	amitriptyline:ti,ab
#14	#10 or #11 or #12 or #13
#15	#9 or #14
#16	#4 and #15
#17	('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk
#18	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compared':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab
#19	#17 or #18
#20	#16 and #19
#21	#20 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#22	#20 not #21
#23	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp
#24	'human'/exp
#25	#23 and #24
#26	#23 not #25
#27	#22 not #26
#28	#27 and [english]/lim
#29	#27 and [medline]/lim
#30	#28 not #29

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Migraine Prophylactic Treatments



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two systematic reviews on the preventive treatment of migraines: 1) topiramate for the prevention of migraines in patients with episodic migraine and 2) CGRP inhibitors for the prevention of migraines in patients with chronic and episodic migraine. We also identified one health technology assessment evaluating onabotulinum toxin A for the prevention of migraines in patients with chronic migraine. These reviews and assessment are summarized below.

Linde, M., et al. (2016). "Topiramate for the prophylaxis of episodic migraine in adults (Review)." Cochrane Database Systematic Reviews.

This systematic review included 17 prospective, randomized controlled trials of topiramate taken regularly without concomitant prophylactic medications to prevent migraine attacks or improve migraine-related quality of life in patients 16 years and older with episodic migraine (<15 headache days per month). Combined analysis of nine trials showed topiramate reduced headache frequency on average by 1.2 attacks per month compared to placebo with between-arm mean differences ranging from -0.52 to -3.80. A combined analysis also showed patients receiving topiramate were twice as likely to experience a ≥50% reduction in headache frequency than those receiving placebo (RR 2.02). Separate analyses of three dose-ranging studies showed topiramate 200 mg was no more effective than topiramate 100 mg in reducing headache frequency. When compared to an active treatment, topiramate did not show a statistically significant difference in reducing headache frequency in five of the seven active-controlled trials identified in this review. In a pooled analysis of two trials comparing topiramate to sodium valproate, topiramate demonstrated a slight reduction in headache days over the active comparator (mean difference -0.90). All AEs except nausea were significantly more common in the topiramate 100 mg arms compared to placebo. There was no statistically significant difference in the frequency of AEs between the topiramate 50 mg and placebo arms except for taste disturbance and weight loss. The reviewers raised several concerns about the design of the included trials such as an inadequate description of how allocation sequences were generated or how allocation was concealed in more than half of the 17 trials and the risk of detection bias in 16 of the 17 trials.

Ibekwe, A., et al. (2018). "Monoclonal antibodies to prevent migraine headaches." CADTH Issues in Emerging Health Technologies (167).

This systematic review summarized the available evidence on the efficacy and safety of erenumab, fremanezumab, galcanezumab, and included another CGRP inhibitor, eptinezumab. A literature search through December 2017 identified five randomized, double-blind, placebo-controlled trials conducted in patients with chronic migraine including one erenumab, two fremanezumab, and one galcanezumab trial. Changes from baseline in migraine days per month compared to placebo were -

2.1, -2.1, and -2.5 days with erenumab, fremanezumab, and galcanezumab treatment, respectively. The search also identified three erenumab, two fremanezumab, and two galcanezumab trials conducted in patients with episodic migraine. Erenumab showed significant reductions in migraines days compared to placebo, ranging from -1.1 to -1.4 days in the 70 mg arms and reaching -1.9 days in the 140 mg arm. Treatment with 225 mg of fremanezumab reduced migraine days per month compared to placebo by 1.5 days in one trial and 2.81 days in another, while treatment with 120 mg of galcanezumab resulted in a 2-day reduction in migraine days compared to placebo. At the time of this review, safety data primarily gathered from phase II trials showed 48% to 72% of patients experiencing adverse events including upper respiratory tract infection, nasopharyngitis, and urinary tract infection in the CGRP inhibitor arms compared to a range of 39% to 67% in the placebo arms. None of the trials reported deaths due to treatment. The reviewers discussed the need to assess the efficacy of CGRP inhibitors in comparison to standard prophylactic treatment for migraine in head-to-head trials and raised concerns over the generalizability of trial results as most participants were female and Caucasian.

CADTH (2013). "OnabotulinumtoxinA Common Drug Report." CADTH Common Drug Report.

This assessment included two randomized, double-blind, placebo-controlled trials (PREEMPT 1 and PREEMPT 2) that assessed the effectiveness and harms of onabotulinum toxin A at doses ranging from 155U to 195U in adults with chronic migraine (≥15 headache days per month lasting 4 hours or longer). In the quality of life assessment of both trials, patients receiving onabotulinum toxin A achieved within-group minimally clinically important differences (MCID), established by a previous randomized controlled trial in patients with chronic migraine, in each of the MSQ role restrictive (MCID: -10.9), role preventive (-8.3), and emotional function (-12.2) domain scores at week 12 and 24. The reviewers found that the subgroup of patients for whom three or more treatments had failed responded consistently to onabotulinum toxin A treatment with the overall populations and achieved within-group MCID for all three MSQ domains. The frequency of headache was reduced by approximately 8 to 9 days per month for those receiving onabotulinum toxin A in both trials, while patients receiving placebo experienced a reduction of 6 to 7 days per month at week 24. In the subgroup of patients for whom three or more treatments had failed, reductions in headache frequency ranged from 6 to 8 days per month in the onabotulinum toxin A arms compared to 4 to 5 days per month in the placebo arms at week 24. The frequency of AEs was higher in the onabotulinum toxin A arms, and the most common AEs included neck pain and muscular weakness. There were no deaths during the double-blind and OLE phases of both trials. The reviewers noted the limitations of the available evidence including the difficulty of maintaining blinding in the trials and the lack of comparisons between onabotulinum toxin A and standard preventive treatments for CM.

Appendix C. Ongoing Studies

Appendix Table C1. Ongoing Studies of CGRP Inhibitors

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Erenumab					
A Safety and Efficacy Study to Evaluate AMG 334 in Migraine Prevention, Amgen NCT02630459	Phase II, randomized, parallel assignment, triple-blind trial followed by open-label extension Enrollment: 475 Estimated follow-up: 24 weeks (randomized treatment period); NR (open-label extension)	1. Erenumab 'low dose' once monthly 2. Erenumab 'middle dose' once monthly 3. Erenumab 'high dose' once monthly 4. Placebo	Inclusion: • 20-65 years • History of migraine according to ICHD-3 for at least 12 months • Fulfills criteria for episodic migraine (4-14 migraine days per month with less than 15 headache days per month) Exclusion: • Older than 50 at time of migraine onset • History of cluster headache or hemiplegic migraine headache • Used prohibited treatment prior to or during baseline • Used more than one migraine prophylactic medication within two months • Received botulinum within four months • Ergotamine-derivatives, steroids, and triptans used for migraine prophylaxis within two months • No response with more than two preventive medication categories	Primary: • Change from baseline in mean monthly migraine days at week 24 Secondary: • ≥50% reduction in mean monthly migraine days at week 24 • Change from baseline in acute migraine-specific medication treatment days at week 24	June 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
A Phase 2 Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention, Amgen NCT01952574 *52-week results reported in Ashina, 2017*[152]	Open-label extension of a phase II, randomized, parallel assignment, triple-blind trial Enrollment: 383 Estimated follow-up: five years	1. Erenumab 70 mg subcutaneous injection once monthly	Patients from the parent study[40] were eligible to enter the open-label extension if they completed the double-blind treatment period. Parent study inclusion: • 18-60 years • History of migraine according to ICHD-2 for at least 12 months • Fulfills criteria for episodic migraine (4-14 migraine days per month with less than 15 headache days per month) Parent study exclusion: • Older than 50 at migraine onset • No response to more than two preventive medication categories	Outcome assessed at five years assumed to be the same as those assessed at one year. [152] • Change from baseline in monthly migraine days • ≥50%, ≥75%, and 100% reduction in monthly migraine days • Change from baseline in migraine-specific acute medication use	November 2019
Study of Efficacy and Safety of AMG 334 in Adult Episodic Migraine Patients (EMPOwER), Novartis NCT03333109	Phase III, randomized, parallel assignment, quadruple-blind trial Estimated enrollment: 880 Estimated follow-up: 12 weeks (randomized treatment period); 12	1. Erenumab 'dose 1' subcutaneous injection once monthly 2. Erenumab 'dose 2' subcutaneous injection once monthly 3. Placebo	Inclusion: • 18-65 years • History of migraine for at least 12 months • Fulfills criteria for episodic migraine (4-14 migraine days per month) Exclusion: • Older than 50 at time of migraine onset • History of cluster or hemiplegic headache • Active chronic pain syndrome	Primary: • Change from baseline in monthly migraine days at week 12 Secondary: • Change from baseline in monthly acute migraine-specific medication treatment days and HIT-6 score at week 12 • ≥50% reduction in monthly migraine days at week 12	February 2020

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
	weeks (safety follow-up)				
A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies (LIBERTY), Novartis NCT03096834	Phase III, randomized, parallel assignment, double-blind trial Estimated enrollment: 220 Estimated follow-up: 12 weeks	1. Erenumab subcutaneous injection once monthly 2. Placebo	Inclusion: • 18-65 years • History of migraine for at least 12 months • Fulfills criteria for episodic migraine (4-14 migraine days per month) • Failure of previous migraine prophylactic treatments Exclusion: • Older than 50 at time of migraine onset • History of cluster or hemiplegic headache • Active chronic pain syndrome	Primary: • ≥50% reduction in monthly migraine days at week 12 Secondary: • Change from baseline in monthly migraine days, Migraine Physical Function Impact Diary score, and acute migraine-specific medication treatment days at week 12 • ≥75% and 100% reduction in monthly migraine days at week 12	January 2021

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Fremanezumab					
Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Chronic Migraine, Otsuka Pharmaceutical Co., Ltd. NCT03303079	Phase II/III, randomized, parallel assignment, quadruple blind trial Estimated enrollment: 540 Estimated follow-up: 12 weeks	1. Fremanezumab 675 mg subcutaneous injection at start of month one followed by 225 mg subcutaneous injection at months two and three 2. Fremanezumab 675 mg subcutaneous injection at start of month one followed by placebo at months two and three 3. Placebo	Inclusion: • 18-70 years • History of migraine according to ICHD or clinical judgment suggests a migraine diagnosis • Chronic migraine Exclusion: • Older than 50 at time of migraine onset • Use of migraine-related medicine within two months prior to study start	Primary: • Change from baseline in average number of monthly headache days of at least moderate severity at week 12 Secondary: • Change from baseline in average number of monthly acute migraine-specific medication treatment days and monthly migraine days at week 12 • ≥50% reduction in monthly average number of headache days of at least moderate severity at week 12	April 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Episodic Migraine, Otsuka Pharmaceutical Co., Ltd. NCT03303092	Phase II/III, randomized, parallel assignment, quadruple-blind trial Estimated enrollment: 330 Estimated follow-up: 12 weeks	1. Fremanezumab 225 mg subcutaneous injection every month 2. Fremanezumab 675 mg subcutaneous injection at baseline followed by placebo 3. Placebo	Inclusion: • 18-70 years • History of migraine according to ICHD or clinical judgment suggests a migraine diagnosis • Episodic migraine Exclusion: • Older than 50 at time of migraine onset • History of hypersensitivity reactions to injected proteins	Primary: • Change from baseline in monthly average number of migraine days at week 12 Secondary: • ≥50% reduction in monthly average number of migraine days at week 12 • Change from baseline in monthly average number of acute medication treatment days at week 12	December 2018
Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine (HALO), Teva NCT02638103	Phase III, randomized, parallel assignment, quadruple-blind trial Enrollment: 1578 Estimated follow-up: 76 weeks	1. Fremanezumab 'dose 1' with matching placebo 2. Fremanezumab 'dose 2' with matching placebo	Patients rolling over were eligible to enter HALO if they completed the parent studies without major protocol violations. For patients not rolling over, Inclusion: • 18-70 years • History of migraine or clinical judgment suggests a migraine diagnosis • Fulfills the criteria for episodic or chronic migraine Exclusion: • History of hypersensitivity reactions to injected proteins	Primary: • Adverse events through 76 weeks Secondary: • Change from baseline in monthly average of migraine days and headache days at 76 weeks	December 2018

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
An Efficacy and Safety Study of Fremanezumab in Adults With Migraine (FOCUS), Teva NCT03308968	Phase III, randomized, parallel assignment, quadruple-blind trial followed by open-label extension Estimated enrollment: 804 Estimated follow-up: 12 weeks (randomized treatment period); 12 weeks (open-label extension)	1. Fremanezumab monthly 2. Fremanezumab quarterly 3. Placebo	Inclusion: • 18-70 years • History of migraine for at least 12 months • Episodic or chronic migraine • Inadequate response to two to four classes of prior preventive treatments Exclusion: • Older than 50 at time of migraine onset • Received any preventive migraine medication for more than five days at screening and expected to continue with these medications • Received onabotulinumtoxinA during the three months prior to screening • Used an intervention/device for migraine during the two months prior to screening • Used triptans/ergots or non-steroidal anti-inflammatory drugs for migraine prevention	Primary: • Change from baseline in monthly average of migraine days at week 12 Secondary: • Change from baseline in monthly average of acute medication treatment days and headache days at week 12 • ≥50% reduction in monthly average of migraine days at week 12 • Percentage of participants with adverse events at week 12	August 2019
Long-term Safety and Tolerability of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine, Otsuka Pharmaceutical Co., Ltd. NCT03303105	Phase III, non-randomized, parallel assignment, open label trial Estimated enrollment: 40 Estimated follow-up: 80 weeks	1. Fremanezumab 225 mg subcutaneous injection every month 2. Fremanezumab 675 mg subcutaneous injection every three months	Inclusion: • 18-70 years • History of migraine or clinical judgment suggests a migraine diagnosis • Fulfills the criteria for episodic or chronic migraine Exclusion: • Older than 50 at time of migraine onset • History of hypersensitivity reactions to injected proteins	Primary: • Adverse events through 80 weeks Secondary: • Change from baseline in monthly average of migraine days and headache days at 48 weeks	February 2020

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Galcanezumab					
Evaluation of Galcanezumab in the Prevention of Chronic Migraine (REGAIN), Eli Lily NCT02614261	Phase III, randomized, parallel assignment, double-blind trial Enrollment: 1113 Estimated follow-up: 12 weeks	1. Galcanezumab 120 mg subcutaneous injection once monthly 2. Galcanezumab 240 mg subcutaneous injection once monthly 3. Placebo	Inclusion: • 18-65 years • Diagnosis of chronic migraine according to ICHD-3 • History of migraine headaches for at least one year • Migraine onset before age 50 Exclusion: • Prior exposure to galcanezumab or other CGRP antibody • History of persistent daily headache, cluster headache, or migraine subtypes	Primary: • Change form baseline in number of migraine days per month at week 12 Secondary: • ≥50%, ≥75% and 100% reduction in migraine days per month at week 12 • Change from baseline in MSQ score, MIDAS score, number of days using acute medication, and number of headache hours at week 12 • Pharmacokinetics at week 12	May 2021
A Study of LY2951742 (Galcanezumab) in Japanese Participants With Episodic Migraine, Eli Lilly NCT02959177	Phase II, randomized, parallel treatment, double blind trial Estimated enrollment: 451 Estimated follow-up: 24 weeks	1. Galcanezumab 'dose 1' subcutaneous injection once monthly 2. Galcanezumab 'dose 2' subcutaneous injection once monthly 3. Placebo	Inclusion: • 18-65 years • Diagnosis of migraine according to ICHD-3 • Episodic migraine • History of migraine for at least one year • Migraine onset prior to age 50 Exclusion: • Prior exposure to galcanezumab or other antibodies to CGRP or its receptor • History of other major headaches	Primary: • Change from baseline in monthly migraine days at week 24 Secondary: • ≥50%, ≥75% and 100% reduction in monthly migraine days at week 24 • Change from baseline in acute medication treatment days, headache hours, MSQ score, and MIDAS score at week 24	February 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
A Safety Study of Galcanezumab in Participants With Migraine, With or Without Aura, Eli Lily NCT02614287	Phase III, randomized, parallel assignment, open label trial Enrollment: 270 Estimated follow-up: one year	1. Galcanezumab 120 mg subcutaneous injection once monthly following 240 mg loading dose 2. Galcanezumab 240 mg subcutaneous injection once monthly	Inclusion: • 18-65 years • Diagnosis of episodic or chronic migraine according by ICHD-3 • History of migraine for at least one year • Migraine onset before age 50 Exclusion: • Prior exposure to galcanezumab or other antibodies of CGRP or its receptor • History of other major headaches	Primary: • Percentage of patients who discontinue through month 12 Secondary: • Pharmacokinetics through month 12 • Change from baseline in number of migraine days, number of headache days, frequency of acute medication use, MIDAS score, and MSQ score at month 12 • ≥50% reduction in number of migraine days	December 2018
A Study of LY2951742 (Galcanezumab) in Japanese Participants With Migraine, Eli Lilly NCT02959190	Phase III, randomized, parallel assignment, open label trial Estimated enrollment: 300 Estimated follow-up: one year	1. Galcanezumab 'dose 1' subcutaneous injection once monthly 2. Galcanezumab 'dose 2' subcutaneous injection once monthly	Patients with episodic migraine who completed the treatment period in the CGAN study and patients with chronic migraine who met the criteria listed below were eligible to participate. Inclusion: • 18-65 years • Diagnosis of chronic migraine according to ICHD-3 • History of migraine for at least one year • Migraine onset before age 50 Exclusion: • Prior exposure to galcanezumab or other CGRP antibodies	Primary: • Percentage of patients who discontinue through month 12 Secondary: • Pharmacokinetics through month 12 • Change from baseline in number of migraine days, number of headache days, frequency of acute medication use, MIDAS score, and MSQ score at month 12	August 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
			• History of other major headaches • Failure to respond to three or more migraine preventive treatments from different classes	• ≥50% reduction in number of migraine days at month 12	

Source: http://www.clinicaltrials.gov/ (NOTE: studies listed on site include both clinical trials and observational studies)

MIDAS: Migraine Disability Assessment; MSQ: Migraine-Specific Quality of Life Questionnaire; mg: milligram

Appendix D. Comparative Clinical Effectiveness Supplemental Information

Systematic Review Supplemental Information

We performed screening at both the abstract and full-text level. The title and abstract of each citation was independently screened by two reviewers using DistillerSR; a third reviewer worked with the initial reviewers to resolve any issues of disagreement through consensus. No study was excluded at abstract level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Each full-text was independently reviewed by two reviewers and conflicts resolved by a third reviewer. Reasons for exclusion were categorized according to the PICOTS elements during both title/abstract and full-text review.

Studies assessing other headache or migraine conditions including tension-type headaches, cluster headaches, and other secondary headaches arising from another existing condition were excluded. We included studies on migraine that contained participants with or without aura or participants with medication overuse headaches, as long as they met all other eligibility criteria. For all interventions and comparators, we included any studies that used them as monotherapy or add-on treatments.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs, crossovers, and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table D7-D8)[120] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

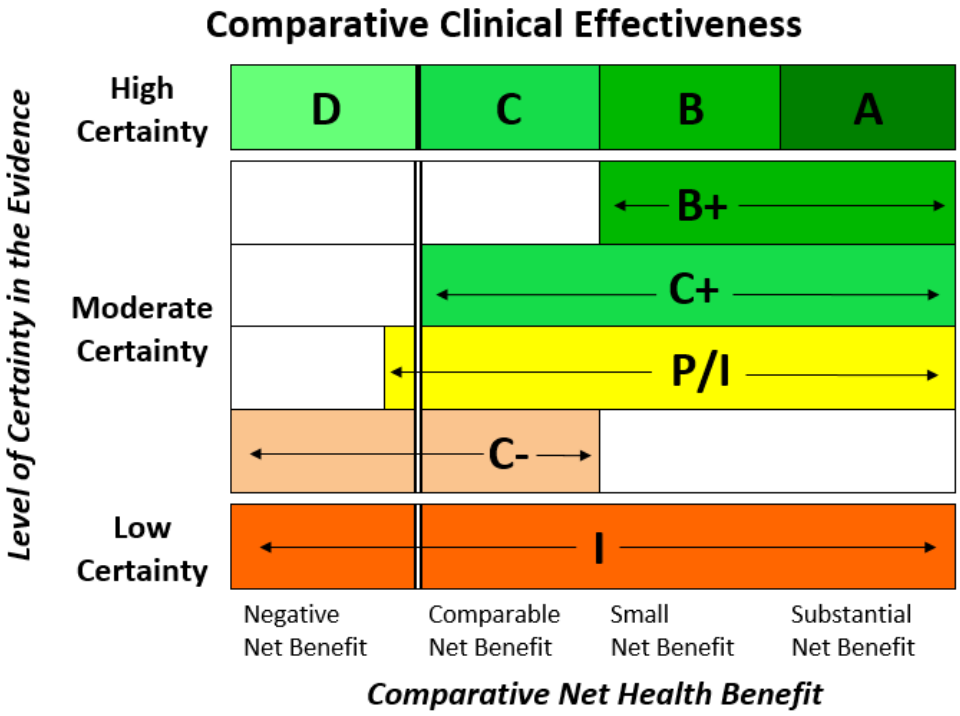
Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[121]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Table D1. Key Baseline Characteristics for CGRP Inhibitor Trials in Chronic Migraine

Study/ Phase	Arm	N	Mean Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Erenumab								
Tepper, 2017 [90] Phase II	Erenumab 70 mg/month	191	41.4 (11.3)	0	20.7 (12.8)	17.9 (4.4)	20.5 (3.8)	8.8 (7.2) migraine-specific
	Erenumab 140 mg/month	190	42.9 (11.1)	0	21.9 (11.8)	17.8 (4.7)	20.7 (3.8)	9.7 (7.0) migraine-specific
	Placebo	286	42.1 (11.3)	0	22.2 (12.6)	18.2 (4.7)	21.1 (3.9)	9.5 (7.6) migraine-specific
Fremanezumab								
Bigal, 2015a [26] Phase II	Fremanezumab 675/225 mg/month	88	40.0 (11.6)	40	15.8 (11.2)	17.2 (5.4)	16.5 (6.7)	15.1 (7.0) any acute
	Fremanezumab 900 mg/month	87	41.5 (12.9)	38	18.8 (12.2)	16.4 (5.3)	15.9 (6.5)	16.2 (6.7) any acute
	Placebo	89	40.7 (11.5)	43	20.4 (13.1)	16.8 (5.0)	16.5 (6.3)	15.7 (6.2) any acute
Silberstein, 2017 HALO-CM[28] Phase III	Fremanezumab 675 mg/3 months	376	42 (12.4)	20	19.7 (12.8)	16.2 (4.9)	20.4 (3.9)	13.1 (6.8) headache-specific; 11.3 (6.2) migraine-specific
	Fremanezumab 675/225 mg/month	379	40.6 (12.0)	22	20.1 (12.0)	16.0 (5.2)	20.3 (4.3)	13.1 (7.2) headache-specific; 11.1 (6.0) migraine-specific
	Placebo	375	41.4 (12.0)	21	19.9 (12.9)	16.4 (5.2)	20.3 (4.2)	13.0 (6.9) headache-specific; 10.7 (6.3) migraine-specific

NR: not reported; SD: standard deviation

Table D2. Key Baseline Characteristics for Current Preventive Therapy Trials in Chronic Migraine

Study/Phase	Arm	N	Mean Age (SD) or [range]	% Add-On Preventive Therapy	Mean Years Since Onset (SD) or [range]	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD) or [range]	Mean Days of Acute Medication Use per Month (SD)
Onabotulinum toxin A								
Aurora, 2010 PREEMPT 1[34]	Onabotulinum toxin A 155U	341	41.2 (NR)	0	20.3 (NR)	19.1 (4.0)	20.0 (3.7)	NR
	Placebo	338	42.1 (NR)	0	20.6 (NR)	19.1 (4.1)	19.8 (3.7)	NR
Diener, 2010 PREEMPT 2[35]	Onabotulinum toxin A 155U	347	41.0 (NR)	0	18.5 (NR)	19.2 (3.9)	19.9 (3.6)	NR
	Placebo	358	40.9 (NR)	0	17.6 (NR)	18.7 (4.1)	19.7 (3.7)	NR
Cady, 2014 [38]	Onabotulinum toxin A 155U	10	NR	NR	NR	23.4 (SE: 1.9)	NR	NR
	Placebo	10	NR	NR	NR	24.8 (SE: 1.9)	NR	NR
Freitag, 2008 [36]	Onabotulinum toxin A 100U	30	42.2 [19-64]	NR	NR	NR	23 [16-28]	NR
	Placebo	30	42.4 [25-55]	NR	NR	NR	23 [16-28]	NR
Sandrini, 2011 [37]	Onabotulinum toxin A 100U	33	48.5 (9.2)	0	19.7 (NR)	NR	24.2 (5.0)	22.7 (6.4) any acute
	Placebo	35	49.0 (10.1)	0	20.3 (NR)	NR	25.5 (5.6)	23.6 (6.6) any acute
Topiramate								
Silberstein, 2007 [32]	Topiramate 100 mg/day	165	37.8 (12.38)	0	9.3 (10.5)	17.1 (5.4)	20.4 (4.8)	11.9 (7.0) any acute
	Placebo	163	38.6 (11.80)	0	9.1 (10.6)	17.0 (5.0)	20.8 (4.6)	11.4 (6.6) any acute
Diener, 2007 [33]	Topiramate 100 mg/day	32	47.8 (9.4)	12.5	NR	15.5 (4.6)	NR	NR
	Placebo	27	44.4 (9.6)	22.2	NR	16.4 (4.4)	NR	NR
Mei, 2006 [139]	Topiramate 100 mg/day	30	45.80 (9.07)	0	5.00 (1.93)	NR	24.38 (3.93)	NR
	Placebo	20	45.93 (8.41)	0	4.95 (2.19)	NR	23.50 (3.70)	NR
Silvestrini, 2003 [142]	Topiramate 50 mg/day	14	43 [34-58]	0	3 [2-5]	NR	20 [16-27]	NR
	Placebo	14	44 [36-51]	0	3 [2-4]	NR	20 [16-28]	NR

Study/Phase	Arm	N	Mean Age (SD) or [range]	% Add-On Preventive Therapy	Mean Years Since Onset (SD) or [range]	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD) or [range]	Mean Days of Acute Medication Use per Month (SD)
Head-to-Head								
Cady, 2011 [39]	Total	59	39.6 [19.6-64.0]	NR	Median: 16	11.1 (NR)	21.1 (NR)	14.5 (NR) headache-specific
	Onabotulinum toxin A 200 U	29	NR	NR	NR	11.9 (NR)	21.8 (NR)	13.9 (NR) headache-specific
	Topiramate 200 mg/day	30	NR	NR	NR	10.3 (NR)	20.5 (NR)	15.1 (NR) headache-specific
Magalhães, 2010 [138]	Amitriptyline 50 mg/day	37	38 (10)	0	NR	NR	NR	NR
	Onabotulinum toxin A 250 U	35	30 (10)	0	NR	NR	NR	NR
Mathew, 2009 [137]	Total	60	36.8 (10.3)	0	NR	NR	NR	NR
	Onabotulinum toxin A 200 U	30	NR	0	NR	NR	15.6 (7.0)	NR
	Topiramate 100 mg/day	30	NR	0	NR	NR	15.5 (7.2)	NR
Silberstein, 2012 [143]	Topiramate 100 mg/day	95	Median 42 [18-67]	0	NR	NR	NR	NR
	Topiramate 100 mg/day + propranolol 240 mg/day	96	Median 39 [18-62]	0	NR	NR	NR	NR

NR: not reported; SD: standard deviation

Table D3. Key Baseline Characteristics for CGRP Inhibitor Trials in Episodic Migraine

Study/ Phase	Arm	N	Mean Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Erenumab								
Sun, 2016 [40] Phase II	Erenumab 7 mg/month	108	40.3 (10.9)	0	19.0 (11.4)	8.6 (2.8)	9.8 (2.7)	4.2 (3.5) migraine-specific; 7.0 (2.9) non-migraine-specific
	Erenumab 21 mg/month	108	39.9 (12.3)	0	20.1 (12.5)	8.9 (2.9)	10.1 (2.7)	4.2 (3.7) migraine-specific; 6.9 (2.8) non-migraine-specific
	Erenumab 70 mg/month	107	42.6 (9.9)	0	21.5 (11.7)	8.6 (2.5)	9.9 (2.5)	4.3 (3.5) migraine-specific; 6.9 (2.9) non-migraine-specific
	Placebo	160	41.4 (10.0)	0	20.7 (11.5)	8.8 (2.7)	9.7 (2.7)	4.5 (3.9) migraine-specific; 7.1 (3.0) non-migraine-specific
Goadsby, 2017 STRIVE[41] Phase III	Erenumab 70 mg/month	317	41.1 (11.3)	2.8	NR	8.3 (2.5)	9.1 (2.6)	3.2 (3.4) migraine specific
	Erenumab 140 mg/month	319	40.4 (11.1)	2.5	NR	8.3 (2.5)	9.3 (2.5)	3.4 (3.5) migraine specific
	Placebo	319	41.3 (11.2)	3.1	NR	8.2 (2.5)	9.3 (2.6)	3.4 (3.4) migraine specific
Dodick, 2018 ARISE[42] Phase III	Erenumab 70 mg/month	286	42 (11)	6.6	22 (13)	8.1 (2.7)	9.1 (2.7)	3.7 (3.6) migraine-specific
	Placebo	291	42 (12)	5.5	20 (12)	8.4 (2.6)	9.3 (2.7)	3.4 (3.6) migraine-specific
Fremanezumab								
Bigal, 2015b [25] Phase II	Fremanezumab 225 mg/month	96	40.8 (12.4)	34	18.9 (12.9)	11.5 (1.9)	12.6 (3.1)	10.4 (3.6) any acute; 8.2 (4.0) triptans
	Fremanezumab 675 mg/month	97	40.7 (12.6)	27	16.9 (12.3)	11.3 (2.2)	12.5 (2.65)	9.8 (4.0) any acute; 6.9 (3.5) triptans

Study/ Phase	Arm	N	Mean Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD)	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
	Placebo	104	42 (11.6)	27	21.1 (14.1)	11.5 (2.24)	12.4 (2.3)	10.4 (3.6) any acute; 8.5 (3.4) triptans
Dodick, 2018 HALO-EM[43] Phase III	Fremanezumab 225 mg/month	290	42.9 (12.7)	21.4	20.7 (12.9)	8.9 (2.6)	6.8 (2.9)	6.1 (3.1) migraine-specific; 7.7 (3.4) any acute
	Fremanezumab 675 mg/3 months	291	41.1 (11.4)	19.9	20.0 (12.1)	9.3 (2.7)	7.2 (3.1)	6.6 (3.1) migraine-specific; 7.8 (3.7) any acute
	Placebo	294	41.3 (12.0)	21.1	19.9 (11.9)	9.1 (2.7)	6.9 (3.1)	7.1 (3.0) migraine-specific; 7.7 (3.6) any acute
Galcanezumab								
Dodick, 2014 [27] Phase II	Galcanezumab 150 mg/2 weeks	108	40.9 (11.4)	0	NR	8.1 (2.9)	NR	NR
	Placebo	110	41.9 (11.7)	0	NR	8.4 (2.9)	NR	NR
Skljarevski, 2018 [44] Phase II	Galcanezumab (all doses)	273	40.6 (11.9)	0	NR	8.4 (3.2)	NR	NR
	Placebo	137	39.5 (12.1)	0	NR	8.0 (3.1)	NR	NR
Stauffer, 2018 EVOLVE-1[45]	Galcanezumab 120 mg/month	213	40.9 (11.9)	0	21.1 (13.0)	9.2 (3.1)	NR	7.4 (3.7) migraine-specific
	Galcanezumab 240 mg/month	212	39.1 (11.5)	0	19.3 (11.9)	9.1 (2.9)	NR	7.3 (3.3) migraine-specific
	Placebo	433	41.3 (11.4)	0	19.9 (12.3)	9.1 (3.0)	NR	7.4 (3.5) migraine-specific
Skljarevski, 2018 EVOLVE-2[46]	Galcanezumab 120 mg/month	233	40.9 (11.2)	0	19.93 (11.7)	9.07 (2.9)	10.56 (3.4)	7.47 (3.3) migraine-specific
	Galcanezumab 240 mg/month	226	41.9 (10.8)	0	20.01 (12.1)	9.06 (2.9)	10.74 (3.7)	7.47 (3.3) migraine-specific
	Placebo	463	42.3 (11.3)	0	21.2 (12.8)	9.2 (3.0)	10.7 (3.5)	7.6 (3.4) migraine-specific

NR: not reported; SD: standard deviation

Table D4. Key Baseline Characteristics for Current Preventive Therapy Trials in Episodic Migraine

Study/Phase	Arm	N	Mean Age (SD) or [range]	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD) or [range]	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Amitriptyline								
Couch, 1979 [164]	Amitriptyline 100 mg/day	NR	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR
Couch, 2011 [165]	Amitriptyline 100 mg/day	194	34.1 (NR)	0	NR	NR	NR	NR
	Placebo	197	35.7 (NR)	0	NR	NR	NR	NR
Lampl, 2009 [166]	Amitriptyline 25 mg/day	66	Median: 32 [19-53]	NR	NR	Median: 7 [4-14]	NR	NR
	Amitriptyline 50 mg/day	66	Median: 33 [19-51]	NR	NR	Median: 7 [4-14]	NR	NR
Gonçalves, 2016 [47] Phase III	Amitriptyline 25 mg/day	66	37.2 (11.2)	0	24.1 (9.1)	7.2 (2.5)	NR	NR
	Placebo	65	36.6 (13.7)	0	20.2 (10.6)	7.3 (3.1)	NR	NR
Propranolol								
Diener, 1996 [48]	Propranolol 120 mg/day	78	40 (13)	0	21 (13)	NR	NR	NR
	Placebo	55	39 (11)	0	19 (11)	NR	NR	NR
Jafarpour, 2016 [167]	Propranolol 60 mg/day	30	37.74 (12.39)	0	14.04 (11.23)	NR	NR	NR
	Placebo	30	41.73 (11.92)	0	11.10 (8.85)	NR	NR	NR
Pradalier, 1989 [168]	Propranolol 160 mg/day	40	37.1 (1.7)	0	NR	NR	NR	NR
	Placebo	34	37.7 (1.8)	0	NR	NR	NR	NR
Sargent, 1985 [169]	Total	161	30 [16-62]	0	20	NR	NR	NR
Weber, 1972 [170]	Total	25	40.6 [19-61]	0	NR	NR	NR	NR
Topiramate								

Study/Phase	Arm	N	Mean Age (SD) or [range]	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD) or [range]	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Lipton, 2011 [49]	Topiramate 100 mg/day	188	39.6 (10.6)	0	19.8 (10)	11.6 (2.0)	13.0 (2.5)	8.6 (3.2) headache-specific
	Placebo	197	40.9 (11.2)	0	20.8 (10.8)	11.8 (2.2)	13.1 (2.6)	8.6 (3.5) headache-specific
Brandes, 2004 [50] Phase III	Topiramate 50 mg/day	120	39 (12.09)	NR	NR	6.4 (2.88)	NR	5.7 (2.72) any acute
	Topiramate 100 mg/day	122	39.1 (12.58)	NR	NR	6.9 (3)	NR	6.2 (2.13) any acute
	Topiramate 200 mg/day	121	39.1 (12.71)	NR	NR	6.1 (2.54)	NR	5.8 (2.52) any acute
	Placebo	120	38.3 (11.96)	NR	NR	6.7 (2.84)	NR	5.8 (2.67) any acute
Silberstein, 2004 [51] Phase III	Topiramate 50 mg/day	125	40.2 (11.5)	0	NR	6.4 (2.7)	NR	5.8 (2.5) any acute
	Topiramate 100 mg/day	128	40.6 (11.0)	0	NR	6.4 (2.7)	NR	5.9 (2.5) any acute
	Topiramate 200 mg/day	117	40.5 (11.4)	0	NR	6.6 (3.1)	NR	6.1 (2.6) any acute
	Placebo	117	40.4 (11.5)	0	NR	6.4 (2.6)	NR	6.1 (3.0) any acute
Gode, 2010 [171]	Topiramate 50 mg/day	15	37.1 (NR)	0	NR	NR	NR	NR
	Topiramate 100 mg/day	15	40 (NR)	0	NR	NR	NR	NR
Lo, 2010 [172]	Total	40	38 (NR)	0	NR	NR	NR	NR
	Topiramate 25 mg/day	10	NR	0	NR	NR	10.2 (5.1)	NR
	Topiramate 50 mg/day	10	NR	0	NR	NR	6.9 (2.6)	NR
	Topiramate 75 mg/day	10	NR	0	NR	NR	8.8 (4.4)	NR
	Topiramate 100 mg/day	10	NR	0	NR	NR	8.0 (2.5)	NR
Mei, 2004 [52]	Topiramate 100 mg/day	58	39.74 (12.02)	0	NR	NR	NR	6.17 (1.8) any acute

Study/Phase	Arm	N	Mean Age (SD) or [range]	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD) or [range]	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
	Placebo	57	38.7 (11.04)	0	NR	NR	NR	6.49 (1.29) any acute
Silberstein, 2006 [53]	Topiramate 200 mg/day	138	39.9 (11.8)	0	NR	NR	NR	NR
	Placebo	73	41.7 (9.4)	0	NR	NR	NR	NR
Storey, 2001 [54]	Topiramate 200 mg/day	19	38.3 [19-62]	63	NR	NR	NR	NR
	Placebo	21	38.1 [24-56]	43	NR	NR	NR	NR
Head-to-Head								
Diener, 2004 [55]	Propranolol 160 mg/day	144	40.6 (11.13)	0	NR	6.1 (2.70)	NR	5.4 (2.54) any acute
	Topiramate 100 mg/day	141	39.8 (10.88)	0	NR	5.8 (2.21)	NR	5.0 (2.21) any acute
	Topiramate 200 mg/day	144	42.6 (11.29)	0	NR	6.2 (2.76)	NR	5.5 (2.62) any acute
	Placebo	146	40.4 (10.11)	0	NR	6.1 (2.60)	NR	5.3 (2.52) any acute
Ashtari, 2008 [175]	Topiramate 50 mg/day	31	31.7 (8)	0	NR	NR	NR	NR
	Propranolol 80 mg/day	31	29.93 (9)	0	NR	NR	NR	NR
Dodick, 2009 [56]	Topiramate 100 mg/day	178	39.7 (10.7)	0	NR	7.4 (2.9)	8.7 (3.1)	6.5 (3.0) any acute
	Amitriptyline 100 mg/day	169	37.9 (11.3)	0	NR	7.1 (2.6)	8.4 (2.9)	6.1 (3.1) any acute
Dogan, 2015 [177]	Propranolol 80 mg/day	26	32.0 (11.8)	0	NR	NR	NR	NR
	Topiramate 50 mg/day	25	34.2 (8.7)	0	NR	NR	NR	NR
Duman, 2015 [176]	Total	108	34.2 (9.3)	0	5.9 (3.9)	NR	NR	NR
	Amitriptyline		NR	0	NR	NR	NR	NR
	Propranolol		NR	0	NR	NR	NR	NR

Study/Phase	Arm	N	Mean Age (SD) or [range]	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Mean Migraine Days per Month (SD) or [range]	Mean Headache Days per Month (SD)	Mean Days of Acute Medication Use per Month (SD)
Keskinbora, 2008 [178]	Topiramate 200 mg/day	24	35.25 (9.39)	0	NR	NR	NR	NR
	Amitriptyline 150 mg/day	28	37.86 (8.67)	0	NR	NR	NR	NR
	Topiramate 200 mg/day + amitriptyline 150 mg/day	23	39.14 (9.13)	0	NR	NR	NR	NR
Mathew, 1981 [179]	Propranolol 160 mg/day	44	35 (NR)	NR	NR	NR	NR	NR
	Amitriptyline 75 mg/day	42	36 (NR)	NR	NR	NR	NR	NR
	Amitriptyline 75 mg/day + propranolol 160 mg/day	41	31 (NR)	NR	NR	NR	NR	NR
	Placebo	45	32 (NR)	NR	NR	NR	NR	NR

NR: not reported; SD: standard deviation

Table D5. Study Designs of the Studies on CGRP Inhibitors and the Commonly Used Preventive Treatments in Chronic Migraine

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Erenumab									
Tepper, 2017 [90]	Multicenter	North America, Europe	Industry	4	12	24	≥15 headache days per month, of which ≥8 are migraine days	Previously failed >3 preventive medications	Not allowed
Fremanezumab									
Bigal, 2015a [26]	Multicenter	US	Industry	4	12	12	ICHD-III beta	Previously failed >2 medication categories or >3 preventive medications	Allowed
Silberstein, 2017 HALO-CM[28]	Multicenter	Global	Industry	4	12	12	ICHD-III beta	Previously failed >2 preventive medication categories	Allowed
Onabotulinum toxin A									
Aurora, 2010 PREEMPT 1[34]	Multicenter	North America	Industry	4	24	56	ICHD-II	NA	Not allowed
Diener, 2010 PREEMPT 2[35]	Multicenter	North America, Europe	Industry	4	24	56	ICHD-II	NA	Not allowed
Cady, 2014 [38]	Multicenter	US	Industry	NR	16	28	ICHD-II	NA	Allowed

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Freitag, 2008 [36]	Unclear	US	Industry	4	16	16	ICHD-I	NA	Allowed
Sandrini, 2011 [37]	Multicenter	Italy	Industry	4	12	24	ICHD-II	NA	Not allowed
Topiramate									
Silberstein, 2007 [32]	Multicenter	US	Industry	4	16	18	≥15 headache days per month, of which ≥8 are migraine days	Previously failed >2 preventive medications or failed topiramate	Not allowed
Diener, 2007 [33]	Multicenter	Europe	Industry	4	16	23	ICHD-II	NA	Allowed
Mei, 2006 [139]	Unclear	Italy	NR	4	12	12	ICHD-II	NA	Not allowed
Silvestrini, 2003 [142]	Single center	Italy	NR	8	9	9	Not specified	Previously <4 preventive medications	Not allowed
Head-to-head									
Cady, 2011 [39]	Multicenter	US	NR	4	12	24	ICHD-II	NA	Allowed

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Magalhães, 2010 [138]	Single center	Brazil	Government/ nonprofit	4	12	12	ICHD-II	NA	Not allowed
Mathew, 2009 [137]	Single center	US	Industry	4	36	38	Not specified	NA	Not allowed
Silberstein, 2012 [143]	Multicenter	US	Government/ nonprofit	4	24	28	ICHD-II	NA	Not allowed

ICHD: The International Classification of Headache Disorders; NR: not reported, N/A: not applicable

Table D6. Study Designs of the Studies on CGRP Inhibitors and the Commonly Used Preventive Treatments in Episodic Migraine

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Erenumab									
Sun, 2016 [40]	Multicenter	North America, Europe	Industry	4	12	280	ICHD-II	Previously failed >2 preventive medication categories	Not allowed
Goadsby, 2017 STRIVE[41]	Multicenter	North America, Europe	Industry	4	24	64	ICHD-III beta	Previously failed >2 preventive medication categories	Allowed
Dodick, 2018 ARISE[42]	Multicenter	North America, Europe	Industry	4	12	40	ICHD-III beta	Previously failed >2 preventive medication categories	Allowed
Fremanezumab									
Bigal, 2015b [25]	Multicenter	US	Industry	4	12	12	ICHD-III beta	Previously failed > 2 medication categories or > 3 preventive medication	Allowed
Dodick, 2018 HALO-EM[43]	Multicenter	Global	Industry	4	12	12	ICHD-III beta	Previously failed ≥2 preventive medication categories	Allowed

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Galcanezumab									
Dodick, 2014 [27]	Multicenter	US	Industry	4-5	12	24	ICHD-II	Previously failed >2 preventive medications	Not allowed
Skljarevski, 2018 [44]	Multicenter	US	Industry	4-5	12	24	4 to 14 migraine headache days	Previously failed >2 preventive medications	Not allowed
Stauffer, 2018 EVOLVE-1[45]	Multicenter	North America	Industry	4-6	24	40	ICHD-III beta	Previously failed ≥3 classes of migraine preventive treatments	Not allowed
Skljarevski, 2018 EVOLVE-2[46]	Multicenter	Global	Industry	4-6	24	40	ICHD-III beta	Previously failed ≥3 classes of migraine preventive treatments	Not allowed
Amitriptyline									
Couch, 1979 [164]	Single center	US	NR	4	4	12	Not specified	NA	NR
Couch, 2011 [165]	Unclear	US	Industry	4	16	20	≥2 moderate or worse migraine headaches per month	NA	Not allowed
Lampl, 2009 [166]	Multicenter	NR	NR	NR	16	24	ICHD-II	NA	Allowed
Gonçalves, 2016 [47]	Multicenter	Brazil	Government/ nonprofit/academic	4	12	12	ICHD-III beta	NA	Not allowed
Propranolol									

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Diener, 1996 [48]	Multicenter	NR	NR	4	14	16	ICHD-I	NA	Not allowed
Jafarpour, 2016 [167]	Single center	Iran	NR	NR	4	4	ICHD-II	NA	Not allowed
Pradalier, 1989 [168]	Multicenter	NR	NR	4	12	12	ICHD-I	Previously failed ≥2 preventive medication categories	Not allowed
Sargent, 1985 [169]	Unclear	NR	NR	NR	14	17	Average of 12 migraine headache days over at least six migraine attacks	NA	Not allowed
Weber, 1972 [170]	Unclear	US	Industry provided supplies	NR	12	24	NIH Ad Hoc Committee on Classification of Headache, 1962	NA	Not allowed
Topiramate									
Lipton, 2011 [49]	Multicenter	US	Industry	4	26	26	ICHD-II	Previously failed >2 preventive medication categories	Not allowed
Brandes, 2004 [50]	Multicenter	US	Industry	4	26	33	ICHD-I	Previously failed >2 preventive medications	Allowed

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Silberstein, 2004 [51]	Multicenter	US	Industry	4	26	26	ICHD-I	Previously failed >2 preventive medications	Not allowed
Gode, 2010 [171]	Single center	Turkey	NR	4	24	24	ICHD-II	NA	Not allowed
Lo, 2010 [172]	Single center	Singapore	Industry	4	12	12	ICHD-II	NA	Not allowed
Mei, 2004 [52]	Single center	Italy	NR	4	16	16	ICHD-I	NA	Not allowed
Silberstein, 2006 [53]	Multicenter	US	Industry	4	20	20	ICHD-I	NA	Not allowed
Storey, 2001 [54]	Single center	US	Industry	4	16	16	ICHD-I	NA	Allowed
Head-to-Head									
Diener, 2004 [55]	Multicenter	Global	Industry	4	26	52	ICHD-I	Previously failed >2 preventive medications	Not allowed
Ashtari, 2008 [175]	Single center	Iran	NR	NR	8	8	ICHD-II	NA	Not allowed
Dodick, 2009 [56]	Multicenter	US	Industry	4	26	26	ICHD-I	Previously failed >2 preventive medications	Not allowed
Dogan, 2015 [177]	Single center	Turkey	NR	NR	4	4	ICHD-II	NA	Not allowed
Duman, 2015 [176]	Single center	Turkey	NR	4	12	12	ICHD-II	N/A	Not allowed

Study	Number of Centers	Location of Sites	Funding	Baseline (Weeks)	Intervention (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria Regarding Migraine History	Exclusion Criteria Regarding Prior Failures	Ongoing Preventive Therapy
Keskinbora, 2008 [178]	Single center	Turkey	NR	NR	12	12	ICHD-I	NA	Not allowed
Mathew, 1981 [179]	Unclear	US	NR	4	24	24	Not specified	NA	NR

ICHD: The International Classification of Headache Disorders; NR: not reported, N/A: not applicable

Table D7. Quality Ratings for CGRP Inhibitor and Comparator RCTs in Chronic Migraine

Study	Comparable Groups	Non-Differential Follow-up	Patient/Physician Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Approach to Missing Data	USPSTF Rating
CGRP Inhibitors							
Tepper, 2017 [90]	Yes	Yes	Yes	Yes	Yes	No Imputation	Good
Bigal, 2015a [26]	Yes	Yes	Yes	Yes	Yes	Single Imputation	Good
Silberstein, 2017 HALO-CM[28]	Yes	Yes	Yes	Yes	Yes	No Imputation	Good
Onabotulinum Toxin A							
Aurora, 2010 PREEMPT 1[34]	Yes	Yes	Yes	Yes	Yes	Single Imputation	Good
Diener, 2010 PREEMPT 2[35]	Yes	Yes	Yes	Yes	Yes	Single Imputation	Good
Cady, 2014 [38]	No Data	No Data	Yes	Yes	Yes	No Data	Poor
Freitag, 2008 [36]	No Data	Yes	Yes	Yes	No	LOCF	Poor
Sandrini, 2011 [37]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Topiramate							
Silberstein, 2007 [32]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Diener, 2007 [33]	No	No	Yes	Yes	No	LOCF	Poor
Mei, 2006 [139]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Silvestrini, 2003 [142]	Yes	Yes	No Data	Yes	No	No Data	Poor
Head-to Head							
Cady, 2011 [39]	Yes	Yes	Yes	Yes	No	No Imputation	Poor
Magalhães, 2010 [138]	Yes	No Data	No	Yes	Yes	No Data	Poor
Mathew, 2009 [137]	No	Yes	Yes	Yes	Yes	LOCF	Fair
Silberstein, 2012 [143]	Yes	No	Yes	Yes	Yes	Multiple Imputation	Fair

LOCF: last observation carried forward; USPSTF: United States Preventive Services Task Force

Table D8. Quality Ratings for CGRP Inhibitor and Comparator RCTs in Episodic Migraine

Study	Comparable Groups	Non-Differential Follow-up	Patient/Physician Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Approach to Missing Data	USPSTF Rating
CGRP Inhibitors							
Sun, 2016 [40]	Yes	Yes	Yes	Yes	Yes	LOCF and Multiple Imputation	Good
Goadsby, 2017 STRIVE[41]	Yes	Yes	Yes	Yes	Yes	Non-responder and Multiple Imputation	Good
Dodick, 2018 ARISE[42]	Yes	Yes	Yes	Yes	Yes	Non-responder	Good
Bigal, 2015b [25]	Yes	Yes	Yes	Yes	Yes	Single Imputation	Good
Dodick, 2018 HALO-EM[43]	Yes	Yes	Yes	Yes	Yes	Single and Multiple Imputation	Good
Dodick, 2014 [27]	Yes	Yes	Yes	Yes	Yes	No Imputation	Good
Skljarevski, 2018 [44]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Stauffer, 2018 EVOLVE-1[45]	Yes	Yes	Yes	Yes	Yes	No imputation	Good
Skljarevski, 2018 EVOLVE-2[46].	Yes	Yes	Yes	Yes	Yes	No imputation	Good
Amitriptyline							
Couch, 1979 [164]	No Data	Yes	Yes	Yes	No	No Data	Poor
Couch, 2011 [165]	No Data	Yes	Yes	Yes	Yes	No Imputation	Fair
Lampl, 2009 [166]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Gonçalves, 2016 [47]	Yes	Yes	Yes	Yes	Yes	Single Imputation	Good
Propranolol							
Diener, 1996 [48]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Jafarpour, 2016 [167]	No	No	Yes	Yes	Yes	No Data	Poor

Study	Comparable Groups	Non-Differential Follow-up	Patient/Physician Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Approach to Missing Data	USPSTF Rating
Pradalier, 1989 [168]	No Data	Yes	Yes	Yes	Yes	No Data	Fair
Sargent, 1985 [169]	No Data	No Data	Yes	Yes	Yes	No Data	Poor
Weber, 1972 [170]	No Data	No Data	Yes	Yes	No	No Data	Poor
Topiramate							
Lipton, 2011 [49]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Brandes, 2004 [50]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Silberstein, 2004 [51]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Gode, 2010 [171]	No Data	No	No Data	Yes	No	No Data	Poor
Lo, 2010 [172]	No Data	No Data	No Data	Yes	No	No Data	Poor
Mei, 2004 [52]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Silberstein, 2006 [53]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Storey, 2001 [54]	No	Yes	Yes	Yes	Yes	No Data	Fair
Head-to-Head							
Diener, 2004 [55]	Yes	No	Yes	Yes	Yes	No Imputation	Fair
Ashtari, 2008 [175]	Yes	Yes	Yes	Yes	No	No Data	Poor
Dodick, 2009 [56]	Yes	Yes	Yes	Yes	No	LOCF	Poor
Dogan, 2015 [177]	Yes	Yes	Yes	Yes	Yes	No Data	Fair
Duman, 2015 [176]	Yes	No Data	No Data	No	No	No Data	Poor
Keskinbora, 2008 [178]	Yes	Yes	Yes	Yes	Yes	No Data	Fair

Study	Comparable Groups	Non-Differential Follow-up	Patient/Physician Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Approach to Missing Data	USPSTF Rating
Mathew, 1981 [179]	No Data	Yes	No Data	Yes	No	No Data	Poor

LOCF: last observation carried forward; USPSTF: United States Preventive Services Task Force

Table D9. Migraine-Related Outcomes from the RCTs on CGRP Inhibitors and Commonly Used Preventive Treatments in Chronic Migraine

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
Tepper, 2017 [90]	4	Erenumab 70 mg/month	-5.03 (SE: 0.42)	NR	-3.1 (SE: 0.3)¤	45/188 (24%)
		Erenumab 140 mg/month	-5.1 (SE: 0.42)	NR	-3.5 (SE: 0.3)¤	53/187 (28%)
		Placebo	-2.67 (SE: 0.34)	NR	-1.3 (SE: 0.2)¤	32/281 (11%)
	8	Erenumab 70 mg/month	-6.21 (SE: 0.42)	NR	-3.4 (SE: 0.3)¤	73/188 (39%)
		Erenumab 140 mg/month	-6.45 (SE: 0.42)	NR	-4.2 (SE: 0.3)¤	75/187 (40%)
		Placebo	-3.56 (SE: 0.35)	NR	-1.5 (SE: 0.2)¤	53/281 (19%)
	12	Erenumab 70 mg/month	-6.6 (SE: 0.4)	NR	-3.5 (SE: 0.3)¤	75/188 (40%)
		Erenumab 140 mg/month	-6.6 (SE: 0.4)	NR	-4.1 (SE: 0.3)¤	77/187 (41%)
		Placebo	-4.2 (SE: 0.4)	NR	-1.6 (SE: 0.2)¤	66/281 (23%)
Bigal, 2015a [26]	4	Fremanezumab 675/225 mg/month	-2.07 (95%CI: -3.7, -0.5)‡	-2.13 (95%CI -3.8, -0.5)‡	-1.99 (95%CI: -3.6, -0.4)‡	36/87 (41%)**
		Fremanezumab 900 mg/month	-2.99 (95%CI: -4.6, -1.4)‡	-2.99 (95%CI -4.7, -1.3)‡	-2.15 (95%CI: -3.8, -0.5)‡	47/85 (55%)**
		Placebo	–	–	–	22/89 (25%)**
	8	Fremanezumab 675/225 mg/month	-1.64 (95%CI: -3.4, 0.13)‡	-1.31 (95%CI -3.1, 0.5)‡	-2.16 (95%CI: -3.9 , -0.5)‡	42/87 (48%)**
		Fremanezumab 900 mg/month	-1.73 (95%CI: -3.49, 0.03)‡	-2.03 (95%CI -3.8, -0.3)‡	-1.39 (95%CI: -3.1 , -0.3)‡	47/85 (55%)**
		Placebo	–	–	–	35/89 (39%)**
	12	Fremanezumab 675/225 mg/month	-1.72 (95%CI: -3.7, 0.2)‡	-1.74 (95%CI -3.6, 0.1)‡	-2.15 (95%CI: -4.0, 0.3)‡	46/87 (53%)**
		Fremanezumab 900 mg/month	-2.00 (95%CI: -3.9, -0.1)‡	-2.74 (95%CI -4.6, -0.9)‡	-2.04 (95%CI: -3.9, -0.2)‡	47/85 (55%)**
		Placebo	–	–	–	28/89 (31%)**
HALO-CM[28,145-147]	4	Fremanezumab 675 mg/3 months	-4.80 (SE: 0.32)	-4.67 (SE: 0.39)	-3.9 (SE: 0.31)	NR
		Fremanezumab 675/225 mg/month	-4.73 (SE: 0.27)	-4.61 (SE: 0.26)	-4.1 (SE: 0.31)	NR
		Placebo	-2.67 (SE: 0.33)	-2.50 (SE: 0.28)	-1.6 (SE: 0.31)	NR
	8	Fremanezumab 675 mg/3 months	-4.87 (SE: 0.31)	-4.93 (SE: 0.41)	-3.59 (SE: 0.30)	NR

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
		Fremanezumab 675/225 mg/month	-5.27 (SE: 0.30)	-5.27 (SE: 0.39)	-4.30 (SE: 0.34)	NR
		Placebo	-3.33 (SE: 0.41)	-3.12 (SE: 0.32)	-1.99 (SE: 0.36)	NR
	12	Fremanezumab 675 mg/3 months	-5.08 (SE: 0.35)	-4.80 (SE: 0.38)	-3.71 (SE: 0.38)	NR
		Fremanezumab 675/225 mg/month	-5.43 (SE: 0.30)	-5.21 (SE: 0.40)	-4.49 (SE: 0.35)	NR
		Placebo	-3.80 (SE: 0.4)	-3.31 (SE: 0.36)	-2.31 (SE: 0.33)	NR
	12*	Fremanezumab 675 mg/3 months	-4.9 (SE: 0.4)	-4.8 (SE: 0.41)	-3.7 (SE: 0.3)	115/375 (30.7%)
		Fremanezumab 675/225 mg/month	-5.0 (SE: 0.4)	-5.0 (SE: 0.39)	-4.2 (SE: 0.3)	125/375 (33.3%)
		Placebo	-3.2 (SE: 0.4)	-2.9 (SE: 0.33)	-1.9 (SE: 0.3)	74/371 (19.9%)
Detke, 2017 REGAIN[134]†	12*	Galcanezumab 120 mg/month	-4.83 (NR)§	NR	NR	NR
		Galcanezumab 240 mg/month	-4.62 (NR)§	NR	NR	NR
		Placebo	-2.74 (NR)§	NR	NR	NR
Aurora, 2010 PREEMPT 1[34]	4	Onabotulinum toxin A 155U	NR	-4.94 (SE: 0.35)	NR	NR
		Placebo	NR	-3.78 (SE: 0.31)	NR	NR
	8	Onabotulinum toxin A 155U	NR	-6.64 (SE: 0.31)	NR	NR
		Placebo	NR	-5.67 (SE: 0.33)	NR	NR
	12	Onabotulinum toxin A 155U	NR	-6.92 (SE: 0.34)	NR	NR
		Placebo	NR	-5.99 (SE: 0.38)	NR	NR
	16	Onabotulinum toxin A 155U	NR	-7.05 (SE: 0.38)	NR	NR
		Placebo	NR	-6.17 (SE: 0.35)	NR	NR
	20	Onabotulinum toxin A 155U	NR	-7.97 (SE: 0.41)	NR	NR
		Placebo	NR	-6.57 (SE: 0.43)	NR	NR
	24	Onabotulinum toxin A 155U	-7.6 (NR)	-7.8 (SE: 0.33)	NR	NR
		Placebo	-6.1 (NR)	-6.4 (SE: 0.43)	NR	NR
Diener, 2010 PREEMPT 2[35]	4	Onabotulinum toxin A 155U	NR	-5.46 (SE: 0.33)	NR	NR
		Placebo	NR	-4.17 (SE: 0.32)	NR	NR
	8	Onabotulinum toxin A 155U	NR	-7.5 (SE: 0.36)	NR	NR

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
		Placebo	NR	-5.18 (SE: 0.29)	NR	NR
	12	Onabotulinum toxin A 155U	NR	-7.41 (SE: 0.3)	NR	NR
		Placebo	NR	-5.81 (SE: 0.34)	NR	NR
	16	Onabotulinum toxin A 155U	NR	-8.3 (SE: 0.31)	NR	NR
		Placebo	NR	-6.59 (SE: 0.28)	NR	NR
	20	Onabotulinum toxin A 155U	NR	-9.06 (SE: 0.33)	NR	NR
		Placebo	NR	-6.86 (SE: 0.33)	NR	NR
	24	Onabotulinum toxin A 155U	-8.7 (NR)	-9.0 (SE: 0.18)	NR	NR
		Placebo	-6.3 (NR)	-6.7 (SE: 0.18)	NR	NR
Sandrini, 2011 [37]	12	Onabotulinum toxin A 100U	NR	NR	NR	19/27 (70.3%)††
		Placebo	NR	NR	NR	9/29 (31%)††
	12*	Onabotulinum toxin A 100U	NR	NR	NR	14/27 (51.8%)††
		Placebo	NR	NR	NR	7/29 (24.2%)††
Silberstein, 2007 [32,141]	16	Topiramate 100 mg/day	-6.4 (SD: 5.8)	-5.8 (SD: 5.6)	-4.4 (SD: 5.8)	57/153 (37.3%)
		Placebo	-4.7 (SD: 6.1)	-4.7 (SD: 5.6)	-3.4 (SD: 5.3)	44/153 (28.8%)
Diener, 2007 [33]	16	Topiramate 100 mg/day	-3.5 (SD: 6.3)§	NR	-3.0 (SD: 5.9)	9/32 (29%)‡‡
		Placebo	0.2 (SD: 4.7)§	NR	-0.7 (SD: 6.2)	0/27 (0%)‡‡
Silvestrini, 2003 [142]	4	Topiramate 50 mg/day	NR	NR	NR	4/14 (28%)††
		Placebo	NR	NR	NR	0/14 (0%)††
	8	Topiramate 50 mg/day	NR	NR	NR	10/14 (71%)††
		Placebo	NR	NR	NR	1/14 (7%)††
Mathew, 2009 [137]	12	Onabotulinum toxin A 200 U	NR	NR	NR	10/26 (38.5%)††
		Topiramate 100 mg/day	NR	NR	NR	5/22 (22.7%)††
	24	Onabotulinum toxin A 200 U	NR	NR	NR	14/24 (58.3%)††

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
		Topiramate 100 mg/day	NR	NR	NR	7/22 (31.8%)††
	36	Onabotulinum toxin A 200 U	NR	NR	NR	9/22 (40.9%)††
		Topiramate 100 mg/day	NR	NR	NR	9/21 (42.9%)††
Cady, 2011 [39]	4	Onabotulinum toxin A 200 U	NR	-3.0 (NR)	NR	NR
		Topiramate 200 mg/day	NR	-4.4 (NR)	NR	NR
	12	Onabotulinum toxin A 200 U	NR	-8.0 (NR)	NR	NR
		Topiramate 200 mg/day	NR	-8.1 (NR)	NR	NR
Silberstein, 2012 [143]	12	Topiramate 100 mg/day + Propranolol 240 mg/day	NR	-4.0 (95%CI: -5.5, -2.6)	NR	23/86 (26.7%)**
		Topiramate 100 mg/day	NR	-3.2 (95%CI: -4.6, -1.9)	NR	22/87 (25.3%)**
	24	Topiramate 100 mg/day + Propranolol 240 mg/day	NR	-6.2 (95%CI: -7.9, -4.5)	NR	26/84 (31%)**
		Topiramate 100 mg/day	NR	-6.1 (95%CI: -7.8, -4.4)	NR	23/82 (28%)**

*Outcomes measured over 1-12 weeks; †Data only available in conference abstracts; ‡Difference versus placebo; §Change from baseline in migraine days only; ¤ Change from baseline in migraine-specific acute medication only; **50% reduction in headache days of at least moderate severity; ††50% reduction in headache days; ‡‡50% reduction in migraine days only

95%CI: 95% confidence interval; NR: not reported; SD: standard deviation; SE: standard error

Table D10. Migraine-Related Outcomes from the RCTs on CGRP Inhibitors and Commonly Used Preventive Treatments in Episodic Migraine

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
Sun, 2016 [40]	4	Erenumab 7 mg/month	-1.27 (SE: 0.35)	NR	NR	NR
		Erenumab 21 mg/month	-1.56 (SE: 0.38)	NR	NR	NR
		Erenumab 70 mg/month	-2.59 (SE: 0.37)	NR	NR	39/103 (38%)
		Placebo	-1.63 (SE: 0.29)	NR	NR	34/151 (23%)
	8	Erenumab 7 mg/month	-1.33 (SE: 0.35)	NR	NR	NR
		Erenumab 21 mg/month	-2.65 (SE: 0.37)	NR	NR	NR
		Erenumab 70 mg/month	-3.31 (SE: 0.36)	NR	NR	47/103 (46%)
		Placebo	-2.29 (SE: 0.31)	NR	NR	48/144 (33%)
	12	Erenumab 7 mg/month	-2.2 (SE: 0.4)	-2.2 (SE: 0.4)	NR	30/104 (29%)
		Erenumab 21 mg/month	-2.4 (SE: 0.4)	-2.5 (SE: 0.4)	NR	32/93 (34%)
		Erenumab 70 mg/month	-3.4 (SE: 0.4)	-3.5 (SE: 0.4)	-2.5 (SE: 0.3)	46/99 (46%)
		Placebo	-2.3 (SE: 0.3)	-2.4 (SE: 0.3)	-1.4 (SE: 0.3)	43/144 (30%)
STRIVE[41,155]	13-24	Erenumab 70 mg/month	-3.2 (SE: 0.2)	NR	-2.5 (NR)	135/312 (43.3%)
		Erenumab 140 mg/month	-3.7 (SE: 0.2)	NR	-2.9 (NR)	159/318 (50%)
		Placebo	-1.8 (SE: 0.2)	NR	-1.4 (NR)	84/316 (26.6%)
	4	Erenumab 70 mg/month	-2.32 (95%CI: -2.73, -1.92)	NR	-1.66 (95%CI: -2.01, -1.33)	102/312 (32.7%)
		Erenumab 140 mg/month	-2.72 (95%CI: -3.12, -2.32)	NR	-2.25 (95%CI: -2.53, -1.90)	113/318 (35.5%)
		Placebo	-0.90 (95%CI: -1.30, -0.50)	NR	-0.6 (95%CI: -0.973, -0.283)	49/316 (15.5%)
	8	Erenumab 70 mg/month	-2.93 (95%CI: -3.34, -2.52)	NR	-2.11 (95%CI: -2.43, -1.80)	124/312 (39.7%)
		Erenumab 140 mg/month	-3.10 (95%CI: -3.50, -2.70)	NR	-2.52 (95%CI: -2.83, -2.22)	143/318 (45%)
		Placebo	-1.39 (95%CI: -1.80, -0.99)	NR	-1.11 (95%CI: -1.46 , 0.790)	77/316 (24.4%)
	12	Erenumab 70 mg/month	-2.97	NR	-2.11	129/312 (41.3%)

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
			(95%CI: -3.38, -2.56)		(95%CI: -2.45, -1.76)	
		Erenumab 140 mg/month	-3.50 (95%CI: -3.91, -3.10)	NR	-2.71 (95%CI: -3.02, -2.35)	153/318 (48.1%)
		Placebo	-1.71 (95%CI: -2.12, -1.30)	NR	-1.22 (95%CI: -1.58, -0.862)	83/316 (26.3%)
	16	Erenumab 70 mg/month	-3.09 (95%CI: -3.50, -2.67)	NR	-2.33 (95%CI: -2.66, -1.98)	128/312 (41%)
		Erenumab 140 mg/month	-3.52 (95%CI: -3.93, -3.11)	NR	-2.84 (95%CI: -3.14, -2.47)	158/318 (49.7%)
		Placebo	-1.94 (95%CI: -2.35, -1.52)	NR	-1.36 (95%CI: -1.71, -1.01)	91/316 (28.8%)
	20	Erenumab 70 mg/month	-3.34 (95%CI: -3.75, -2.93)	NR	-2.48 (95%CI: -2.84, -2.15)	147/312 (47.1%)
		Erenumab 140 mg/month	-3.74 (95%CI: -4.15, -3.33)	NR	-2.94 (95%CI: -3.29, -2.63)	153/318 (48.1%)
		Placebo	-1.88 (95%CI: -2.29, -1.46)	NR	-1.55 (95%CI: -1.91, -1.19)	92/316 (29.1%)
	24	Erenumab 70 mg/month	-3.26 (95%CI: -3.67, -2.84)	NR	-2.42 (95%CI: -2.81, 2.10)	147/312 (47.1%)
		Erenumab 140 mg/month	-3.76 (95%CI: -4.17, -3.35)	NR	-2.99 (95%CI: -3.30, -2.62)	156/318 (49.1%)
		Placebo	-1.67 (95%CI: -2.08, -1.25)	NR	-1.19 (95%CI: -1.53, -0.825)	93/316 (29.4%)
Dodick, 2018 ARISE[42]	4	Erenumab 70 mg/month	-1.99 (95%CI: -2.41, -1.59)	NR	-0.890 (95%CI:-1.15, -0.626) §	76/282 (27%)
		Placebo	-0.959 (95%CI: -1.37, -0.567)	NR	-0.417 (95%CI: -0.690, -0.166) §	47/288 (16.3%)
	8	Erenumab 70 mg/month	-2.64 (95%CI: -3.06, -2.23)	NR	-1.07 (95%CI: -1.34, -0.809) §	101/282 (35.8%)
		Placebo	-1.8 (95%CI: -2.19, -1.40)	NR	-0.502 (95%CI: -0.766, -0.243) §	77/288 (26.7%)

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
	12	Erenumab 70 mg/month	-2.9 (SE: 0.2)	NR	-1.2 (SE: 0.1) §	112/282 (39.7%)
		Placebo	-1.8 (SE: 0.2)	NR	-0.6 (SE: 0.1) §	85/288 (29.5%)
Bigal, 2015b [25]	4	Fremanezumab 225 mg/month	-4.27 (SD: 5.23)	-3.80 (SD: 5.09)	NR	42/95 (44%)
		Fremanezumab 675 mg/month	-4.57 (SD: 5.11)	-3.71 (SD: 4.96)	NR	50/96 (52%)
		Placebo	-2.14 (SD: 5.33)	-1.66 (SD: 5.19)	NR	20/104 (19%)
	8	Fremanezumab 225 mg/month	-5.38 (SD: 5.45)	-5.27 (SD: 5.34)	NR	52/95 (55%)
		Fremanezumab 675 mg/month	-5.55 (SD: 5.32)	-5.04 (SD: 5.19)	NR	53/96 (55%)
		Placebo	-2.89 (SD: 5.50)	-2.65 (SD: 5.38)	NR	36/104 (35%)
	12	Fremanezumab 225 mg/month	-6.27 (SD: 5.38)	-6.14 (SD: 5.42)	-4.86 (SD: 4.64)	53/95 (56%)
		Fremanezumab 675 mg/month	-6.09 (SD: 5.22)	-6.10 (SD: 5.26)	-4.80 (SD: 4.50)	55/96 (57%)
		Placebo	-3.46 (SD: 5.40)	-3.52 (SD: 5.43)	-3.10 (SD: 4.64)	36/104 (35%)
	12*	Fremanezumab 225 mg/month	NR	NR	NR	45/85 (53%)
		Fremanezumab 675 mg/month	NR	NR	NR	52/88 (59%)
		Placebo	NR	NR	NR	28/100 (28%)
HALO-EM[43,158,159]	4	Fremanezumab 225 mg/month	-3.3 (95%CI: -3.80, -2.74)	-2.70 (SE: 0.19)	-2.9 (SE: 0.24)	135/287 (47.1%)
		Fremanezumab 675 mg/3 months	-3.00 (95%CI: -3.55, -2.48)	-2.82 (SE: 0.23)	-2.8 (SE: 0.24)	127/288 (44.2%)
		Placebo	-1.4 (95%CI: -1.97, -0.92)	-0.934 (SE: 0.23)	-1.1 (SE: 0.24)	72/290 (24.8%)
	8	Fremanezumab 225 mg/month	-3.80 (95%CI: -4.34, -3.28)	-3.13 (SE: 0.21)	-3.09 (SE: 0.22)	132/274 (48.3%)
		Fremanezumab 675 mg/3 months	-3.59 (95%CI: -4.13, -3.08)	-3.25 (SE: 0.19)	-2.97 (SE: 0.21)	128/274 (46.6%)
		Placebo	-2.51 (95%CI: -3.08, -2.01)	-1.71 (SE: 0.19)	-1.77 (SE: 0.2)	95/274 (34.8%)
	12	Fremanezumab 225 mg/month	-3.88 (95%CI: -4.45, -3.35)	-3.15 (SE: 0.20)	-2.99 (SE: 0.24)	134/263 (51.1%)
		Fremanezumab 675 mg/3 months	-3.69 (95%CI: -4.29, -3.21)	-3.00 (SE: 0.20)	-3.0 (SE: 0.22)	131/269 (48.7%)

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
		Placebo	-2.70 (95%CI: -3.24, -2.20)	-1.95 (SE: 0.28)	-1.99 (SE: 0.25)	99/268 (36.9%)
	12*	Fremanezumab 225 mg/month	-3.7 (95%CI: -4.14, -3.19)	-2.9 (SE: 0.24)	-3.0 (95%CI: -3.43, -2.58)	137/287 (47.7%)
		Fremanezumab 675 mg/3 months	-3.5 (95%CI: -3.93, -2.97)	-3.0 (SE: 0.24)	-2.9 (95%CI: -3.35, -2.49)	128/288 (44.4%)
		Placebo	-2.2 (95%CI: -2.71, -1.77)	-1.5 (SE: 0.23)	-1.7 (95%CI: -2.09, -1.24)	81/290 (27.9%)
Dodick, 2014 [27]	4	Galcanezumab 150 mg/2 weeks	-4.3 (90%CI: -4.79, -3.79) ‡	-4.3 (90%CI: -4.81, -3.72)	NR	NR
		Placebo	-2.5 (90%CI: -3.00, -1.98) ‡	-2.3 (90%CI: -2.89, -1.81)	NR	NR
	8	Galcanezumab 150 mg/2 weeks	-4.7 (90%CI: -5.29, -3.98) ‡	-4.6 (90%CI: -5.20 -3.29)	NR	NR
		Placebo	-3.5 (90%CI: -4.18, -2.88) ‡	-3.7 (90%CI: -4.42, -3.01)	NR	NR
	12	Galcanezumab 150 mg/2 weeks	-4.8 (SD: 4.1) ‡	-4.9 (SD: 4.1)	NR	69/98 (70%)#
		Placebo	-3.5 (SD: 4.2) ‡	-3.7 (SD: 4.2)	NR	47/104 (45%)#
Skljarevski, 2018 [44]	4	Galcanezumab 5 mg/month	-3.8 (SE: 0.32) ‡	NR	NR	NR
		Galcanezumab 50 mg/month	-4.0 (SE: 0.32) ‡	NR	NR	NR
		Galcanezumab 120 mg/month	-3.76 (SE: 0.35) ‡	NR	NR	NR
		Galcanezumab 300 mg/month	-4.2 (SE: 0.35) ‡	NR	NR	NR
		Placebo	-3.0 (SE: 0.24) ‡	NR	NR	NR
	8	Galcanezumab 5 mg/month	-3.73 (SE: 0.37) ‡	NR	NR	NR
		Galcanezumab 50 mg/month	-4.16 (SE: 0.34) ‡	NR	NR	NR
		Galcanezumab 120 mg/month	-4.19 (SE: 0.41) ‡	NR	NR	NR
		Galcanezumab 300 mg/month	-4.5 (SE: 0.33) ‡	NR	NR	NR
		Placebo	-3.6 (SE: 0.29) ‡	NR	NR	NR
	12	Galcanezumab 5 mg/month	NR	NR	NR	NR
		Galcanezumab 50 mg/month	NR	NR	NR	NR

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
		Galcanezumab 120 mg/month	-5.9 (NR)	NR	NR	47/62 (75.8%)#
		Galcanezumab 300 mg/month	NR	NR	NR	NR
		Placebo	-4.0 (NR)	NR	NR	78/126 (61.9%)#
	12*	Placebo	-3.4 (95%CI: -3.8 -2.9) ‡	NR	NR	NR
		Galcanezumab 5 mg/month	NR	NR	NR	NR
		Galcanezumab 50 mg/month	NR	NR	NR	NR
		Galcanezumab 120 mg/month	-4.3 (95%CI: -4.9, -3.7) ‡	NR	NR	NR
		Galcanezumab 300 mg/month	-4.3 (95%CI: -4.9, -3.7) ‡	NR	NR	NR
Lampl, 2009 [166]	26	Amitriptyline 25 mg/day	NR	NR	NR	12/18 (66.7%)¤
		Amitriptyline 50 mg/day	NR	NR	NR	7/11 (63.6%)¤
Stauffer, 2018 EVOLVE-1[45]	4	Galcanezumab 120 mg/month	-3.73 (SE: 0.31)	NR	NR	NR
		Galcanezumab 240 mg/month	-3.57 (SE: 0.31)	NR	NR	NR
		Placebo	-1.65 (SE: 0.25)	NR	NR	NR
	8	Galcanezumab 120 mg/month	-4.37 (SE: 0.33)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.35 (SE: 0.33)	NR	NR	NR
		Placebo	-2.52 (SE: 0.25)	NR	NR	NR
	12	Galcanezumab 120 mg/month	-4.64 (SE: 0.35)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.43 (SE: 0.33)	NR	NR	NR
		Placebo	-2.95 (SE: 0.25)	NR	NR	NR
	16	Galcanezumab 120 mg/month	-5.09 (SE: 0.35)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.50 (SE: 0.33)	NR	NR	NR
		Placebo	-3.17 (SE: 0.26)	NR	NR	NR
	20	Galcanezumab 120 mg/month	-5.36 (SE: 0.33)	NR	NR	NR
		Galcanezumab 240 mg/month	-5.18 (SE: 0.33)	NR	NR	NR
		Placebo	-3.11 (SE: 0.29)	NR	NR	NR
	24	Galcanezumab 120 mg/month	-5.15 (SE: 0.35)	NR	NR	NR
		Galcanezumab 240 mg/month	-5.30 (SE: 0.25)	NR	NR	NR

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
		Placebo	-3.34 (SE: 0.25)	NR	NR	NR
	24*	Galcanezumab 120 mg/month	-4.7 (NR)	NR	-4.0 (NR) §	131/210 (62.3%)
		Galcanezumab 240 mg/month	-4.6 (NR)	NR	-3.8 (NR) §	127/208 (60.9%)
		Placebo	-2.8 (NR)	NR	-2.2 (NR) §	164/425 (38.6%)
Skljarevski, 2018 EVOLVE-2[46].	4	Galcanezumab 120 mg/month	-3.85 (SE: 0.25)	NR	NR	NR
		Galcanezumab 240 mg/month	-3.24 (SE: 0.30)	NR	NR	NR
		Placebo	-1.18 (SE: 0.22)	NR	NR	NR
	8	Galcanezumab 120 mg/month	-3.97 (SE: 0.31)	NR	NR	NR
		Galcanezumab 240 mg/month	-3.74 (SE: 0.26)	NR	NR	NR
		Placebo	-2.16 (SE: 0.22)	NR	NR	NR
	12	Galcanezumab 120 mg/month	-3.77 (SE: 0.25)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.47 (SE: 0.26)	NR	NR	NR
		Placebo	-2.20 (SE: 0.21)	NR	NR	NR
	16	Galcanezumab 120 mg/month	-4.46 (SE: 0.35)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.32 (SE: 0.29)	NR	NR	NR
		Placebo	-2.43 (SE: 0.23)	NR	NR	NR
	20	Galcanezumab 120 mg/month	-4.91 (SE: 0.29)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.65 (SE: 0.26)	NR	NR	NR
		Placebo	-2.86 (SE: 0.20)	NR	NR	NR
	24	Galcanezumab 120 mg/month	-4.56 (SE: 0.34)	NR	NR	NR
		Galcanezumab 240 mg/month	-4.53 (SE: 0.28)	NR	NR	NR
		Placebo	-2.84 (SE: 0.22)	NR	NR	NR
	24*	Galcanezumab 120 mg/month	-4.29 (SE: 0.3)	NR	-3.67 (SE: 0.2) §	134/226 (59.3%)
		Galcanezumab 240 mg/month	-4.18 (SE: 0.3)	NR	-3.63 (SE:0.2) §	124/220 (56.5%)
		Placebo	-2.28 (SE: 0.2)	NR	-1.85 (SE: 0.2) §	162/450 (36%)
Gonçalves, 2016 [47]	12	Amitriptyline 25 mg/day	-2.2 (NR) ‡	NR	NR	23/59 (39.1%)#
		Placebo	-1.1 (NR) ‡	NR	NR	12/59 (20.4%)#
Diener, 1996 [48]	12	Propranolol 120 mg/day	NR	NR	NR	33/78 (42%)**
		Placebo	NR	NR	NR	17/55 (31%)**

Study	Week	Arm	Change from Baseline in Mean Monthly Migraine or Probable Migraine Days	Change from Baseline in Mean Monthly Headache Days of Any Severity	Change from Baseline in Mean Monthly Acute Headache Medication Days	≥50% Reduction in Mean Monthly Migraine or Probable Migraine Days
Lipton, 2011 [49,180]	26	Topiramate 100 mg/day	-6.6 (SD: 3.5) ‡	-6.6 (SD: 3.8)	-4.8 (SD: 3.5)	105/159 (65.8%)#
		Placebo	-5.3 (SD: 3.6) ‡	-5.3 (SD: 3.6)	-3.8 (SD: 3.7)	83/171 (48.5%)#
Brandes, 2004 [50]	26	Topiramate 50 mg/day	-1.7 (NR) ‡	NR	NR	45/116 (39%)**
		Topiramate 200 mg/day	-2.9 (SE: 0.32) ‡	NR	-2.2 (SE: 0.29)	55/117 (47%)**
		Topiramate 100 mg/day	-2.6 (SE: 0.31) ‡	NR	-2.1 (SE: 0.29)	59/120 (49%)**
		Placebo	-1.3 (SE: 0.32) ‡	NR	-1.0 (SE: 0.29)	26/114 (23%)**
Silberstein, 2004 [51]	26	Topiramate 50 mg/day	NR	NR	NR	42/117 (35.9%)**
		Topiramate 200 mg/day	NR	NR	NR	59/112 (52.3%)**
		Topiramate 100 mg/day	NR	NR	NR	68/125 (54%)**
		Placebo	NR	NR	NR	26/115 (22.6%)**
Mei, 2004 [52]	16	Topiramate 100 mg/day	NR	NR	NR	22/35 (63%)**
		Placebo	NR	NR	NR	8/37 (21%)**
Silberstein, 2006 [53]	20	Topiramate 200 mg/day	NR	NR	NR	55/138 (39.9%)**
		Placebo	NR	NR	NR	25/73 (34.2%)**
Storey, 2001 [54]	16*	Topiramate 200 mg/day	NR	NR	NR	5/19 (26.3%)**
		Placebo		NR	NR	2/21 (9.5%)**
Diener, 2004 [55]	26	Topiramate 100 mg/day	-1.8 (SE: 0.25)‡	NR	-1.5 (SE: 0.21)	51/139 (37%)**
		Topiramate 200 mg/day	-1.3 (SE: 0.25) ‡	NR	-0.9 (SE: 0.21)	50/143 (35%)**
		Propranolol 160 mg/day	-1.9 (SE: 0.25) ‡	NR	-1.6 (SE: 0.21)	61/143 (43%)**
		Placebo	-1.1 (SE: 0.24) ‡	NR	-0.8 (SE: 0.20)	31/143 (22%)**
Dodick, 2009 [56]	26	Amitriptyline 100 mg/day	-3.1 (NR) ‡	-3.6 (NR)	-2.8 (NR)	73/159 (45.9%)
		Topiramate 100 mg/day	-3.2 (NR) ‡	-3.6 (NR)	-2.6 (NR)	96/172 (55.6%)

*Outcomes measured over 1-12, 1-16, or 1-24 weeks; †Data only available in conference abstracts; ‡ Change from baseline in migraine days only; §Change from baseline in migraine-specific acute medication only; #50% reduction in migraine days only; ¤50% reduction in median migraine days only; **50% reduction in migraine frequency

95%CI: 95% confidence interval; NR: not reported; SD: standard deviation; SE: standard error

Table D11. Quality of Life Outcomes from the RCTs on CGRP Inhibitors and Commonly Used Preventive Treatments in Chronic Migraine

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
Lipton, 2017 [129]	12	Erenumab 70 mg/month	NR	-5.6 (95%CI: -6.5, -4.6)	17.7 (95%CI: 14.9, 20.6)	13.0 (95%CI: 10.5, 15.6)	18.2 (95%CI: 15.0, 21.3)
		Erenumab 140 mg/month	NR	-5.6 (95%CI: -6.5, -4.6)	19.1 (95%CI: 16.3, 22.0)	13.8 (95%CI: 11.3, 16.4)	18.8 (95%CI: 15.6, 21.9)
		Placebo	NR	-3.1 (95%CI: -3.9, -2.3)	11.8 (95%CI: 9.4, 14.1)	8.9 (95%CI: 6.8, 11.0)	9.9 (95%CI: 7.3, 12.5)
HALO-CM[28,210]	4	Fremanezumab 675 mg/3 months	NR	NR	7.1 (SE: 1.4)‡	5.9 (SE: 1.1)‡	7.1 (SE: 1.5) ‡
		Fremanezumab 675/225 mg/month	NR	NR	7.4 (SE: 1.4)‡	6.3 (SE: 1.2)‡	7.4 (SE: 1.5) ‡
		Placebo	NR	NR	–	–	–
	12	Fremanezumab 675 mg/3 months	NR	-6.4 (SE: 0.5)	6.1 (SE: 1.4)‡	4.6 (SE: 1.3)‡	4.1 (SE: 1.6) ‡
		Fremanezumab 675/225 mg/month	NR	-6.8 (SE: 0.4)	6.9 (SE: 1.4)‡	4.3 (SE: 1.3)‡	3.9 (SE: 1.6) ‡
		Placebo	NR	-4.5 (SE: 0.5)	–	–	–
Freitag, 2008 [36]	16	Onabotulinum toxin A 100U	51 (NR)†	NR	NR	NR	NR
		Placebo	63 (NR)†	NR	NR	NR	NR
Aurora, 2010 PREEMPT 1[34]	24	Onabotulinum toxin A 155U	NR	-4.7 (NR)	NR	NR	NR
		Placebo	NR	-2.4 (NR)	NR	NR	NR
Diener, 2010 PREEMPT 2[35]	24	Onabotulinum toxin A 100U	NR	-4.9 (NR)	NR	NR	NR
		Placebo	NR	-2.4 (NR)	NR	NR	NR
Sandrini, 2011 [37]	4	Onabotulinum toxin A 100U	23.3 (SD: 16.5)†*	55.9 (SD: 12.9)†	NR	NR	NR

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
		Placebo	40.4 (SD: 29.0)†*	61.1 (SD: 13.2)†	NR	NR	NR
	12	Onabotulinum toxin A 100U	18.0 (SD: 13.8)†	51.3 (SD: 11.0)†	NR	NR	NR
		Placebo	33.8 (SD: 25.5)†	58.1 (SD: 10.2)†	NR	NR	NR
Dodick, 2007 [140]	4	Topiramate 100 mg/day	NR	NR	21.7 (NR)	14 (NR)	25.7 (NR)
		Placebo	NR	NR	12.7 (NR)	10.1 (NR)	15.2 (NR)
	8	Topiramate 100 mg/day	NR	NR	23.6 (NR)	15.7 (NR)	25.9 (NR)
		Placebo	NR	NR	17.4 (NR)	11.8 (NR)	19 (NR)
	12	Topiramate 100 mg/day	NR	NR	23.8 (NR)	16.9 (NR)	26.7 (NR)
		Placebo	NR	NR	19.5 (NR)	13.1 (NR)	20.5 (NR)
	16	Topiramate 100 mg/day	NR	NR	24.3 (NR)	16.9 (NR)	26.9 (NR)
		Placebo	NR	NR	18.5 (NR)	12.5 (NR)	20 (NR)
Silberstein, 2007 [141]	16	Topiramate 100 mg/day	-31.4 (SD: 53.8)	NR	23.7 (SD: 23.1)	16.1 (SD: 21.5)	26.3 (SD: 27.8)
		Placebo	-21.0 (SD: 52.2)	NR	18.8 (SD: 22.6)	12.6 (SD: 21.0)	21.0 (SD: 30.2)
Diener, 2007 [33]	16	Topiramate 100 mg/day	-26 (SD: 61)	NR	NR	NR	NR
		Placebo	3 (SD: 21)	NR	NR	NR	NR
Cady, 2011 [39]	4	Onabotulinum toxin A 200 U	NR	-4.84 (NR)	NR	NR	NR
		Topiramate 200 mg/day	NR	-5.87 (NR)	NR	NR	NR

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
	12	Onabotulinum toxin A 200 U	-38.48 (NR)	-6.29 (NR)	NR	NR	NR
		Topiramate 200 mg/day	-26.67 (NR)	-6.00 (NR)	NR	NR	NR
Mathew, 2009 [137]	12	Onabotulinum toxin A 200 U	-10.48 (SD: 24.09)	-3.46 (SD: 6.16)	NR	NR	NR
		Topiramate 100 mg/day	-33.0 (SD: 53.06)	-6.70 (SD: 5.85)	NR	NR	NR
	24	Onabotulinum toxin A 200 U	-11.34 (SD: 22.38)	-5.62 (SD: 6.41)	NR	NR	NR
		Topiramate 100 mg/day	-46.28 (SD: 75.66)	-10.44 (SD: 7.07)	NR	NR	NR
	36	Onabotulinum toxin A 200 U	NR	-3.47 (SD: 5.23)	NR	NR	NR
		Topiramate 100 mg/day	NR	-8.76 (SD: 7.44)	NR	NR	NR
Silberstein, 2012 [143]	12	Topiramate 100 mg/day + propranolol 240 mg/day	-1.98 (95%CI: -7.6, 3.6)	NR	15.0 (95%CI: 9.6, 20.4)	8.7 (95%CI: 3.9, 13.6)	7.7 (95%CI: 1.3, 14.0)
		Topiramate 100 mg/day	-3.8 (95%CI: -9.1, 1.6)	NR	10.1 (95%CI: 4.6, 15.6)	6.68 (95%CI: 1.75, 11.6)	11.9 (95%CI: 5.3, 18.5)

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
	24	Topiramate 100 mg/day + propranolol 240 mg/day	-3.18 (95%CI: -10.4, 4.1)	NR	-0.72 (95%CI:-11.5, 10.1)	NR	8.9 (95%CI: 2.2, 15.7)
		Topiramate 100 mg/day	-3.46 (95%CI: -10.9, 4.0)	NR	-2.17 (95%CI:-13.4, 9.02)	NR	9.8 (95%CI: 2.4, 17.3)

*Modified MIDAS (1-month recall); †Mean score, not change; ‡Difference versus placebo

95%CI: 95% confidence interval; HIT-6: Headache Impact Test; MIDAS: Migraine Disability Assessment; MSQ: Migraine-Specific Quality of Life Questionnaire; RFR: role function-restrictive; RFP: role function-preventive; EF: emotional function; NR: not reported; SD: standard deviation; SE: standard error

Table D12. Quality of Life Outcomes from the RCTs on CGRP Inhibitors and Commonly Used Preventive Treatments in Episodic Migraine

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
Sun, 2016 [40]	4	Erenumab 70 mg/month	NR	-1.2 (95%CI: -2.7, 0.4)*	3.8 (95%CI: -0.4, 8.0)*	1.9 (95%CI: -1.9, 5.6)*	3.4 (95%CI: -1.0, 7.7)*
		Placebo	NR	–	–	–	–
	8	Erenumab 70 mg/month	NR	-2.1 (95%CI: -3.6, -0.6)*	3.9 (95%CI: -0.4, 8.1)*	0.5 (95%CI: -3.3, 4.3)*	3.0 (95%CI: -1.3, 7.4)*
		Placebo	NR	–	–	–	–
	12	Erenumab 70 mg/month	-5.3 (95%CI: -10.9, 0.3)*	-1.0 (95%CI: -2.5, -0.6)*	1.8 (95%CI: -2.5, 6.1)*	2.8 (95%CI: -1.0, 6.5)*	1.9 (95%CI: -2.6, 6.3)*
		Placebo	–	–	–	–	–
STRIVE[156]	13-24	Erenumab 70 mg/month	-19.1 (SE: 1.5)	-6.7 (95%CI: -7.4, -6.0)	16.8 (95%CI: 15.1, 15.8)	12.7 (95%CI: 11.2, 14.2)	12.9 (95%CI: 11.2, 14.6)
		Erenumab 140 mg/month	-22.3 (SE: 1.5)	-6.9 (95%CI: -7.6, -6.3)	18.1 (95%CI: 16.5, 19.8)	13.9 (95%CI: 12.5, 15.4)	14.4 (95%CI: 12.7, 16.1)
		Placebo	-13.3 (SE: 1.6)	-4.6 (95%CI: -5.3, -4.0)	11.7 (95%CI: 10.0, 13.3)	8.5 (95%CI: 7.0, 10.0)	7.7 (95%CI: 6.0, 9.4)
	4	Erenumab 70 mg/month	-5.33 (SE: 0.5) †	-3.52 (SE: 0.4)	13.3 (SE: 1.0)	11.1 (SE: 0.9)	11.2 (SE: 1.0)
		Erenumab 140 mg/month	-6.61 (SE: 0.53) †	-4.80 (SE: 0.4)	14.8 (SE: 1.0)	12.6 (SE: 0.9)	13.0 (SE: 0.9)
		Placebo	-2.90 (SE: 0.52) †	-2.32 (SE: 0.4)	7.73 (SE: 0.93)	5.85 (SE: 0.93)	5.46 (SE: 0.97)
	8	Erenumab 70 mg/month	-6.26 (SE: 0.39) †	-5.48 (SE: 0.42)	14.5 (SE: 1.0)	11.2 (SE: 1.0)	11.7 (SE: 0.9)
		Erenumab 140 mg/month	-7.31 (SE: 0.49) †	-5.99 (SE: 0.38)	17.9 (SE: 0.9)	14.7 (SE: 0.9)	14.7 (SE: 1.0)
		Placebo	-4.61 (SE: 0.53) †	-3.27 (SE: 0.43)	9.85 (SE: 1.04)	7.39 (SE: 0.98)	7.87 (SE: 0.93)
	12	Erenumab 70 mg/month	-6.33 (SE: 0.49) †	-5.99 (SE: 0.38)	15.7 (SE: 1.0)	12.9 (SE: 0.9)	12.5 (SE: 1.0)
		Erenumab 140 mg/month	-7.64 (SE: 0.53) †	-6.49 (SE: 0.43)	18.5 (SE: 0.9)	14.8 (SE: 1.0)	15.5 (SE: 1.1)

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
		Placebo	-4.88 (SE: 0.50) †	-3.88 (SE: 0.42)	11.3 (SE: 1.0)	9.12 (SE: 0.98)	8.38 (SE: 1.07)
	16	Erenumab 70 mg/month	-6.73 (SE: 0.53) †	-6.69 (SE: 0.37)	16.1 (SE: 1.0)	12.2 (SE: 0.85)	12.8 (SE: 1.0)
		Erenumab 140 mg/month	-7.65 (SE: 0.53) †	-7.19 (SE: 0.4)	18.4 (SE: 1.2)	14.3 (SE: 0.85)	14.7 (SE: 0.9)
		Placebo	-4.63 (SE: 0.49) †	-4.37 (SE: 0.43)	11.9 (SE: 0.9)	8.65 (SE: 0.96)	8.56 (SE: 1.06)
	20	Erenumab 70 mg/month	-6.74 (SE: 0.52) †	-6.69 (SE: 0.4)	17.1 (SE: 1.1)	13.4 (SE: 0.9)	13.4 (SE: 1.0)
		Erenumab 140 mg/month	-7.49 (SE: 0.50) †	-6.72 (SE: 0.38)	17.9 (SE: 0.9)	13.6 (SE: 0.9)	14.4 (SE: 1.0)
		Placebo	-4.44 (SE: 0.49) †	-4.89 (SE: 0.41)	12.1 (SE: 1.0)	8.75 (SE: 0.9)	6.99 (SE: 1.02)
	24	Erenumab 70 mg/month	-6.84 (SE: 0.46) †	-6.83 (SE: 0.41)	17.0 (SE: 1.0)	12.4 (SE: 0.8)	12.3 (SE: 1.0)
		Erenumab 140 mg/month	-7.47 (SE: 0.49) †	-6.90 (SE: 0.38)	17.6 (SE: 1.0)	14.2 (SE: 0.7)	14.2 (SE: 1.0)
		Placebo	-4.94 (SE: 0.56) †	-4.71 (SE: 0.38)	10.7 (SE: 1.0)	8.14 (SE: 1.03)	7.45 (SE: 0.97)
Dodick, 2018 ARISE[42]	4	Erenumab 70 mg/month	NR	-3.20 (95%CI: -3.9, -2.51)	11.4 (95%CI: 9.35, 13.3)	9.02 (95%CI: 7.3, 10.8)	9.67 (95%CI: 7.61, 11.8)
		Placebo	NR	-2.30 (95%CI:-3.01, -1.6)	8.48 (95%CI: 6.57, 10.4)	7.64 (95%CI: 5.98, 9.43)	7.61 (95%CI: 5.47, 9.54)
	8	Erenumab 70 mg/month	NR	-5.00 (95%CI: -5.71, -4.3)	14.4 (95%CI: 12.4, 16.2)	11.6 (95%CI: 9.71, 13.3)	11.8 (95%CI: 9.7, 13.9)
		Placebo	NR	-2.79 (95%CI: -3.5, -2.11)	10.2 (95%CI: 8.30, 12.1)	9.02 (95%CI: 7.24, 10.7)	8.25 (95%CI: 6.28, 10.4)
	12	Erenumab 70 mg/month	-5.5 (SE: 0.5) †	-4.9 (SE: 0.4)	15.2 (SE: 1.0)	12.0 (SE: 0.9)	11.8 (SE: 1.1)
		Placebo	-3.8 (SE: 0.5) †	-2.6 (SE: 0.4)	9.7 (SE: 1.0)	8.4 (SE: 0.9)	7.3 (SE: 1.1)
Bigal, 2015b [25]	12	Fremanezumab 225 mg/month	-24.33 (SD: 54.56)	NR	NR	NR	NR
		Fremanezumab 675 mg/month	-24.93 (SD: 62.68)	NR	NR	NR	NR

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
		Placebo	-9.73 (SD: 55.67)	NR	NR	NR	NR
HALO-EM[43,160]	12	Fremanezumab 225 mg/month	-24.6 (95%CI: -27.68, -21.45)	NR	7 (SE: 1.4)*	NR	NR
		Fremanezumab 675 mg/3 months	-23.0 (95%CI: -26.10, -19.82)	NR	4.1 (SE: 1.4)*	NR	NR
		Placebo	-17.5 (95%CI: -20.62, -14.47)	NR	–	NR	NR
Dodick, 2014 [27]	12	Galcanezumab 150 mg/2 weeks	NR	54.6 (SD: 9.2) ‡	71.6 (SD: 26.5) ‡	78.7 (SD: 26.1) ‡	81.6 (SD: 25.2) ‡
		Placebo	NR	58.0 (SD: 9.2) ‡	58.5 (SD: 29.1) ‡	72.1 (SD: 26.7) ‡	76.3 (SD: 29.5) ‡
Skljarevski, 2018 [44]	12	Galcanezumab 120 mg/month	NR	-10.0 (95%CI: -12.2, -7.7)	NR	NR	NR
		Placebo	NR	-7.3 (95%CI: -8.8 , -5.7)	NR	NR	NR
Stauffer, 2018 EVOLVE-1[45]	13-24	Galcanezumab 120 mg/month	NR	NR	32.4 (NR)	5.6 (SE: 1.1)*	8.3 (SE:1 .5)*
		Galcanezumab 240 mg/month	NR	NR	32.1 (NR)	4.7 (SE: 1.2)*	7.2 (SE: 1.5)*
		Placebo	NR	NR	24.7 (NR)	–	–
	24	Galcanezumab 120 mg/month	-21.2 (SE: 1.7)	NR	NR	NR	NR
		Galcanezumab 240 mg/month	-20.1 (SE: 1.7)	NR	NR	NR	NR
		Placebo	-14.9 (SE: 1.4)	NR	NR	NR	NR
Skljarevski, 2018 EVOLVE-2[46].	13-24	Galcanezumab 120 mg/month	NR	NR	28.47 (SE: 1.2)	NR	NR
		Galcanezumab 240 mg/month	NR	NR	27.04 (SE: 1.2)	NR	NR
		Placebo	NR	NR	19.65 (SE: 0.9)	NR	NR
	24	Galcanezumab 120 mg/month	-21.2 (SE: 1.6)	NR	NR	NR	NR

Study	Week	Arm	Change from Baseline in Mean MIDAS Total Score	Change from Baseline in Mean HIT-6 Total Score	Change from Baseline in Mean MSQ-RFR	Change from Baseline in Mean MSQ-RFP	Change from Baseline in Mean MSQ-EF
		Galcanezumab 240 mg/month	-20.2 (SE:1.6)	NR	NR	NR	NR
		Placebo	-12.0 (SE:1.3)	NR	NR	NR	NR
Lipton, 2011 [49]	26	Topiramate 100 mg/day	-29.7 (SD: 33.05)	NR	29.77 (SD: 24.06)	20.52 (SD: 23.98)	34.5 (SD: 32.59)
		Placebo	-22.6 (SD: 36.89)	NR	25.41 (SD: 24.09)	17.92 (SD: 21.68)	27.58 (SD: 28.29)
Brandes, 2006 [173]	26	Topiramate 50 mg/day	NR	NR	71.9 (SE: 1.9) ‡	82.6 (SE: 1.7) ‡	77.6 (SE: 2.1) ‡
		Topiramate 100 mg/day	NR	NR	75.8 (SE: 1.9) ‡	85.5 (SE: 1.7) ‡	82.9 (SE: 2.1) ‡
		Topiramate 200 mg/day	NR	NR	77.9 (SE: 1.9) ‡	87.2 (SE: 1.7) ‡	82.7 (SE: 2.1) ‡
		Placebo	NR	NR	67.2 (SE: 1.8) ‡	80.8 (SE: 1.6) ‡	74.1 (SE: 2.0) ‡
Silberstein, 2006 [174]	26	Topiramate 50 mg/day	NR	NR	72.2 (SE: 1.8) ‡	84.3 (SE: 1.5) ‡	78.5 (SE: 2.0) ‡
		Topiramate 100 mg/day	NR	NR	77.2 (SE: 1.7) ‡	88.3 (SE: 1.4) ‡	84.4 (SE: 1.9) ‡
		Topiramate 200 mg/day	NR	NR	75.8 (SE: 2.0) ‡	84.4 (SE: 1.7) ‡	81.2 (SE: 2.2) ‡
		Placebo	NR	NR	65.8 (SE: 1.8) ‡	80.6 (SE: 1.5) ‡	72.9 (SE: 2.0) ‡
Dodick, 2009 [56]	26	Amitriptyline 100 mg/day	-14.2 (SD: 20.7)	NR	18.4 (NR)	12.5 (NR)	20.5 (NR)
		Topiramate 100 mg/day	-12.1 (SD: 23.4)	NR	23.7 (NR)	16.7 (NR)	25.6 (NR)

*Difference versus placebo; †Modified MIDAS (1-month recall); ‡Mean score, not change

95%CI: 95% confidence interval; HIT-6: Headache Impact Test; MIDAS: Migraine Disability Assessment; MSQ: Migraine-Specific Quality of Life Questionnaire; RFR: role function-restrictive; RFP: role function-preventive; EF: emotional function; NR: not reported; SD: standard deviation; SE: standard error

Table D13. Data for All-Cause Discontinuations in Chronic Migraine

Trial	Week	Treatment	r/n (%)
Tepper, 2017 [90]	12	Placebo	18/286 (6%)
		Erenumab 70 mg/month	9/191 (5%)
		Erenumab 140 mg/month	7/190 (4%)
Bigal, 2015 [26]	12	Placebo	12/89 (13%)
		Fremanezumab 675/225 mg/month	16/88 (18%)
Silberstein, 2017 HALO-CM[28]	12	Placebo	33/375 (9%)
		Fremanezumab 675 mg/3 months	27/376 (7%)
		Fremanezumab 675/225 mg/month	36/379 (9%)
Aurora, 2010 PREEMPT 1[34]	24	Placebo	43/338 (13%)
		Onabotulinum toxin A 155U	45/341 (13%)
Diener, 2010 PREEMPT 2[35]	24	Placebo	24/358 (7%)
		Onabotulinum toxin A 155U	36/347 (10%)
Freitag, 2008 [36]	16	Placebo	3/21 (14%)
		Onabotulinum toxin A 100U	2/20 (10%)
Sandrini, 2011 [37]	12	Placebo	6/35 (17%)
		Onabotulinum toxin A 100U	6/33 (18%)
Silberstein, 2007 [32]	16	Placebo	73/163 (45%)
		Topiramate 100 mg/day	73/165 (44%)
Diener, 2007 [33]	16	Placebo	13/27 (48%)
		Topiramate 100 mg/day	8/32 (25%)
Mei, 2006 [139]	12	Placebo	6/20 (30%)
		Topiramate 100 mg/day	9/30 (30%)
Silvestrini, 2003 [142]	8	Placebo	0/14 (0%)
		Topiramate 50 mg/day	1/14 (7%)
Cady, 2011 [39]	12	Onabotulinum toxin A 200 U	7/29 (24%)
		Topiramate 200 mg/day	8/30 (27%)
Mathew, 2009 [137]	36	Topiramate 100 mg/day	15/30 (50%)
		Onabotulinum toxin A 200 U	12/30 (40%)

Data are r: number of patients discontinuing / n: sample size (%)

Table D14. Data for All-Cause Discontinuations in Episodic Migraine

Trial	Week	Treatment	r/n (%)
Sun, 2016 [40]	12	Placebo	17/160 (11%)
	12	Erenumab 70 mg/month	5/107 (5%)
Goadsby, 2017 STRIVE[41]	24	Placebo	37/319 (12%)
	24	Erenumab 70 mg/month	33/317 (10%)
	24	Erenumab 140 mg/month	27/319 (8%)
Bigal, 2015 [25]	12	Placebo	6/104 (6%)
	12	Fremanezumab 225 mg/month	13/96 (14%)
Dodick, 2018 HALO-EM[43]	12	Placebo	29/294 (10%)
	12	Fremanezumab 675 mg/3 months	27/291 (9%)
	12	Fremanezumab 225 mg/month	29/290 (10%)
Skljarevski, 2018 [44]	12	Placebo	11/137 (8%)
	12	Galcanezumab 120 mg/month	8/70 (11%)
Stauffer, 2018 EVOLVE-1[45]	24	Placebo	82/433 (19%)
	24	Galcanezumab 120 mg/month	36/213 (17%)
	24	Galcanezumab 240 mg/month	37/212 (17%)
Skljarevski, 2018 EVOLVE-2[46]	24	Placebo	74/461 (16%)
	24	Galcanezumab 120 mg/month	28/231 (12%)
	24	Galcanezumab 240 mg/month	27/223 (12%)
Couch, 1979 [164]	4	Placebo	8/61 (13%)
	4	Amitriptyline 100 mg/day	8/55 (15%)
Couch, 2011 [165]	16	Placebo	106/197 (54%)
	16	Amitriptyline 100 mg/day	93/194 (48%)
Gonçalves, 2016 [47]	12	Placebo	6/65 (9%)
	12	Amitriptyline 25 mg/day	7/66 (11%)
Diener, 1996 [48]	12	Placebo	8/55 (15%)
	12	Propranolol 120 mg/day	12/78 (15%)
Jafarpour, 2016 [167]	4	Placebo	0/30 (0%)
	4	Propranolol 60 mg/day	4/30 (13%)
Pradalier, 1989 [168]	12	Placebo	5/24 (21%)
	12	Propranolol 160 mg/day	9/31 (29%)
Lipton, 2011 [49]	26	Placebo	86/197 (44%)
	26	Topiramate 100 mg/day	69/188 (37%)
Brandes, 2004 [50]	26	Placebo	57/120 (48%)
	26	Topiramate 100 mg/day	59/122 (48%)
	26	Topiramate 50 mg/day	61/120 (51%)
	26	Topiramate 200 mg/day	51/121 (42%)
Silberstein, 2004 [51]	26	Placebo	48/117 (41%)
	26	Topiramate 100 mg/day	45/128 (35%)
	26	Topiramate 50 mg/day	57/125 (46%)
	26	Topiramate 200 mg/day	72/117 (62%)

Gode, 2010 [171]	24	Topiramate 100 mg/day	4/15 (27%)
	24	Topiramate 50 mg/day	0/15 (0%)
Mei, 2004 [52]	16	Placebo	20/57 (35%)
	16	Topiramate 100 mg/day	23/58 (40%)
Silberstein, 2006 [53]	20	Placebo	13/73 (18%)
	20	Topiramate 200 mg/day	45/140 (32%)
Storey, 2001 [54]	16	Placebo	2/21 (10%)
	16	Topiramate 200 mg/day	3/19 (16%)
Diener, 2004 [55]	26	Placebo	47/146 (32%)
	26	Topiramate 100 mg/day	47/141 (33%)
	26	Propranolol 160 mg/day	42/144 (29%)
	26	Topiramate 200 mg/day	79/144 (55%)
Ashtari, 2008 [175]	8	Propranolol 80 mg/day	1/31 (3%)
	8	Topiramate 50 mg/day	1/31 (3%)
Dodick, 2009 [56]	26	Topiramate 100 mg/day	76/178 (43%)
	26	Amitriptyline 100 mg/day	74/169 (44%)
Dogan, 2015 [177]	4	Propranolol 80 mg/day	2/26 (8%)
	4	Topiramate 50 mg/day	0/25 (0%)
Keskinbora, 2008 [178]	12	Amitriptyline 150 mg/day	6/28 (21%)
	12	Topiramate 200 mg/day	4/24 (17%)
Mathew, 1981 [179]	24	Placebo	12/45 (27%)
	24	Amitriptyline 75 mg/day	10/42 (24%)
	24	Propranolol 160 mg/day	6/44 (14%)

Data are r: number of patients discontinuing / n: sample size (%)

Table D15. Data for Discontinuations from Adverse Events in Chronic or Episodic Migraine

Trial	Week	Treatment	r/n (%)
Tepper, 2017 [90]	12	Placebo	2/286 (1%)
	12	Erenumab 70 mg/month	0/191 (0%)
	12	Erenumab 140 mg/month	2/190 (1%)
Sun, 2016 [40]	12	Placebo	2/160 (1%)
	12	Erenumab 70 mg/month	3/107 (3%)
Goadsby, 2017 STRIVE[41]	24	Placebo	8/319 (3%)
	24	Erenumab 70 mg/month	7/317 (2%)
	24	Erenumab 140 mg/month	7/319 (2%)
Dodick, 2018 ARISE[42]	12	Placebo	1/289 (0%)
	12	Erenumab 70 mg/month	5/283 (2%)
Bigal, 2015 [26]	12	Placebo	1/89 (1%)
	12	Fremanezumab 675/225 mg/month	4/88 (5%)
Silberstein, 2017 HALO-CM[28]	12	Placebo	8/375 (2%)
	12	Fremanezumab 675 mg/3 months	5/376 (1%)
	12	Fremanezumab 675/225 mg/month	7/379 (2%)
Bigal, 2015 [25]	12	Placebo	0/104 (0%)
	12	Fremanezumab 225 mg/month	4/96 (4%)
Dodick, 2018 HALO-EM[43]	12	Placebo	5/294 (2%)
	12	Fremanezumab 675 mg/3 months	5/291 (2%)
	12	Fremanezumab 225 mg/month	5/290 (2%)
Stauffer, 2018 EVOLVE-1[45]	24	Placebo	10/433 (2%)
	24	Galcanezumab 120 mg/month	9/213 (4%)
	24	Galcanezumab 240 mg/month	7/212 (3%)
Skljarevski, 2018 EVOLVE-2[46]	24	Placebo	8/461 (2%)
	24	Galcanezumab 120 mg/month	5/231 (2%)
	24	Galcanezumab 240 mg/month	9/223 (4%)
Aurora, 2010 PREEMPT 1[34]	24	Placebo	3/334 (1%)
	24	Onabotulinum toxin A 155U	14/340 (4%)
Diener, 2010 PREEMPT 2[35]	24	Placebo	5/358 (1%)
	24	Onabotulinum toxin A 155U	12/347 (3%)
Sandrini, 2011 [37]	12	Placebo	0/29 (0%)
	12	Onabotulinum toxin A 100U	2/27 (7%)
Silberstein, 2007 [32]	16	Placebo	10/163 (6%)
	16	Topiramate 100 mg/day	18/165 (11%)
Diener, 2007 [33]	16	Placebo	3/27 (11%)
	16	Topiramate 100 mg/day	6/32 (19%)
Mei, 2006 [139]	12	Placebo	6/20 (30%)
	12	Topiramate 100 mg/day	9/30 (30%)
Couch, 1979 [164]	4	Placebo	0/61 (0%)
	4	Amitriptyline 100 mg/day	2/55 (4%)

Couch, 2011 [165]	16	Placebo	13/197 (7%)
	16	Amitriptyline 100 mg/day	23/194 (12%)
Diener, 1996 [48]	12	Placebo	1/55 (2%)
	12	Propranolol 120 mg/day	6/78 (8%)
Pradalier, 1989 [168]	12	Placebo	1/24 (4%)
	12	Propranolol 160 mg/day	0/31 (0%)
Lipton, 2011 [49]	26	Placebo	18/185 (10%)
	26	Topiramate 100 mg/day	21/176 (12%)
Brandes, 2004 [50]	26	Placebo	14/120 (12%)
	26	Topiramate 100 mg/day	32/122 (26%)
	26	Topiramate 50 mg/day	20/120 (17%)
	26	Topiramate 200 mg/day	25/122 (20%)
Silberstein, 2004 [51]	26	Placebo	11/117 (9%)
	26	Topiramate 100 mg/day	24/128 (19%)
	26	Topiramate 50 mg/day	21/125 (17%)
	26	Topiramate 200 mg/day	38/117 (32%)
Gode, 2010 [171]	24	Topiramate 100 mg/day	4/15 (27%)
	24	Topiramate 50 mg/day	0/15 (0%)
Mei, 2004 [52]	16	Placebo	2/37 (5%)
	16	Topiramate 100 mg/day	17/35 (49%)
Silberstein, 2006 [53]	20	Placebo	4/73 (5%)
	20	Topiramate 200 mg/day	21/140 (15%)
Storey, 2001 [54]	16	Placebo	0/21 (0%)
	16	Topiramate 200 mg/day	2/19 (11%)
Diener, 2004 [55]	26	Placebo	15/146 (10%)
	26	Topiramate 100 mg/day	37/141 (26%)
	26	Propranolol 160 mg/day	29/144 (20%)
	26	Topiramate 200 mg/day	63/144 (44%)
Ashtari, 2008 [175]	8	Propranolol 80 mg/day	1/31 (3%)
	8	Topiramate 50 mg/day	1/31 (3%)
Mathew, 2009 [137]	36	Topiramate 100 mg/day	8/30 (27%)
	36	Onabotulinum toxin A 200 U	3/30 (10%)
Dodick, 2009 [56]	26	Topiramate 100 mg/day	35/178 (20%)
	26	Amitriptyline 100 mg/day	38/169 (22%)
Keskinbora, 2008 [178]	12	Amitriptyline 150 mg/day	3/22 (14%)
	12	Topiramate 200 mg/day	2/20 (10%)
Mathew, 1981 [179]	24	Placebo	4/45 (9%)
	24	Amitriptyline 75 mg/day	4/42 (10%)
	24	Propranolol 160 mg/day	1/44 (2%)

Data are r: number of patients discontinuing / n: sample size (%)

Table D16. Data for Serious Adverse Events in Chronic or Episodic Migraine

Trial	Week	Treatment	r/n (%)
Tepper, 2017 [90]	12	Placebo	7/282 (2%)
	12	Erenumab 70 mg/month	6/190 (3%)
	12	Erenumab 140 mg/month	2/188 (1%)
Sun, 2016 [40]	12	Placebo	0/153 (0%)
	12	Erenumab 70 mg/month	1/106 (1%)
Goadsby, 2017 STRIVE[41]	24	Placebo	7/319 (2%)
	24	Erenumab 70 mg/month	8/314 (3%)
	24	Erenumab 140 mg/month	6/319 (2%)
Dodick, 2018 ARISE[42]	12	Placebo	5/289 (2%)
	12	Erenumab 70 mg/month	3/283 (1%)
Bigal, 2015 [26]	12	Placebo	1/89 (1%)
	12	Fremanezumab 675/225 mg/month	1/88 (1%)
Silberstein, 2017 HALO-CM[28]	12	Placebo	6/375 (2%)
	12	Fremanezumab 675 mg/3 months	3/376 (1%)
	12	Fremanezumab 675/225 mg/month	5/379 (1%)
Bigal, 2015 [25]	12	Placebo	0/104 (0%)
	12	Fremanezumab 225 mg/month	2/96 (2%)
Dodick, 2018 HALO-EM[43]	12	Placebo	7/293 (2%)
	12	Fremanezumab 675 mg/3 months	3/291 (1%)
	12	Fremanezumab 225 mg/month	3/290 (1%)
Skljarevski, 2018 [44]	12	Placebo	0/137 (0%)
	12	Galcanezumab 120 mg/month	1/70 (1%)
Stauffer, 2018 EVOLVE-1[45]	24	Placebo	5/432 (1%)
	24	Galcanezumab 120 mg/month	6/206 (3%)
	24	Galcanezumab 240 mg/month	0/220 (0%)
Skljarevski, 2018 EVOLVE-2[46]	24	Placebo	5/461 (1%)
	24	Galcanezumab 120 mg/month	5/226 (2%)
	24	Galcanezumab 240 mg/month	7/228 (3%)
Aurora, 2010 PREEMPT 1[34]	24	Placebo	8/334 (2%)
	24	Onabotulinum toxin A 155U	18/340 (5%)
Diener, 2010 PREEMPT 2[35]	24	Placebo	8/358 (2%)
	24	Onabotulinum toxin A 155U	15/347 (4%)
Diener, 2007 [33]	16	Placebo	1/27 (4%)
	16	Topiramate 100 mg/day	1/32 (3%)
Couch, 2011 [165]	16	Placebo	10/197 (5%)
	16	Amitriptyline 100 mg/day	30/194 (15%)
Lipton, 2011 [49]	26	Placebo	5/185 (3%)
	26	Topiramate 100 mg/day	4/176 (2%)
Silberstein, 2006 [53]	20	Placebo	1/73 (1%)

	20	Topiramate 200 mg/day	2/140 (1%)
Storey, 2001 [54]	16	Placebo	1/21 (5%)
	16	Topiramate 200 mg/day	1/19 (5%)
Dodick, 2009 [56]	26	Topiramate 100 mg/day	4/177 (2%)
	26	Amitriptyline 100 mg/day	8/169 (5%)

Data are r: number of patients with serious adverse event / n: sample size (%)

Table D17. Adverse Event Rates ≥ 5% in CGRP Inhibitor Trials in Both Chronic and Episodic Migraine

Study	Treatment	N	Wks	% Dizziness	% Injection Pain	% Injection Reaction	% Naso-pharyngitis	% Nausea	% Paresthesia	% Sinusitis	% Upper Respiratory Tract Infection	% Urinary Tract Infection
Erenumab												
Dodick 2018 (ARISE) [42]	Erenumab 70 mg	283	12		6		5.3				6.4	
	Placebo	289	12		4.2		5.9				4.8	
Goadsby 2017 (STRIVE) [41]	Erenumab 70 mg	314	24				9.9				6.7	
	Erenumab 140 mg	319	24				11				4.7	
	Placebo	319	24				10				5.6	
Sun 2016 [40]	Erenumab 7 mg	108	12			6	9					
	Erenumab 21 mg	105	12			5	5					
	Erenumab 70 mg	106	12			5	6					
	Placebo	153	12			3	8					
Tepper, 2017 [90]	Erenumab 70 mg	190	12									
	Erenumab 140 mg	188	12									
	Placebo	282	12									
Fremanezumab												
Bigal, 2015a [26]	Fremanezumab 675/225 mg	88	12		7	5(P)			5	5		5
	Fremanezumab 900 mg	86	12		9	2(P)			0	0		2
	Placebo	89	12		3	0(P)			0	1		1
Bigal 2015b [25]	Fremanezumab 225 mg	96	12	1	9					0		
	Fremanezumab 675 mg	96	12	5	4					5		
	Placebo	104	12	0	6					3		
Silberstein, 2017	Fremanezumab 675 mg*	376	12		30	21(Er) 20(I)	5				5	

Study	Treatment	N	Wks	% Dizziness	% Injection Pain	% Injection Reaction	% Naso-pharyngitis	% Nausea	% Paresthesia	% Sinusitis	% Upper Respiratory Tract Infection	% Urinary Tract Infection
(HALO-CM)[28]	Fremanezumab 675/225 mg	379	12		26	20(Er) 24(I)	4				4	
	Placebo	375	12		28	16 (Er) 18(I)	5				4	
Dodick, 2018 HALO-EM[43]	Fremanezumab 225 mg	290	12		30	17.9 (Er) 24.5 (I)					5.5	
	Fremanezumab 675 mg*	291	12		29.6	18.9 (Er) 19.6 (I)					3.8	
	Placebo	293	12		25.9	14.0 (Er) 15.4 (I)					5.1	
Galcanezumab												
Dodick 2014 [27]	Galcanezumab 150 mg†	107	12	5	17	5					17	
	Placebo	110	12	3	6	0					9	
Skljarevski 2018 [44]	Galcanezumab 5 mg	68	12		8.8		11.8	1.5			10.3	
	Galcanezumab 50 mg	68	12		8.8		4.4	2.9			11.8	
	Galcanezumab 120 mg	70	12		14.3		8.6	0			11.4	
	Galcanezumab 300 mg	67	12				3	6			6	
	Placebo	137	12				2.2	2.9			8.8	
Stauffer, 2018 EVOLVE-1[45]	Galcanezumab 120 mg	206			16.0	3.4	7.8					3.9
	Galcanezumab 240 mg	220			20.5	5.5	2.7					5.9
	Placebo	432			17.4	0.9	6.3					3.5
Skljarevski, 2018 EVOLVE-2[46]	Galcanezumab 120 mg	226			9.3	3.1	8.4				5.8	
	Galcanezumab 240 mg	228			8.8	7.9	7.0				5.3	
	Placebo	461			8.5	0	8.9				3.5	

Study	Treatment	N	Wks	% Dizziness	% Injection Pain	% Injection Reaction	% Naso-pharyngitis	% Nausea	% Paresthesia	% Sinusitis	% Upper Respiratory Tract Infection	% Urinary Tract Infection

Doses are monthly unless otherwise stated:
*every 3 months
†every 2 weeks
Injection-site reaction includes erythema (Er), induration (I), and pruritis (P).

Table D18. Adverse Event Rates ≥20% in the Commonly Used Preventive Treatment Trials in Both Chronic and Episodic Migraine

Study	Treatment	N	Wks	% Cognitive Symptoms	% GI Symptoms	% Dry Mouth	% Fatigue	% Injection Pain	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Couch 2011 [165]	Amitriptyline 100 mg	194	16		11.86(Cn)	35.05(B)	7.73(F) 27.32(S)					
	Placebo	197	16		4.06(Cn)	7.11(B)	4.06(F) 8.63 (S)					
Goncalves 2016[211]	Amitriptyline 25 mg	59	12		6.8 (Cn)	10.17	40.68(Sp)					5.1 (Wg)
	Placebo	59	12		6.8 (Cn)	1.69	11.86(Sp)					0 (Wg)
Pradalier 1989 [168]	Propranolol 160 mg	22	12		9.09(Cn) 4.55(D)		13.64(T)					
	Placebo	19	12		10.53(Cn)		10.53(T)					
Silberstein, 2012 [143]	Top 100 mg/Prop 240 mg	96	24	13(Cd) 6(M)			23(F)		13			
	Topiramate 100 mg	95	24	7(Cd) 8(M)			12(F)		11			
Brandes 2004[50]	Topiramate 50 mg	117	26	5(M)	10(D)		19(F)			34	11	8(A) 6(Wl)
	Topiramate 100 mg	119	26	10(M)	11(D)		14(F)			50	8	13(A) 11(Wl)
	Topiramate 200 mg	117	26	15(M)	12(D)		18(F)			49	14	15(A) 9(Wl)
	Placebo	113	26	4(M)	4(D)		9(F)			4	0	8(A) 3(Wl)
Diener, 2007 [33]	Topiramate 100 mg	32	16	6(Cx)			6(F)		9	53		6(A)
	Placebo	27	16	4(Cx)			0(F)		0	7		4(A)

Study	Treatment	N	Wks	% Cognitive Symptoms	% GI Symptoms	% Dry Mouth	% Fatigue	% Injection Pain	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Lipton 2011 [49]	Topiramate 100 mg	176	26		6.25(D)	6.82	14.77(F) 5.11(S)		10.8	32.39	9.66	8.52(A)
	Placebo	185	26		3.24(D)	2.7	8.65(F) 1.62(S)		9.19	7.03	1.62	2.70(A)
Lo 2010 [172]	Topiramate 25 mg	10	12		30(D)		10(F)		10	40		
	Topiramate 50 mg	10	12		0(D)		10(F)		10	50		
	Topiramate 75 mg	10	12		0(D)		30(F)		0	60		
	Topiramate 100 mg	10	12		0(D)		20(F)		20	70		
Mei 2004 [52]	Topiramate 100 mg	35	16	8(Cd)			11(F) 6(S)			23	6	23(Wl)
	Placebo	37	16	0(Cd)			0(F) 23(S)			6	0	0(Wl)
Mei, 2006 [139]	Topiramate 100 mg	30	12	19.05(Cx) 23.81(M) 28.57(L)			38.1(F) 9.52(S)			85.71	47.62	42.86(A) 33.33(Wl)
	Placebo	20	12	14.29(Cx) 14.29(M) 0(L)			7.14(F) 0(S)			14.29	0	0(A) 0(Wl)
Silberstein 2004 [51]	Topiramate 50 mg	118	26	2.54(Cx) 9.32(M) 5.93(L)			9.32(F) 7.63(S)		6.78	36.44	19.49	11.02(A) 5.08(Wl)
	Topiramate 100 mg	126	26	3.97(Cx) 7.14(M) 7.94(L)			11.11(F) 8.73(S)		15.87	46.83	10.32	12.70(A) 9.52(Wl)
	Topiramate 200 mg	113	26	9.73(Cx) 12.39(M) 13.27(L)			17.70(F) 8.85(S)		14.16	46.9	14.16	14.16(A) 11.50(Wl)

Study	Treatment	N	Wks	% Cognitive Symptoms	% GI Symptoms	% Dry Mouth	% Fatigue	% Injection Pain	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
	Placebo	116	26	<1(Cx) 2.59(M) <1(L)			10.34(F) 6.03(S)		12.07	6.9	1.72	4.31(A) <1(Wl)
Silberstein 2006 [53]	Topiramate 200 mg	140	20	10.7(M)			15.7(F) 11.4(S)		14.3	45		13.6(A) 13.6(Wl)
	Placebo	73	20	1.4(M)			8.2(F) 5.5(S)		4.1	5.5		6.8(A) 1.4(Wl)
Silberstein, 2007 [32]	Topiramate 100 mg	160	16	9.4(Cx) 6.9 (M)		9.4	11.9(F) 5.6(S)		8.8	28.8	9.4	5.6(A)
	Placebo	161	16	2.5(Cx) 6.2 (M)		3.1	9.9(F) 4.3(S)		8.1	7.5	2.5	5.0(A)
Silvestrini, 2003 [142]	Topiramate 50 mg	14	8				14.29(S)			14.29		
	Placebo	14	8				0(S)			7.14		
Storey 2001 [54]	Topiramate 200 mg	19	16	21.05(M) 15.79(L)						68.42	36.84	21.05(A) 52.63(Wl)
	Placebo	21	16	4.76(M) 0(L)						19.05	0	4.76(A) 28.57(Wl)
Cady, 2011[39]	Onabotulinum toxin A 200 U	22	12	59.1(M&Cx)			72.7(MF)		59.1			
	Topiramate 200 mg	30	12	50(M&Cx)			68.2(MF)		27.3			
Magalhaes, 2010 [138]	Amitriptyline 50 mg	37	12		38.8(Cn)	44	52.7(S)					58.3(Wg)
	Onabotulinum toxin A 250 U	35	12		0(Cn)	14	4(S)	35				11.8(Wg)
Ashtari 2008 [175]	Topiramate 50 mg	31	8				12.90(S)		22.58			16.13(Wl)
	Propranolol		8									

Study	Treatment	N	Wks	% Cognitive Symptoms	% GI Symptoms	% Dry Mouth	% Fatigue	% Injection Pain	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Diener 2004 [55]	Propranolol 160 mg	142	26	5(Cx) 3(M)			22(F) 9(S)		13	12	0	0(Wl)
	Topiramate 100 mg	141	26	9(Cx) 4(M)			19(F) 5(S)		13	55	5	7(Wl)
	Topiramate 200 mg	144	26	15(Cx) 7(M)			24(F) 8(S)		17	56	14	9(Wl)
	Placebo	143	26	4(Cx) 1(M)			15(F) 2(S)		8	6	1	1(Wl)
Dodick 2009 [56]	Amitriptyline 100 mg	169	26	6.8(Cx)	8.3(Cn)	35.5	24.3(F) 17.8(S)		10.2	29.9	5.6	4.7(A) 13.6 (Wg)
	Topiramate 100 mg	177	26	3.0(Cx)	3.4(Cn)	6.8	16.9(F) 11.9(S)		7.1	4.7	3.6	6.8(A) 0(Wg)
Keskinbora 2008 [212]	Amitriptyline 150 mg	22	12	15(M)	45.4(Cn)	~100	54.6(S)					27.3 (Wg)
	Topiramate 200 mg	20	12							40		35(Wl)

Doses are daily for amitriptyline, propranolol, and topiramate and every three months for onabotulinum toxin A.
Cognitive symptoms include cognitive difficulties (Cd) , difficulty with memory (M), difficulty with concentration (Cx), and difficulty with language (L).
GI symptoms include constipation (Cn) and diarrhea (D).
Dry mouth includes dry mucous membrane (B).
Fatigue includes fatigue (F), mild fatigue (MF), somnolence (S), sleepiness (Sp), and tiredness (T).
Weight loss includes weight loss (Wl), weight gain (Wg), and anorexia (A).

Network Meta-Analysis Supplemental Information

Methods

As described in the report, we conducted random effect network meta-analyses (NMA) where feasible. A NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[213,214]

NMAs were conducted using a Bayesian framework. For continuous outcomes (e.g., migraine frequency), the NMA model corresponds to a generalized linear model with identity link.[123] For binary outcomes (e.g., a reduction in migraine frequency of at least 50%), the NMA model corresponds to a generalized linear model with a logit link.[123] For all analyses, we included random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) was assumed constant across all treatment comparisons. We used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was assessed visually using trace plots.

Furthermore, for any network where there were "loops" in evidence, we empirically compared the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[215] As there was no evidence of inconsistency, we present the full NMA results in the report.

In separate analyses, we analyzed the efficacy outcomes by week of assessment (4 weeks, 8 weeks, 12 weeks, and 26 weeks), where feasible. Results from these analyses are presented in tables below. In addition, we conducted a meta-regression analysis with a covariate for the timepoint with results below. As these models did not provide a better fit to the data based on deviance information criteria (DIC), we present the results without covariate adjustment in the report.

All analyses were conducted in R using the gemtc package.[122] In the report, results are presented for each treatment versus placebo only. Below, results for all pairwise comparisons are presented tabularly in terms of a point estimate and 95% credible intervals. Diagrams illustrating the network of studies reporting data for each outcome are also presented below.

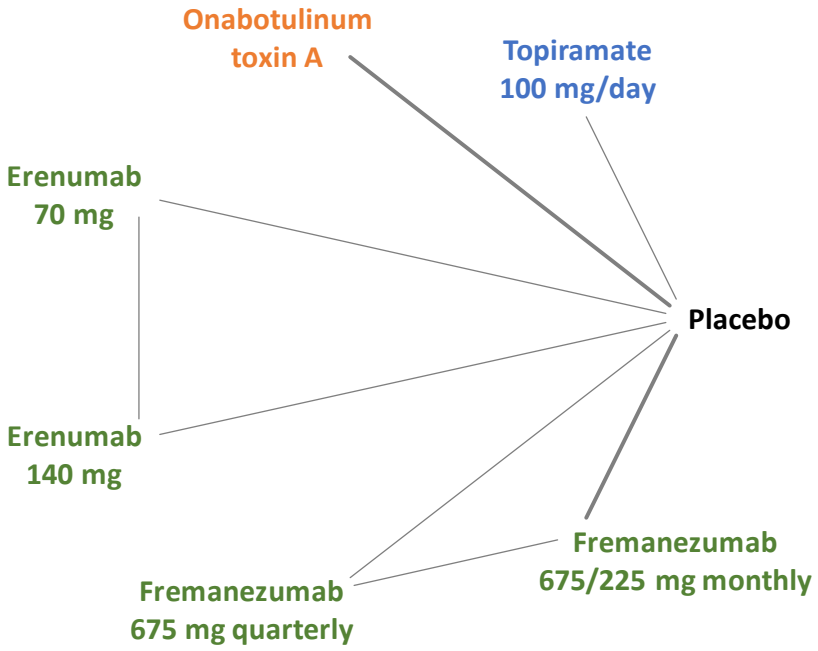
Supplemental NMA Results

We provide the network diagram for each analysis presented in the report, followed by the respective league table that presents results for all pairwise comparisons. To interpret the network figures, note that the lines indicate the presence of a trial directly assessing the connecting interventions, with the thickness of the line corresponding to the number of trials. The location of treatments and the distances between them does not have any meaning. In all figures, the CGRP

inhibitors are depicted in green, the existing oral preventive therapies in blue, onabotulinum toxin A in orange (chronic migraine), and placebo in black.

For the league tables, each column is a treatment, which is compared to the treatments in each row. The treatments are listed in order based on surface under the cumulative ranking curves (SUCRA), where treatments more likely to be ranked higher are listed first (top). Additional details are provided in the legends.

Figure D1. Network of Studies Assessing Monthly Migraine Days in Chronic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, onabotulinum toxin A in orange, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

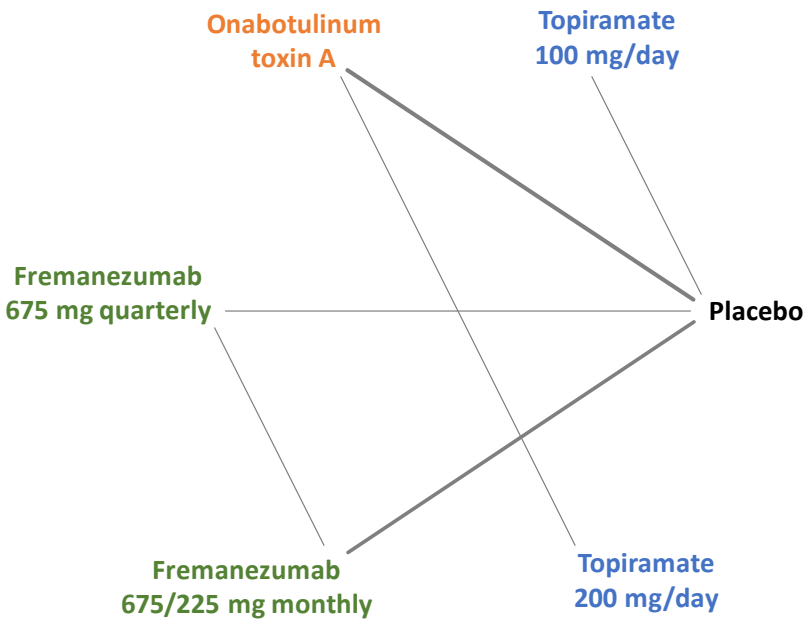
Table D19. Network Meta-Analysis Results for Change from Baseline in Monthly Migraine Days in Chronic Migraine

Erenumab 140 mg						
0.00 (-2.40, 2.41)	**Erenumab 70 mg**					
-0.45 (-3.34, 2.47)	-0.45 (-3.35, 2.48)	**Onabotulinum toxin A quarterly**				
-0.70 (-4.13, 2.75)	-0.71 (-4.14, 2.77)	-0.26 (-3.26, 2.73)	**Topiramate 100 mg/day**			
-0.74 (-3.7, 2.28)	-0.74 (-3.73, 2.27)	-0.29 (-2.74, 2.17)	-0.03 (-3.1, 3.04)	**Fremanezumab 675/225 mg**		
-1.10 (-4.35, 2.18)	-1.11 (-4.37, 2.18)	-0.65 (-3.45, 2.15)	-0.39 (-3.73, 2.94)	-0.36 (-2.59, 1.84)	**Fremanezumab 675 mg quarterly**	
-2.40 (-4.77, 0.00)	**-2.40 (-4.79, 0.00)**	**-1.95 (-3.62, -0.28)**	-1.7 (-4.18, 0.79)	-1.66 (-3.47, 0.12)	-1.3 (-3.54, 0.93)	**Placebo**

Tau: 0.65 (0.03, 2.19); DIC: 24.6

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated mean difference in change from baseline and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 0.

Figure D2. Network of Studies Assessing Monthly Headache Days in Chronic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

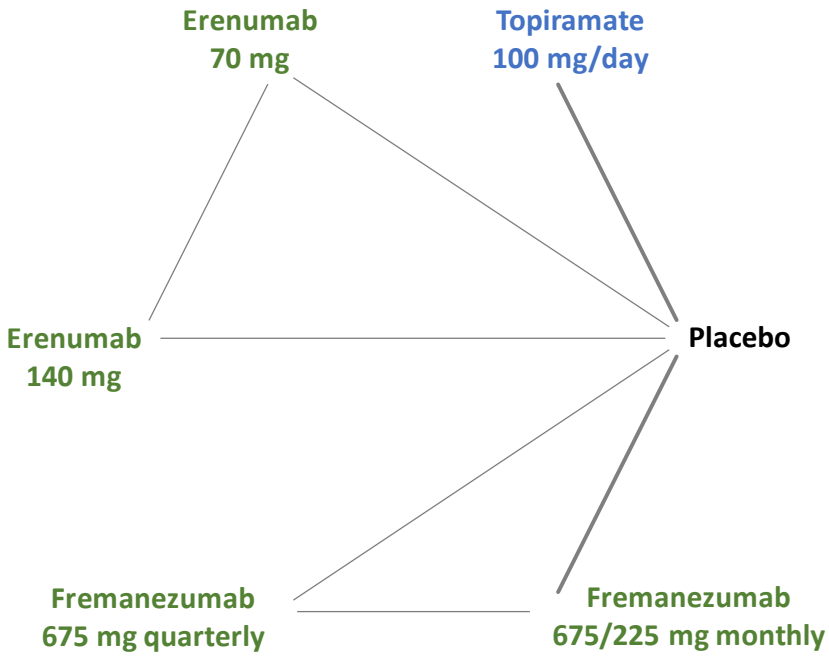
Table D20. Network Meta-Analysis Results for Change from Baseline in Monthly Headache Days in Chronic Migraine

Onabotulinum toxin A quarterly					
0.10 (-3.69, 3.88)	**Topiramate 200 mg/day**				
-0.21 (-2.5, 2.07)	-0.29 (-4.69, 4.06)	**Fremanezumab 675/225 mg**			
-0.58 (-3.26, 2.07)	-0.68 (-5.26, 3.89)	-0.38 (-2.65, 1.9)	**Fremanezumab 675 mg quarterly**		
-0.95 (-3.82, 1.88)	-1.04 (-5.76, 3.61)	-0.74 (-3.79, 2.32)	-0.37 (-3.71, 2.98)	**Topiramate 100 mg/day**	
-2.06 (-3.48, -0.63)	**-2.14 (-6.16, 1.86)**	**-1.85 (-3.63, -0.06)**	-1.47 (-3.72, 0.79)	-1.10 (-3.56, 1.38)	**Placebo**

Tau: 0.58 (0.03, 2.76); DIC: 27.8

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated mean difference in change from baseline and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 0.

Figure D3. Network of Studies Assessing Days Using Acute Medication per Month in Chronic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

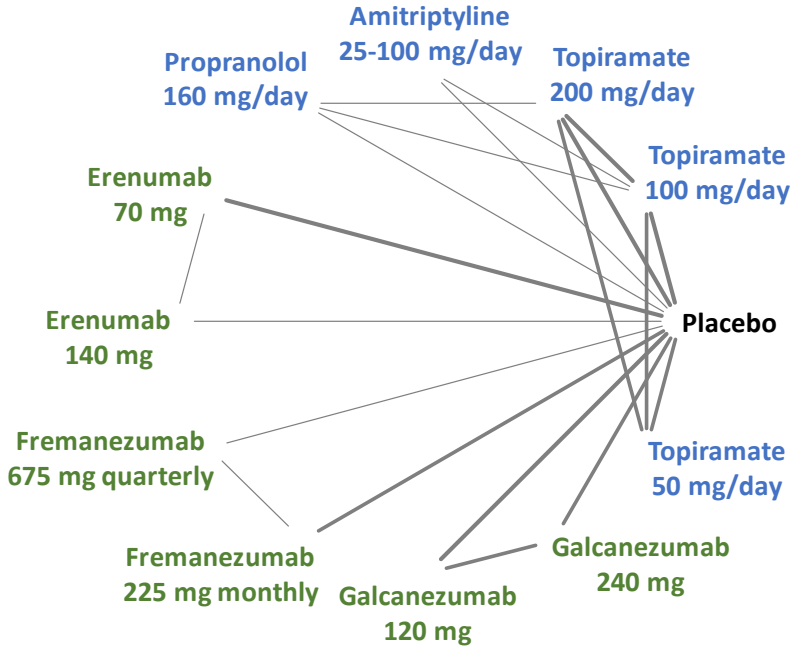
Table D21. Network Meta-Analysis Results for Change from Baseline in Days Using Acute Medication per Month in Chronic Migraine

Erenumab 140 mg					
-0.32 (-3.41, 2.79)	**Fremanezumab 675/225 mg**				
-0.59 (-3.10, 1.90)	-0.27 (-3.36, 2.81)	**Erenumab 70 mg**			
-1.10 (-4.52, 2.35)	-0.78 (-3.17, 1.61)	-0.50 (-3.91, 2.91)	**Fremanezumab 675 mg quarterly**		
-1.23 (-4.25, 2.21)	-0.90 (-3.54, 2.1)	-0.63 (-3.66, 2.79)	-0.13 (-3.14, 3.25)	**Topiramate 100 mg/day**	
-2.49 (-4.95, -0.01)	**-2.17 (-4.05, -0.28)**	-1.90 (-4.34, 0.57)	-1.40 (-3.77, 1.00)	-1.27 (-3.54, 0.66)	**Placebo**

Tau: 0.7 (0.03, 2.31); DIC: 19.9

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated mean difference in change from baseline and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 0.

Figure D4. Network of Studies Assessing Monthly Migraine Days in Episodic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

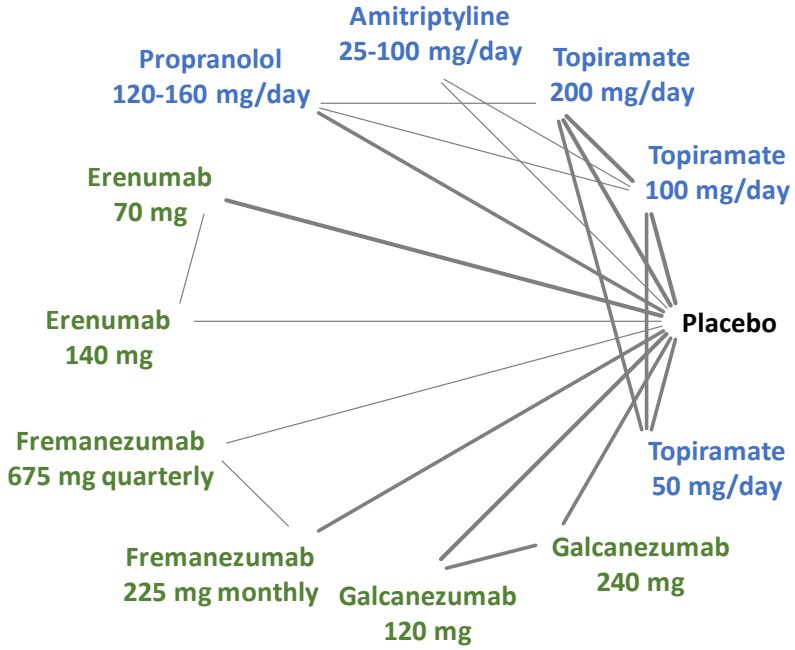
Table D22. Network Meta-Analysis Results for Change from Baseline in Monthly Migraine Days in Episodic Migraine

Erenumab 140 mg										
-0.10 (-1.07, 0.87)	**Galcanezumab 240 mg**									
-0.15 (-1.09, 0.82)	-0.04 (-0.73, 0.65)	**Galcanezumab 120 mg**								
-0.35 (-1.42, 0.81)	-0.25 (-1.28, 0.83)	-0.20 (-1.20, 0.85)	**Fremanezumab 225 mg**							
-0.65 (-1.40, 0.10)	-0.54 (-1.36, 0.25)	-0.50 (-1.29, 0.27)	-0.29 (-1.31, 0.64)	**Erenumab 70 mg**						
-0.74 (-1.81, 0.37)	-0.64 (-1.65, 0.38)	-0.60 (-1.57, 0.40)	-0.40 (-1.56, 0.74)	-0.10 (-1.01, 0.86)	**Propranolol 160 mg/day**					
-0.76 (-1.94, 0.47)	-0.65 (-1.81, 0.50)	-0.61 (-1.73, 0.52)	-0.40 (-1.40, 0.54)	-0.11 (-1.17, 0.99)	-0.02 (-1.24, 1.22)	**Fremanezumab 675 mg quarterly**				
-0.78 (-1.66, 0.13)	-0.68 (-1.44, 0.12)	-0.64 (-1.38, 0.14)	-0.43 (-1.41, 0.51)	-0.13 (-0.81, 0.58)	-0.04 (-0.82, 0.75)	-0.02 (-1.09, 1.04)	**Topiramate 100 mg/day**			
-0.87 (-2.25, 0.52)	-0.77 (-2.09, 0.56)	-0.73 (-2.02, 0.58)	-0.52 (-1.99, 0.88)	-0.23 (-1.50, 1.06)	-0.13 (-1.47, 1.22)	-0.11 (-1.63, 1.38)	-0.09 (-1.23, 1.03)	**Amitriptyline 25-100 mg/day**		
-0.99 (-1.89, -0.02)	**-0.89 (-1.69, -0.03)**	**-0.84 (-1.63, -0.01)**	-0.64 (-1.65, 0.34)	-0.34 (-1.06, 0.44)	-0.25 (-1.03, 0.57)	-0.23 (-1.32, 0.87)	-0.21 (-0.74, 0.35)	-0.12 (-1.34, 1.13)	**Topiramate 200 mg/day**	
-1.77 (-2.85, -0.66)	**-1.67 (-2.66, -0.65)**	**-1.62 (-2.60, -0.62)**	**-1.42 (-2.59, -0.29)**	**-1.12 (-2.05, -0.17)**	-1.03 (-2.06, 0.01)	-1.01 (-2.27, 0.22)	**-0.99 (-1.77, -0.21)**	-0.90 (-2.24, 0.47)	-0.78 (-1.59, 0.01)	**Topiramate 50 mg/day**
-1.95 (-2.68, -1.19)	**-1.84 (-2.48, -1.22)**	**-1.80 (-2.40, -1.20)**	**-1.59 (-2.46, -0.79)**	**-1.30 (-1.79, -0.79)**	**-1.20 (-2.01, -0.43)**	**-1.19 (-2.16, -0.25)**	**-1.17 (-1.66, -0.70)**	-1.07 (-2.24, 0.11)	**-0.96 (-1.53, -0.42)**	-0.17 (-0.97, 0.61)	**Placebo**

Tau: 0.21 (0.01, 0.60); DIC: 65.1

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated mean difference in change from baseline and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 0.

Figure D5. Network of Studies Assessing 50% Response in Episodic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

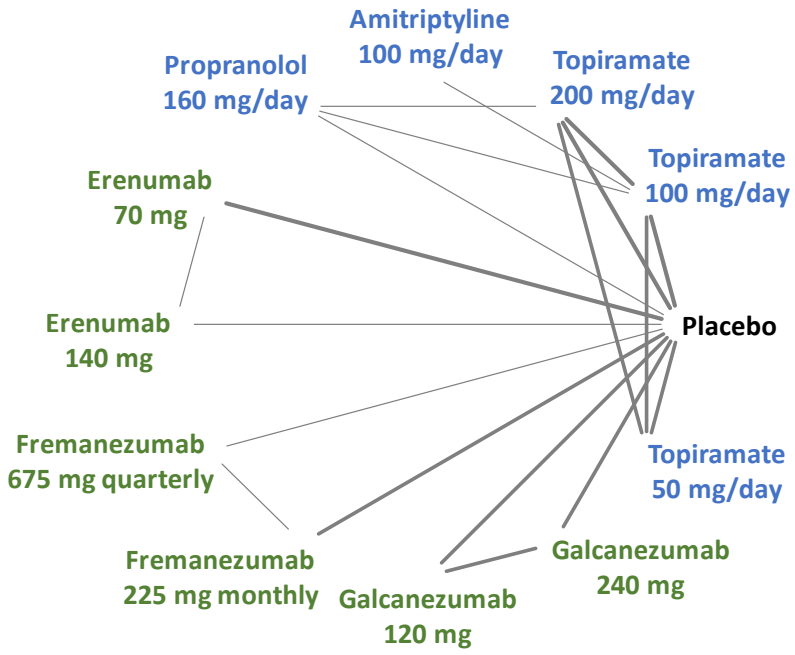
Table D23. Network Meta-Analysis Results for 50% Response in Episodic Migraine

Topiramate 100 mg/day										
1.00 (0.65, 1.58)	**Propranolol 120-160 mg/day**									
1.06 (0.73, 1.62)	1.07 (0.64, 1.78)	**Galcanezumab 120 mg**								
1.14 (0.76, 1.74)	1.14 (0.67, 1.92)	1.07 (0.76, 1.49)	**Galcanezumab 120 mg**							
1.17 (0.86, 1.59)	1.17 (0.74, 1.81)	1.09 (0.72, 1.65)	1.02 (0.66, 1.57)	**Topiramate 200 mg/day**						
1.24 (0.77, 2.03)	1.25 (0.68, 2.22)	1.17 (0.70, 1.89)	1.09 (0.65, 1.81)	1.06 (0.64, 1.77)	**Erenumab 140 mg**					
1.37 (0.86, 2.15)	1.38 (0.73, 2.49)	1.29 (0.71, 2.23)	1.21 (0.66, 2.12)	1.17 (0.69, 1.98)	1.10 (0.58, 2.07)	**Amitriptyline 25-100 mg/day**				
1.38 (0.87, 2.18)	1.38 (0.77, 2.40)	1.29 (0.79, 2.05)	1.21 (0.73, 1.95)	1.18 (0.73, 1.90)	1.11 (0.64, 1.91)	1.01 (0.54, 1.87)	**Fremanezumab 225 mg**			
1.42 (0.97, 2.11)	1.43 (0.85, 2.35)	1.33 (0.88, 1.99)	1.25 (0.82, 1.90)	1.22 (0.81, 1.84)	1.15 (0.77, 1.72)	1.04 (0.60, 1.85)	1.03 (0.65, 1.67)	**Erenumab 70 mg**		
1.58 (0.94, 2.64)	1.58 (0.85, 2.88)	1.48 (0.86, 2.47)	1.39 (0.80, 2.35)	1.36 (0.79, 2.28)	1.27 (0.70, 2.31)	1.15 (0.60, 2.24)	1.15 (0.74, 1.79)	1.11 (0.66, 1.87)	**Fremanezumab 675 mg quarterly**	
1.70 (1.16, 2.51)	1.70 (0.99, 2.89)	1.59 (0.97, 2.57)	1.49 (0.90, 2.43)	1.46 (0.98, 2.17)	1.37 (0.78, 2.40)	1.24 (0.70, 2.22)	1.24 (0.72, 2.12)	1.19 (0.74, 1.94)	1.08 (0.60, 1.93)	**Topiramate 50 mg/day**
2.68 (2.07, 3.54)	**2.69 (1.74, 4.08)**	**2.52 (1.87, 3.35)**	**2.36 (1.72, 3.21)**	**2.30 (1.72, 3.10)**	**2.16 (1.45, 3.26)**	**1.96 (1.22, 3.24)**	**1.95 (1.35, 2.86)**	**1.88 (1.43, 2.51)**	**1.70 (1.10, 2.66)**	**1.58 (1.07, 2.34)**	**Placebo**

Tau: 0.10 (0.01, 0.33); DIC: 79.4

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated odds ratio and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 1.

Figure D6. Network of Studies Assessing Days Using Acute Medication per Month in Episodic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

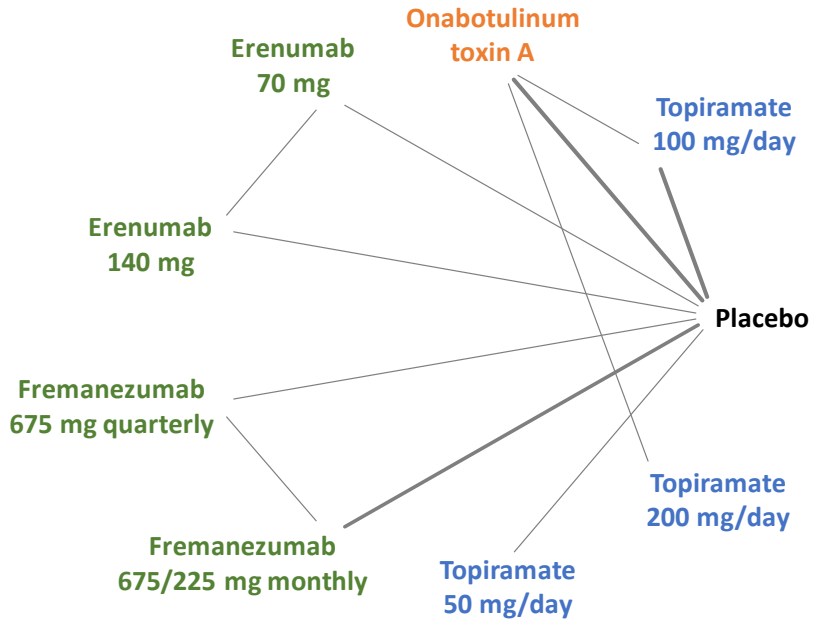
Table D24. Network Meta-Analysis Results for Change from Baseline in Days Using Acute Medication per Month in Episodic Migraine

Galcanezumab 120 mg											
-0.10 (-0.76, 0.55)	**Galcanezumab 240 mg**										
-0.17 (-1.12, 0.81)	-0.07 (-1.02, 0.91)	**Erenumab 140 mg**									
-0.60 (-1.58, 0.43)	-0.49 (-1.48, 0.53)	-0.42 (-1.48, 0.64)	**Fremanezumab 225 mg**								
-0.65 (-2.02, 0.73)	-0.55 (-1.91, 0.84)	-0.48 (-1.90, 0.93)	-0.05 (-1.52, 1.38)	**Amitriptyline 100 mg/day**							
-0.69 (-1.76, 0.41)	-0.59 (-1.66, 0.50)	-0.52 (-1.65, 0.61)	-0.09 (-0.97, 0.76)	-0.04 (-1.54, 1.46)	**Fremanezumab 675 mg quarterly**						
-0.72 (-1.69, 0.28)	-0.62 (-1.59, 0.38)	-0.55 (-1.59, 0.50)	-0.13 (-1.21, 0.95)	-0.06 (-1.42, 1.29)	-0.03 (-1.19, 1.13)	**Propranolol 160 mg/day**					
-0.85 (-1.64, -0.04)	-0.76 (-1.54, 0.07)	-0.68 (-1.55, 0.19)	-0.26 (-1.18, 0.65)	-0.20 (-1.33, 0.92)	-0.16 (-1.17, 0.84)	-0.13 (-0.89, 0.62)	**Topiramate 100 mg/day**				
-0.94 (-1.69, -0.10)	-0.84 (-1.58, 0.00)	-0.77 (-1.46, 0.00)	-0.34 (-1.22, 0.58)	-0.28 (-1.57, 1.04)	-0.25 (-1.21, 0.78)	-0.22 (-1.08, 0.71)	-0.08 (-0.73, 0.63)	**Erenumab 70 mg**			
-1.08 (-1.89, -0.22)	**-0.99 (-1.79, -0.12)**	-0.92 (-1.79, 0.00)	-0.49 (-1.43, 0.46)	-0.43 (-1.66, 0.82)	-0.39 (-1.41, 0.64)	-0.37 (-1.12, 0.42)	-0.23 (-0.75, 0.32)	-0.15 (-0.87, 0.55)	**Topiramate 200 mg/day**		
-1.37 (-2.43, -0.26)	**-1.27 (-2.33, -0.16)**	**-1.20 (-2.33, -0.05)**	-0.77 (-1.95, 0.41)	-0.71 (-2.14, 0.71)	-0.68 (-1.92, 0.57)	-0.65 (-1.73, 0.45)	-0.51 (-1.39, 0.38)	-0.43 (-1.45, 0.55)	-0.28 (-1.17, 0.59)	**Topiramate 50 mg/day**	
-1.80 (-2.44, -1.17)	**-1.71 (-2.33, -1.07)**	**-1.63 (-2.37, -0.92)**	**-1.21 (-2.01, -0.45)**	-1.15 (-2.38, 0.05)	**-1.11 (-2.00, -0.25)**	**-1.08 (-1.86, -0.34)**	**-0.95 (-1.45, -0.48)**	**-0.86 (-1.40, -0.44)**	**-0.72 (-1.28, -0.21)**	-0.44 (-1.34, 0.43)	**Placebo**

Tau: 0.26 (0.02, 0.64); DIC: 59.1

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated mean difference in change from baseline and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 0.

Figure D7. Network of Studies Assessing All-Cause Discontinuations in Chronic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, onabotulinum toxin A in orange, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

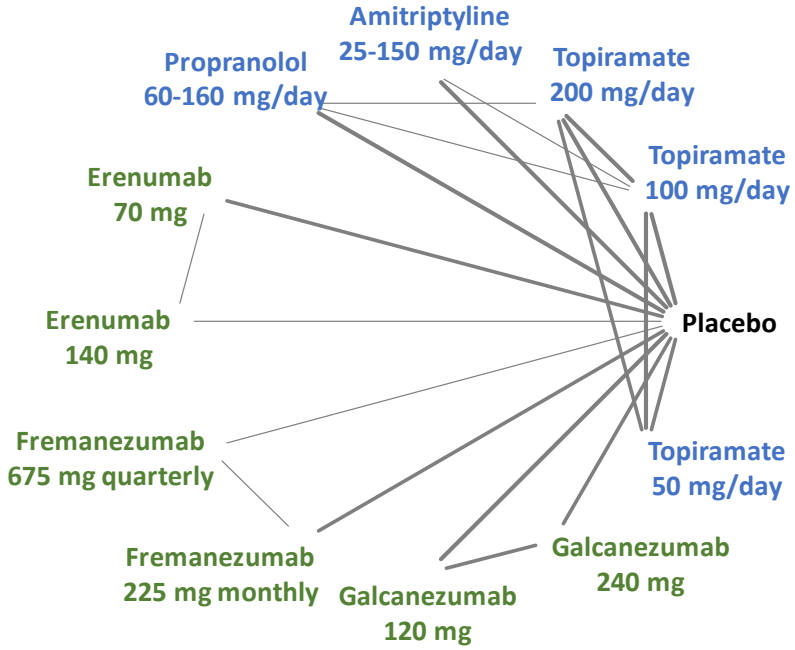
Table D25. Network Meta-Analysis Results for All-Cause Discontinuations in Chronic Migraine

Erenumab 140 mg								
0.76 (0.21, 2.65)	**Erenumab 70 mg**							
0.66 (0.15, 2.66)	0.87 (0.21, 3.39)	**Fremanezumab 675 mg quarterly**						
0.60 (0.16, 2.13)	0.79 (0.23, 2.72)	0.91 (0.34, 2.64)	**Topiramate 100 mg/day**					
0.55 (0.17, 1.67)	0.73 (0.23, 2.13)	0.84 (0.36, 1.99)	0.92 (0.51, 1.57)	**Placebo**				
0.50 (0.14, 1.76)	0.66 (0.20, 2.24)	0.76 (0.30, 2.19)	0.83 (0.43, 1.67)	0.91 (0.57, 1.58)	**Onabotulinum toxin A quarterly**			
0.43 (0.07, 2.93)	0.57 (0.09, 3.83)	0.66 (0.12, 3.83)	0.72 (0.15, 3.47)	0.79 (0.18, 3.61)	0.87 (0.21, 3.56)	**Topiramate 200 mg/day**		
0.46 (0.11, 1.67)	0.61 (0.16, 2.11)	0.70 (0.29, 1.62)	0.77 (0.30, 1.78)	0.84 (0.41, 1.62)	0.93 (0.36, 2.01)	1.06 (0.2, 5.22)	**Fremanezumab 675/225 mg**	
NE	NE	NE	NE	NE	NE	NE	NE	**Topiramate 50 mg/day**

Tau: 0.23 (0.01, 0.83); DIC: 49.1; NE: not able to be estimated

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated odds ratio and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 1.

Figure D8. Network of Studies Assessing All-Cause Discontinuations in Episodic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

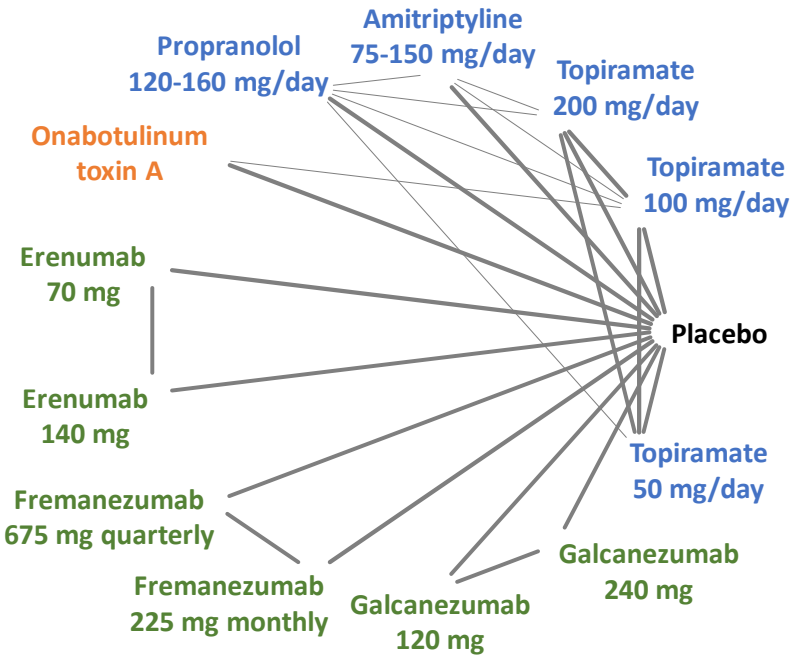
Table D26. Network Meta-Analysis Results for All-Cause Discontinuations in Episodic Migraine

Erenumab 140 mg											
0.90 (0.39, 2.08)	**Erenumab 70 mg**										
0.74 (0.26, 1.97)	0.83 (0.32, 1.94)	**Galcanezumab 240 mg**									
0.71 (0.26, 1.83)	0.80 (0.32, 1.81)	0.96 (0.52, 1.73)	**Galcanezumab 120 mg**								
0.68 (0.24, 1.67)	0.75 (0.30, 1.66)	0.91 (0.41, 1.86)	0.95 (0.45, 1.87)	**Propranolol 60-160 mg/day**							
0.64 (0.25, 1.50)	0.71 (0.31, 1.47)	0.86 (0.44, 1.66)	0.90 (0.48, 1.67)	0.95 (0.56, 1.67)	**Topiramate 100 mg/day**						
0.63 (0.27, 1.39)	0.70 (0.34, 1.34)	0.84 (0.48, 1.50)	0.88 (0.53, 1.50)	0.93 (0.59, 1.57)	0.98 (0.70, 1.41)	**Placebo**					
0.60 (0.22, 1.45)	0.67 (0.28, 1.44)	0.81 (0.38, 1.61)	0.84 (0.42, 1.63)	0.89 (0.49, 1.64)	0.94 (0.57, 1.50)	0.96 (0.60, 1.45)	**Amitriptyline 75-100 mg/day**				
0.58 (0.17, 1.82)	0.64 (0.21, 1.84)	0.77 (0.28, 2.13)	0.80 (0.30, 2.18)	0.85 (0.33, 2.33)	0.90 (0.36, 2.25)	0.92 (0.39, 2.12)	0.96 (0.38, 2.53)	**Fremanezumab 675 mg quarterly**			
0.57 (0.22, 1.52)	0.63 (0.27, 1.49)	0.76 (0.37, 1.73)	0.79 (0.40, 1.76)	0.84 (0.45, 1.79)	0.88 (0.55, 1.60)	0.90 (0.56, 1.58)	0.94 (0.52, 1.95)	0.98 (0.38, 2.79)	**Topiramate 50 mg/day**		
0.45 (0.14, 1.29)	0.51 (0.18, 1.28)	0.61 (0.24, 1.47)	0.64 (0.26, 1.50)	0.67 (0.29, 1.59)	0.71 (0.32, 1.53)	0.73 (0.35, 1.42)	0.76 (0.33, 1.72)	0.79 (0.34, 1.80)	0.80 (0.31, 1.81)	**Fremanezumab 225 mg**	
0.37 (0.15, 0.90)	**0.41 (0.18, 0.88)**	0.50 (0.25, 1.00)	0.52 (0.27, 1.01)	0.55 (0.32, 1.00)	**0.57 (0.38, 0.90)**	**0.59 (0.40, 0.87)**	0.61 (0.37, 1.09)	0.64 (0.26, 1.64)	0.65 (0.37, 1.08)	0.81 (0.38, 1.87)	**Topiramate 200 mg/day**

Tau: 0.31 (0.08, 0.59); DIC: 120.2

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated odds ratio and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 1.

Figure D9. Network of Studies Assessing Discontinuations from Adverse Events in Chronic or Episodic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, onabotulinum toxin A in orange, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

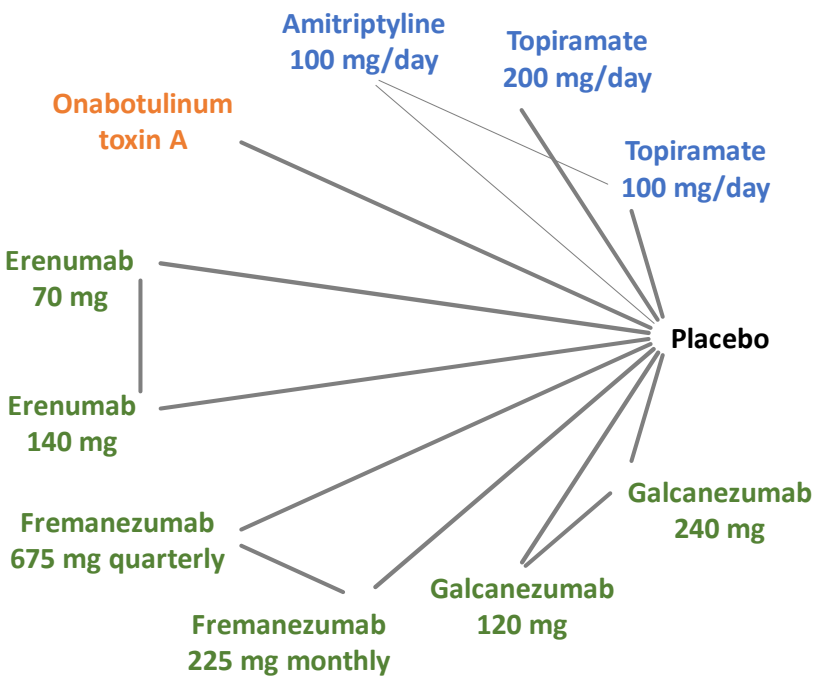
Table D27. Network Meta-Analysis Results for Discontinuations from Adverse Events in Chronic or Episodic Migraine

Placebo												
0.97 (0.33, 2.82)	Fremanezumab 675 mg quarterly											
0.74 (0.28, 1.87)	0.76 (0.18, 3.18)	Erenumab 70 mg										
0.71 (0.34, 1.53)	0.74 (0.20, 2.82)	0.97 (0.30, 3.33)	Propranolol 120-160 mg/day									
0.74 (0.22, 2.39)	0.76 (0.15, 3.72)	1.01 (0.30, 3.27)	1.04 (0.24, 4.09)	Erenumab 140 mg								
0.64 (0.24, 1.74)	0.66 (0.16, 2.91)	0.87 (0.23, 3.48)	0.90 (0.26, 3.11)	0.87 (0.19, 4.20)	Galcanezumab 120 mg							
0.63 (0.32, 1.32)	0.65 (0.18, 2.45)	0.85 (0.27, 2.88)	0.88 (0.35, 2.28)	0.85 (0.22, 3.56)	0.98 (0.30, 3.38)	Topiramate 50 mg/day						
0.60 (0.24, 1.42)	0.62 (0.21, 1.72)	0.82 (0.22, 2.90)	0.85 (0.25, 2.58)	0.82 (0.18, 3.51)	0.94 (0.24, 3.43)	0.96 (0.28, 2.84)	Fremanezumab 675/225 mg					
0.54 (0.20, 1.42)	0.55 (0.13, 2.39)	0.73 (0.19, 2.89)	0.75 (0.22, 2.53)	0.73 (0.16, 3.46)	0.84 (0.30, 2.29)	0.85 (0.25, 2.79)	0.89 (0.25, 3.49)	Galcanezumab 240 mg				
0.39 (0.16, 0.89)	0.40 (0.10, 1.57)	0.53 (0.15, 1.88)	0.54 (0.17, 1.61)	0.52 (0.12, 2.27)	0.60 (0.16, 2.18)	0.62 (0.20, 1.76)	0.64 (0.19, 2.27)	0.72 (0.19, 2.58)	Onabotulinum toxin A quarterly			
0.39 (0.25, 0.59)	0.41 (0.13, 1.27)	0.53 (0.19, 1.49)	0.56 (0.24, 1.15)	0.53 (0.15, 1.88)	0.61 (0.20, 1.76)	0.63 (0.29, 1.20)	0.65 (0.25, 1.79)	0.73 (0.25, 2.07)	1.02 (0.41, 2.51)	Topiramate 100 mg/day		
0.36 (0.17, 0.71)	0.37 (0.10, 1.33)	0.49 (0.15, 1.57)	0.51 (0.19, 1.25)	0.49 (0.12, 1.94)	0.57 (0.16, 1.85)	0.58 (0.21, 1.40)	0.60 (0.20, 1.89)	0.68 (0.20, 2.18)	0.94 (0.31, 2.76)	0.92 (0.45, 1.88)	Amitriptyline 75-150 mg/day	
0.27 (0.16, 0.47)	**0.28 (0.09, 0.94)**	0.37 (0.13, 1.11)	**0.38 (0.17, 0.84)**	0.37 (0.10, 1.39)	0.42 (0.14, 1.31)	**0.43 (0.20, 0.87)**	0.45 (0.17, 1.34)	0.51 (0.17, 1.54)	0.70 (0.27, 1.94)	0.69 (0.41, 1.25)	0.75 (0.35, 1.74)	Topiramate 200 mg/day

Tau: 0.44 (0.13, 0.83); DIC: 147.3

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated odds ratio and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 1.

Figure D10. Network of Studies Assessing Serious Adverse Events in Chronic or Episodic Migraine Patients



Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, onabotulinum toxin A in orange, and placebo in black. The thickness of the connecting lines is related to the number of trials available for each pair of treatments.

Table D28. Network Meta-Analysis Results for Serious Adverse Events in Chronic or Episodic Migraine

Fremanezumab 675 mg quarterly										
0.81 (0.16, 4.08)	**Erenumab 140 mg**									
0.62 (0.17, 1.96)	0.76 (0.17, 3.17)	**Fremanezumab 675/225 mg**								
0.51 (0.15, 1.59)	0.63 (0.20, 1.77)	0.81 (0.31, 2.23)	**Placebo**							
0.47 (0.09, 2.49)	0.59 (0.12, 2.91)	0.77 (0.17, 3.67)	0.94 (0.30, 3.07)	**Topiramate 100 mg/day**						
0.46 (0.10, 1.84)	0.56 (0.18, 1.55)	0.73 (0.20, 2.67)	0.90 (0.38, 2.03)	0.96 (0.21, 3.83)	**Erenumab 70 mg**					
0.43 (0.03, 4.64)	0.53 (0.04, 5.4)	0.70 (0.06, 7.05)	0.86 (0.09, 6.75)	0.89 (0.08, 9.85)	0.95 (0.09, 8.96)	**Topiramate 200 mg/day**				
0.37 (0.07, 2.08)	0.45 (0.09, 2.33)	0.59 (0.14, 3.27)	0.72 (0.23, 2.78)	0.78 (0.15, 4.31)	0.81 (0.20, 3.86)	0.86 (0.08, 11.27)	**Galcanezumab 240 mg**			
0.24 (0.05, 1.00)	0.29 (0.07, 1.13)	0.38 (0.10, 1.44)	0.47 (0.19, 1.11)	0.50 (0.11, 2.03)	0.52 (0.15, 1.74)	0.54 (0.06, 6.07)	0.64 (0.13, 2.63)	**Onabotulinum toxin A quarterly**		
0.19 (0.04, 0.88)	0.24 (0.05, 1.02)	0.31 (0.08, 1.29)	0.38 (0.13, 1.07)	0.41 (0.08, 1.86)	0.43 (0.11, 1.57)	0.45 (0.04, 5.00)	0.53 (0.14, 1.55)	0.82 (0.20, 3.13)	**Galcanezumab 120 mg**	
0.16 (0.03, 0.77)	**0.20 (0.04, 0.89)**	0.26 (0.07, 1.15)	**0.32 (0.12, 0.91)**	0.35 (0.10, 1.12)	0.36 (0.10, 1.39)	0.38 (0.04, 4.43)	0.44 (0.09, 2.03)	0.69 (0.19, 2.77)	0.84 (0.21, 3.88)	**Amitriptyline 100 mg/day**

Tau: 0.28 (0.01, 1.05); DIC: 79.9

Legend: The treatments are arranged from highest surface under the cumulative ranking curves (top left) to lowest (bottom right), where treatments more likely to be ranked higher are listed first. Each box represents the estimated odds ratio and 95% credible interval for the combined direct and indirect comparisons. Estimates in bold signify that the 95% credible interval does not contain 1.

Additional Analyses

Below, we provide the results by timepoint of analysis for each outcome where data were available. We also provide the results from analyses with a covariate for timepoint, along with the results without covariate adjustment for comparison. Results from the NMA are only presented in terms of the difference or odds ratio for each treatment versus placebo.

Table D29. Analysis by Timepoint and with Covariate Adjustment for Monthly Migraine days in Chronic Migraine

	4 weeks	8 weeks	12 weeks	Covariate Adjustment	No Covariate Adjustment	No Covariate Adjustment, without Diener 2007
Erenumab 70 mg monthly	-2.36 (-5.09, 0.38)	-2.65 (-5.17, -0.10)	-2.40 (-4.62, -0.16)	-2.22 (-9.28, 9.74)	-2.4 (-5.17, 0.36)	-2.40 (-4.79, 0.00)
Erenumab 140 mg monthly	-2.43 (-5.17, 0.30)	-2.89 (-5.42, -0.34)	-2.40 (-4.61, -0.17)	-2.22 (-9.30, 9.69)	-2.4 (-5.15, 0.36)	-2.40 (-4.77, 0.00)
Fremanezumab 675 mg quarterly	-2.12 (-4.68, 0.40)	-1.49 (-3.82, 0.89)	-1.29 (-3.38, 0.79)	-1.13 (-8.11, 10.81)	-1.3 (-3.87, 1.28)	-1.30 (-3.54, 0.93)
Fremanezumab 675/225 mg monthly	-2.06 (-4.05, -0.09)	-1.85 (-3.68, 0.06)	-1.65 (-3.34, 0.01)	-1.51 (-8.29, 10.4)	-1.66 (-3.71, 0.37)	-1.66 (-3.47, 0.12)
Onabotulinum toxin A 155U quarterly	-2.10 (-3.99, -0.20)	-1.80 (-3.57, -0.04)	-1.40 (-2.94, 0.13)	-2.15 (-21.39, 8.62)	-1.95 (-3.88, -0.02)	-1.95 (-3.62, -0.28)
Topiramate 100 mg/day				-2.16 (-4.74, 0.16)	-2.23 (-4.7, -0.26)	-1.70 (-4.18, 0.79)
Tau	0.83 (0.06, 2.49)	0.65 (0.03, 2.55)	0.54 (0.02, 2.15)	0.70 (0.03, 3.01)	0.69 (0.03, 2.99)	0.65 (0.03, 2.19)
B				0.27 (-15.17, 28.19)		
DIC	21.5	20.7	20.1	27.7	28.2	24.6

Tau: standard deviation of treatment effect estimates; B: coefficient on the analysis adjusting for timepoint; DIC: deviance information criteria

Table D30. Analysis by Timepoint and with Covariate Adjustment for Monthly Headache days in Chronic Migraine

	4 weeks	8 weeks	12 weeks	Covariate Adjustment	No Covariate Adjustment
Fremanezumab 675 mg quarterly	-2.17 (-4.07, -0.26)	-1.67 (-5.61, 2.36)	-1.47 (-5.07, 2.17)	-1.22 (-4.24, 1.98)	-1.47 (-3.72, 0.79)
Fremanezumab 675/225 mg monthly	-2.12 (-3.59, -0.63)	-1.84 (-4.81, 1.31)	-1.85 (-4.62, 0.96)	-1.60 (-4.22, 1.18)	-1.85 (-3.63, -0.06)
Onabotulinum toxin A 155U quarterly	-1.25 (-2.68, 0.05)	-1.84 (-5.05, 0.42)	-1.46 (-4.65, 0.39)	-2.40 (-5.38, 0.47)	-2.06 (-3.48, -0.63)
Topiramate 100 mg/day				-1.08 (-3.88, 1.76)	-1.10 (-3.56, 1.38)
Topiramate 200 mg/day	-2.65 (-6.29, 0.94)		-1.63 (-7.4, 3.18)	-2.55 (-7.54, 2.30)	-2.14 (-6.16, 1.86)
Tau	0.43 (0.02, 2.22)	1.17 (0.1, 4.64)	0.75 (0.03, 4.90)	0.68 (0.04, 3.14)	0.58 (0.03, 2.76)
B				0.56 (-3.43, 4.75)	
DIC	19.9	19.2	22.6	29.0	27.8

Tau: standard deviation of treatment effect estimates; B: coefficient on the analysis adjusting for timepoint; DIC: deviance information criteria

Table D31. Analysis by Timepoint and with Covariate Adjustment for Monthly Migraine days in Episodic Migraine

	4 weeks	8 weeks	12 weeks	24/26 weeks	Covariate Adjustment	No Covariate Adjustment
Erenumab 70 mg monthly	-1.16 (-2.05, -0.25)	-1.15 (-1.89, -0.39)	-1.16 (-1.79, -0.53)	-1.59 (-2.53, -0.66)	-1.35 (-1.89, -0.78)	-1.30 (-1.79, -0.79)
Erenumab 140 mg monthly	-1.69 (-3.08, -0.29)	-1.52 (-2.65, -0.36)	-1.74 (-2.69, -0.78)	-2.09 (-3.03, -1.16)	-1.92 (-2.70, -1.15)	-1.95 (-2.68, -1.19)
Fremanezumab 675 mg quarterly	-1.64 (-3.17, -0.12)	-1.26 (-2.60, -0.02)	-1.20 (-2.40, -0.13)		-1.33 (-2.42, -0.26)	-1.19 (-2.16, -0.25)
Fremanezumab 225 mg monthly	-1.97 (-3.22, -0.76)	-1.63 (-2.81, -0.62)	-1.62 (-2.68, -0.74)		-1.73 (-2.74, -0.79)	-1.59 (-2.46, -0.79)
Galcanezumab 120 mg monthly	-1.90 (-2.78, -0.95)	-1.49 (-2.26, -0.65)	-1.67 (-2.37, -1.01)	-1.76 (-2.53, -0.99)	-1.77 (-2.39, -1.17)	-1.80 (-2.40, -1.20)
Galcanezumab 240 mg monthly	-1.76 (-2.82, -0.66)	-1.55 (-2.44, -0.61)	-1.96 (-2.72, -1.18)	-1.82 (-2.54, -1.11)	-1.78 (-2.45, -1.12)	-1.84 (-2.48, -1.22)
Topiramate 50 mg/day				-0.18 (-1.03, 0.64)	-0.06 (-0.97, 0.81)	-0.17 (-0.97, 0.61)
Topiramate 100 mg/day				-1.17 (-1.72, -0.65)	-1.06 (-1.69, -0.47)	-1.17 (-1.66, -0.70)
Topiramate 200 mg/day				-0.96 (-1.61, -0.39)	-0.85 (-1.56, -0.19)	-0.96 (-1.53, -0.42)
Amitriptyline 25-100 mg/day	-1.1 (-3.54, 1.33)	-1.21 (-3.52, 1.07)	-1.09 (-3.28, 1.13)	-1.08 (-2.59, 0.42)	-1.05 (-2.25, 0.14)	-1.07 (-2.24, 0.11)
Propranolol 160 mg/day				-1.2 (-2.1, -0.35)	-1.09 (-2.02, -0.22)	-1.2 (-2.01, -0.43)
Tau	0.53 (0.08, 1.46)	0.38 (0.02, 1.26)	0.26 (0.01, 1.06)	0.25 (0.01, 0.80)	0.22 (0.01, 0.65)	0.21 (0.01, 0.6)
B					-0.26 (-1.11, 0.64)	
DIC	42.7	41.8	40.4	43.8	66.3	65.1

Tau: standard deviation of treatment effect estimates; B: coefficient on the analysis adjusting for timepoint; DIC: deviance information criteria

Table D32. Analysis by Timepoint and with Covariate Adjustment for 50% Responders in Episodic Migraine

	4 weeks	8 weeks	12 weeks	Covariate Adjustment	No Covariate Adjustment
Erenumab 70 mg monthly	2.22 (1.37, 3.55)	1.75 (1.15, 2.65)	1.83 (1.21, 2.80)	1.94 (1.46, 2.58)	1.88 (1.43, 2.51)
Erenumab 140 mg monthly	2.72 (1.33, 5.66)	2.34 (1.24, 4.42)	2.51 (1.33, 4.75)	2.12 (1.42, 3.18)	2.16 (1.45, 3.26)
Fremanezumab 675 mg quarterly	2.49 (1.20, 5.28)	1.73 (0.91, 3.39)	1.71 (0.90, 3.36)	1.90 (1.18, 3.04)	1.70 (1.10, 2.66)
Fremanezumab 225 mg monthly	2.89 (1.65, 5.38)	1.91 (1.16, 3.33)	1.96 (1.19, 3.44)	2.16 (1.44, 3.28)	1.95 (1.35, 2.86)
Galcanezumab 120 mg monthly			1.96 (0.80, 4.99)	2.38 (1.76, 3.23)	2.52 (1.87, 3.35)
Galcanezumab 240 mg monthly				2.19 (1.58, 3.08)	2.36 (1.72, 3.21)
Topiramate 50 mg/day				1.45 (0.97, 2.23)	1.58 (1.07, 2.34)
Topiramate 100 mg/day				2.49 (1.87, 3.41)	2.68 (2.07, 3.54)
Topiramate 200 mg/day				2.14 (1.56, 2.96)	2.30 (1.72, 3.10)
Amitriptyline 25-100 mg/day			2.55 (0.93, 7.22)	1.91 (1.19, 3.17)	1.96 (1.22, 3.24)
Propranolol 120-160 mg/day			1.65 (0.66, 4.32)	2.56 (1.69, 3.94)	2.69 (1.74, 4.08)
Tau	0.18 (0.01, 0.90)	0.17 (0.01, 0.74)	0.17 (0.01, 0.76)	0.10 (0.00, 0.33)	0.10 (0.01, 0.33)
B				0.2 (-0.17, 0.55)	
DIC	21.4	21.5	33.5	79.7	79.4

Tau: standard deviation of treatment effect estimates; B: coefficient on the analysis adjusting for timepoint; DIC: deviance information criteria

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[216]

Probabilistic Sensitivity Analyses

Figure E1. Scatterplot of Costs and Effects Comparing Erenumab 140 mg Monthly to No Preventive Treatment in Patients with Chronic Migraine for Whom Prior Preventive Therapies Failed

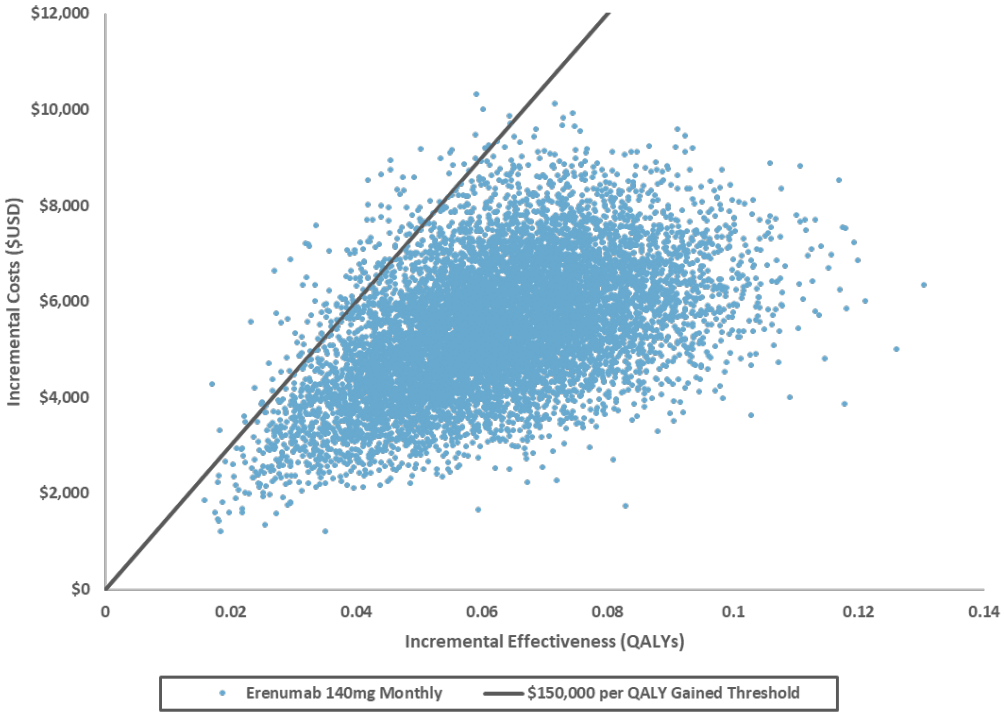


Figure E2. Scatterplot of Costs and Effects Comparing Fremanezumab 625/225mg Monthly to No Preventive Treatment in Patients with Chronic Migraine for whom Prior Preventive Therapies Failed

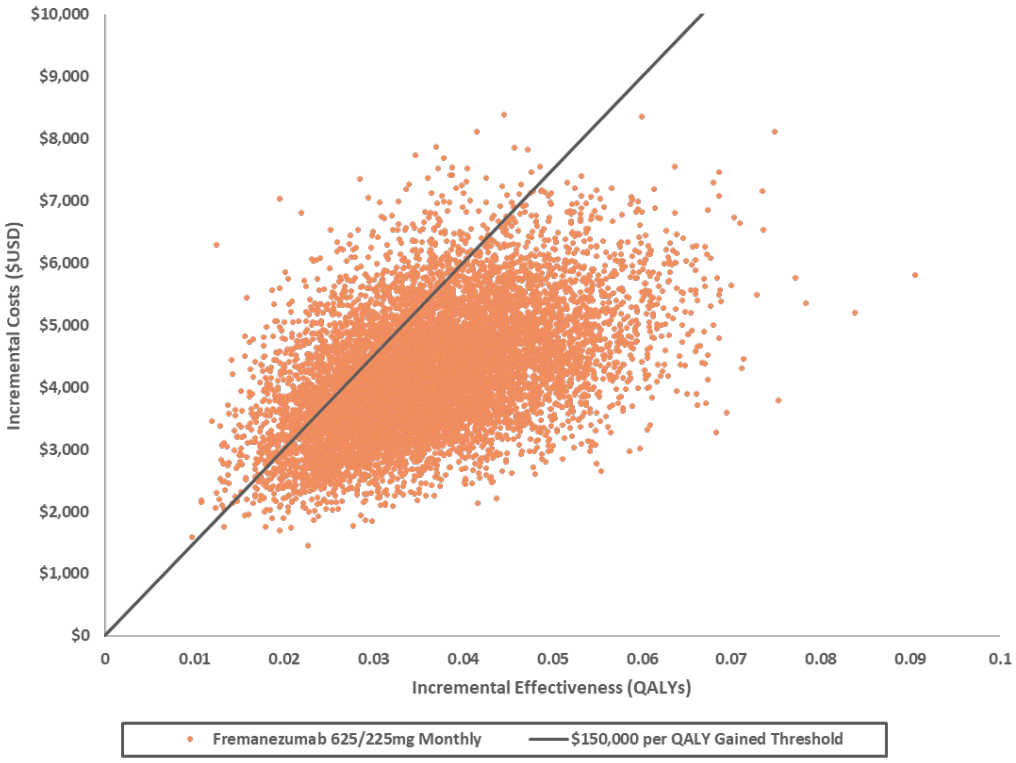


Figure E3. Cost-Effectiveness Acceptability Curves Comparing CGRP Inhibitors to No Preventive Treatment in Chronic Migraine

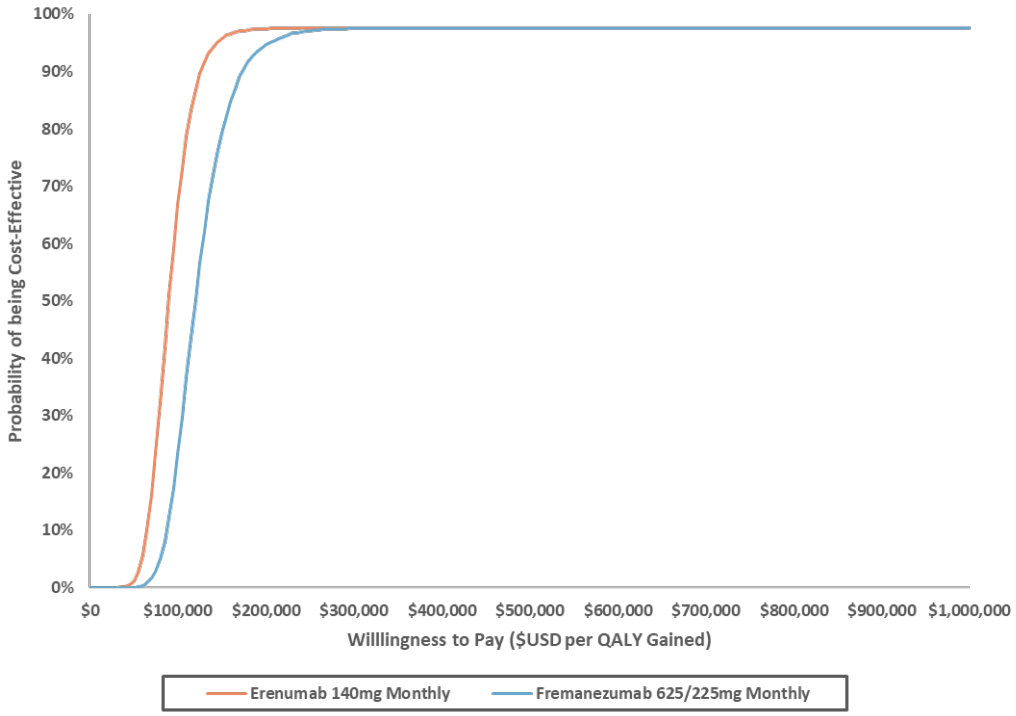


Figure E4. Scatterplot of Costs and Effects Comparing Erenumab 140mg Monthly to No Preventive Treatment in Patients with Episodic Migraine for whom Prior Preventive Therapies Failed

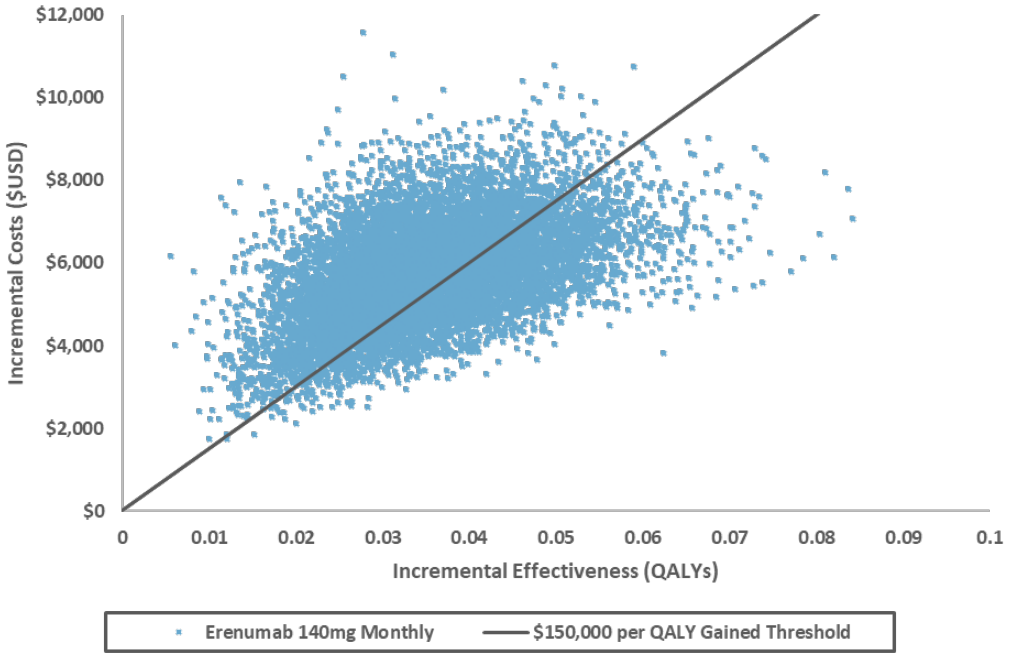


Figure E5. Scatterplot of Costs and Effects Comparing Fremanezumab 225mg Monthly to No Preventive Treatment in Patients with Episodic Migraine for whom Prior Preventive Therapies Failed

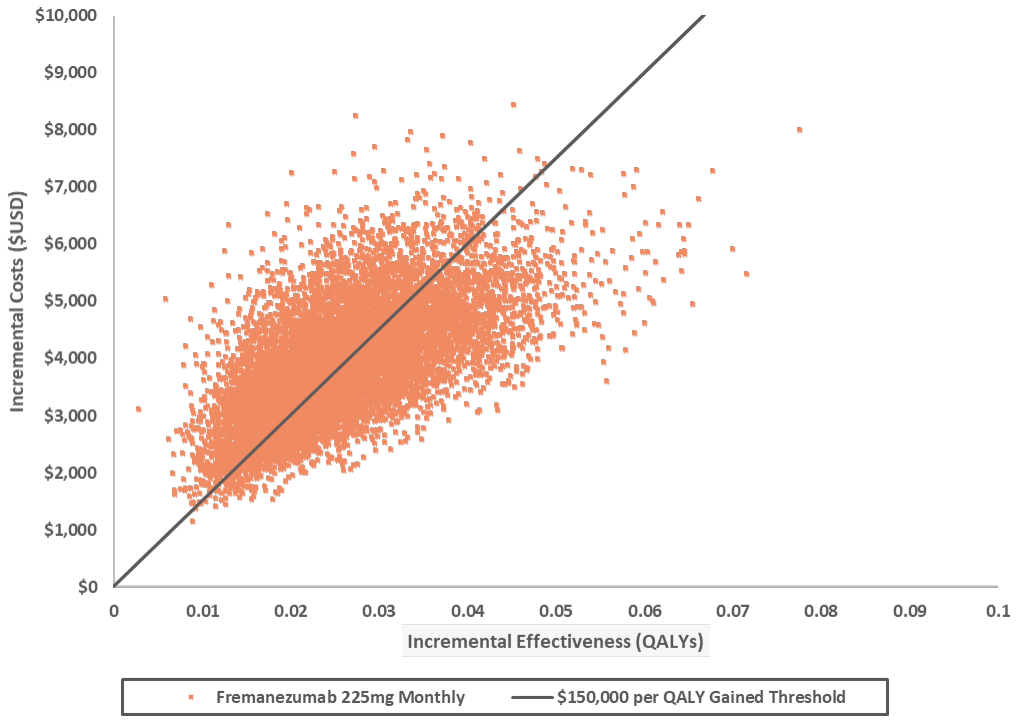
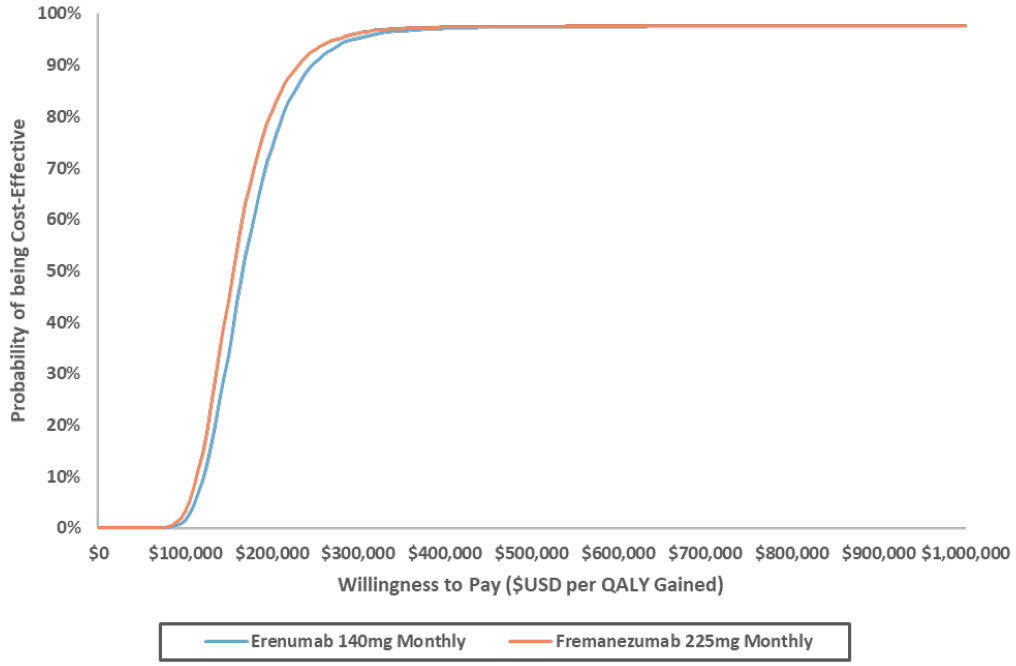


Figure E6. Cost-Effectiveness Acceptability Curves Comparing CGRP Inhibitors to No Preventive Treatment in Episodic Migraine



Scenario Analyses

CGRP Inhibitors Versus Preventive Treatments

Inputs used in the scenario analyses comparing CGRP inhibitors to preventive treatments are shown in Tables E2 – E10.

Table E2. Distribution of Preventive Treatments for Episodic and Chronic Migraine

Drug	Episodic Migraine Distribution (%)*	Chronic Migraine Distribution (%)*	Source
Amitriptyline	16.2	10.1	Ford et al. 2017[6]
Propranolol	26.8	11.1	Ford et al. 2017[6]
Topiramate	56.9	55.6	Ford et al. 2017[6]
Onabotulinum toxin A	--	23.3	Ford et al. 2017[6]

*The distributions from Ford et al. were re-weighted for the preventive treatments included in the review

Table E3. Distribution of Current Treatment Mix for Episodic and Chronic Migraine

Drug	Episodic Migraine Distribution (%)	Chronic Migraine Distribution (%)	Source
Amitriptyline	8.4	9.7	Ford et al. 2017[6]
Propranolol	13.9	10.6	Ford et al. 2017[6]
Topiramate	29.6	53.1	Ford et al. 2017[6]
Onabotulinum toxin A	--	22.2	Ford et al. 2017[6]
No Treatment	48.1	4.4	Ford et al. 2017[6]

*The distributions from Ford et al. were re-weighted for the preventive treatments included in the review

Table E4. Treatment Effects and Migraine Severity Distribution for Onabotulinum toxin A in Chronic Migraine Among Those for Whom Previous Preventive Therapy Failed

Treatment	Mean Reduction in Migraine Days (95% CI)					
	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Onabotulinum toxin A	0.8 (-1.92, 0.22)	1.5 (-2.66, -0.37)	2.0 (-3.18, -0.82)	-1.8 (-3.03, -0.50)	-2.5 (-3.72, -1.20)	-2.0 (-3.25, -0.68)
Severe Migraine, %	51.2%	50.5%	49.8%	49.1%	48.4%	47.7%
Moderate Migraine %	41.2%	41.5%	41.7%	42.0%	42.2%	42.5%
Mild Migraine %	7.6%	8.0%	8.5%	8.9%	9.4%	9.8%

CI: confidence interval

Table E5. Monthly Treatment Effects for CGRP Inhibitors and Active Preventive Treatments in Chronic Migraine

Treatment	Mean Reduction in Migraine Days (95% CI)
Erenumab 140 mg monthly	-2.57 (-5.11, 0.00)
Fremanezumab 675/225 mg monthly	-1.78 (-3.72, 0.11)
Topiramate 100 mg daily	-1.82 (-4.48, 0.73)
Amitriptyline 100 mg daily	-1.15 (-2.86, 0.48)
Propranolol 160 mg daily	-1.30 (-2.36, -0.28)
Onabotulinum toxin A	-2.09 (-3.88, -0.31)

CI: confidence interval

Table E6. Treatment Effects for CGRP Inhibitors and Active Preventive Treatments in Episodic Migraine

Treatment	Mean Reduction in Migraine Days (95% CI)
Erenumab 140 mg monthly	-1.95 (-2.68, -1.19)
Fremanezumab 225 mg monthly	-1.59 (-2.46, -0.79)
Galcanezumab 240 mg monthly	-1.84 (-2.48, -1.22)
Topiramate 100 mg daily	-1.17 (-1.66, -0.70)
Amitriptyline 100 mg daily	-1.07 (-2.24, 0.11)
Propranolol 160 mg daily	-1.20 (-2.01, -0.43)

CI: confidence interval

Table E7. Reduction in Days per Month of Acute Treatments for Active Preventive Treatments

Treatment	Episodic Migraine: Mean Reduction in Acute Treatment Days per Month (95% CI)	Chronic Migraine: Mean Reduction in Acute Treatment Days per Month (95% CI)
Topiramate 100 mg daily	-0.95 (-1.45, -0.48)	-1.36 (-3.79, 0.62)
Amitriptyline 100 mg daily	-1.15 (-2.38, 0.05)	-1.24 (-2.71, 0.17)
Propranolol 160 mg daily	-1.08 (-1.86, -0.34)	--1.17 (-2.14, -0.25)
Onabotulinum toxin A	--	-1.18 (-1.86, -0.65)

CI: confidence interval

Table E8. Monthly Discontinuation Rates for Active Preventive Treatments

Treatment	Episodic Migraine: Discontinuation Rate (95% CI)	Chronic Migraine: Discontinuation Rate (95% CI)
Active Treatments (weighted*)	0.053 (0.037,0.079)	0.055 (0.037,0.085)

CI: confidence interval

*Weighted mean of the mix of active treatments

Table E9. Proportion of Patients Experiencing an Adverse Event Each Cycle for the Active Preventive Treatments

Treatment	Chronic Migraine: Adverse Event Rate	Source	Episodic Migraine: Adverse Event Rate	Source
Topiramate 100 mg daily	28.6%	Dodick et al. 2009	28.6%	Dodick et al. 2009
Amitriptyline 100 mg daily	26.0%	Dodick et al. 2009	26.0%	Dodick et al. 2009
Propranolol 160 mg daily	9.5%	Diamond et al. 1976	9.5%	Diamond et al. 1976
Onabotulinum toxin A	3.5%	Diener et al. 2010[217]	NA	NA

Table E10. Drug Cost for Active Preventive Treatments

Drug	Administration	Unit	WAC per Unit/Dose*	Annual Drug Cost
Amitriptyline	PO	mg	$0.028	$992
Topiramate	PO	mg	$0.0039	$137
Propranolol	PO	mg	$0.0095	$830
Onabotulinum toxin A	SQ	units	$857.28	$3429.12

WAC: wholesale acquisition cost

Table E11. Discounted Costs and Effects for Onabotulinum Toxin A in Chronic Migraine

Treatment	Drug Cost	Total Cost	Migraine-Free Days Gained	QALYs
CGRP Inhibitors vs. Onabotulinum Toxin A				
Erenumab 140mg monthly				
Fremanezumab 625/225 mg monthly				
Onabotulinum Toxin A	$4,017	$11,175	23.86	1.46

Results in this table are redacted to preserve the confidentiality of certain data inputs used in their generation

Table E12. Incremental Cost-Effectiveness Ratios for the Scenario Analysis Comparing CGRP Inhibitors to Onabotulinum Toxin A*

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-free Day Gained
Chronic Migraine			
Erenumab 140mg monthly	Onabotulinum Toxin A	$50,000	$60
Fremanezumab 625/225mg monthly	Onabotulinum Toxin A	$90,000	$80

*To ensure the confidentiality of the data used to generate the results, are rounded to the nearest 10,000 for cost per QALY gained and to the nearest ten for cost per migraine-free day gained

Table E13. Discounted Costs and Effects for CGRP Inhibitors Compared to Preventive Treatments in Chronic Migraine

Treatment	Drug Cost	Total Cost	Migraine-Free Days Gained	QALYs
CGRP Inhibitors vs. Preventive Treatment				
Erenumab 140mg monthly	$7,512	$13,525	52.50	1.497
Fremanezumab 625/225 mg monthly	$6,062	$12,561	40.58	1.485
Preventive Treatment	$2,225	$9,099	39.24	1.484

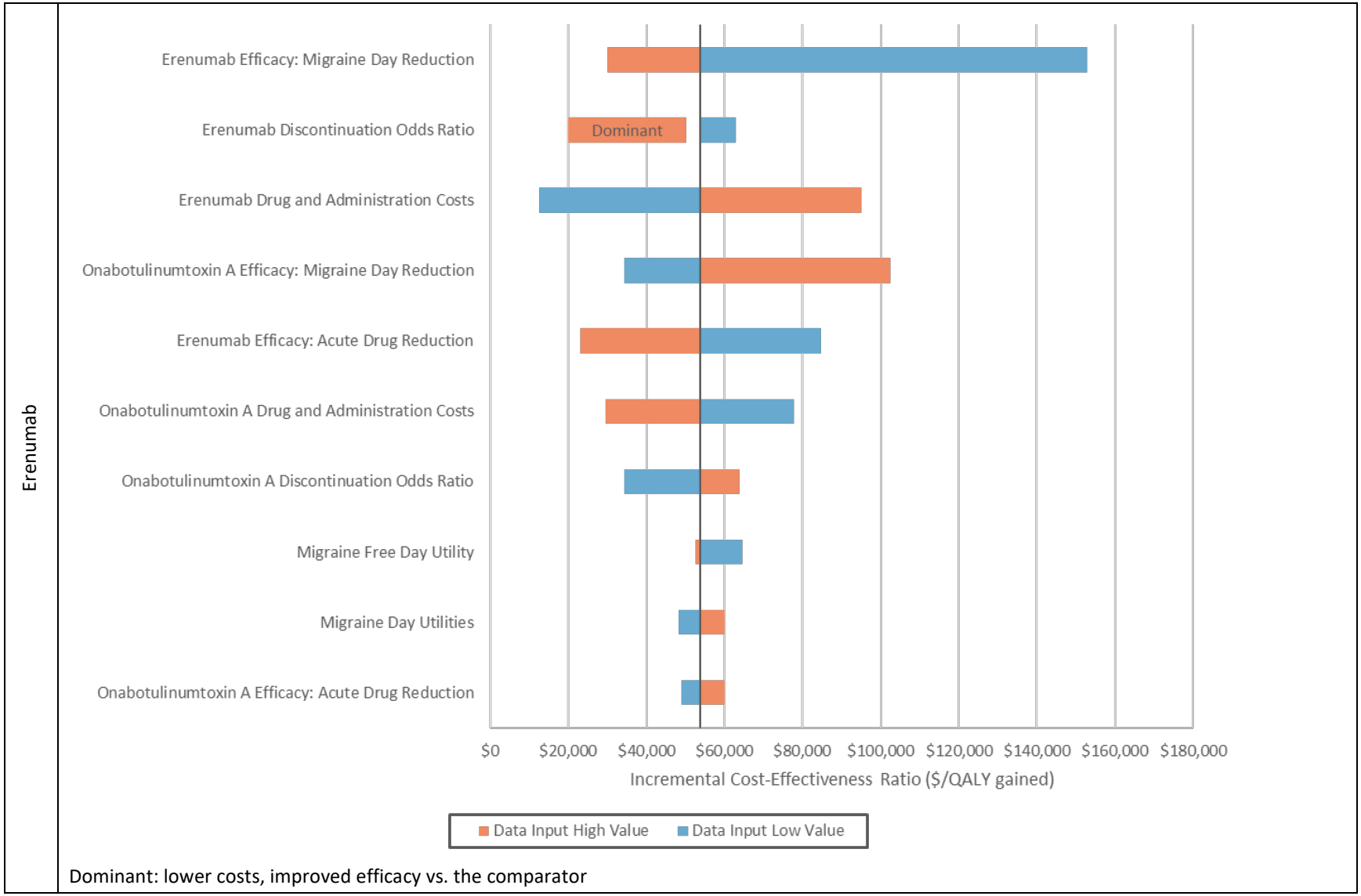
QALYs: quality-adjusted life years

Table E14. Discounted Costs and Effects for CGRP Inhibitors Compared to Preventive Treatments in Episodic Migraine

Treatment	Drug Cost	Total Cost	Migraine-Free Days Gained	QALYs
CGRP Inhibitors vs. Preventive Treatment				
Erenumab 140mg monthly	$6,817	$8,639	36.95	1.693
Fremanezumab 225 mg monthly	$5,012	$7,128	26.90	1.983
Galcanezumab 240 mg monthly	$4,993	$6,881	33.03	1.688
Preventive Treatment	$709	$2,994	22.71	1.679

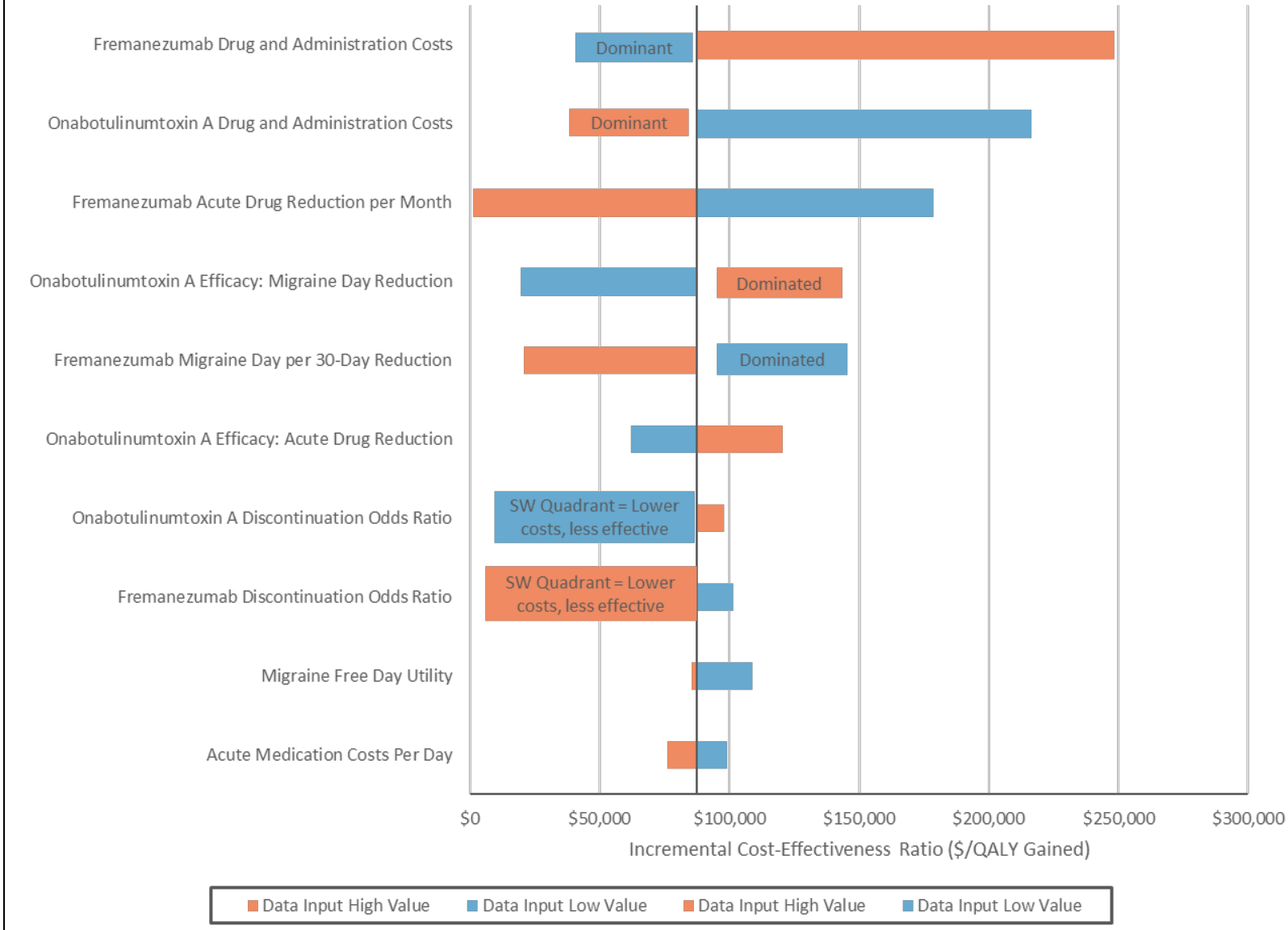
QALYs: quality-adjusted life years

Figure E7. Tornado Diagrams for One-Way Sensitivity Analyses of CGRP Inhibitors versus Onabotulinum Toxin A in Chronic Migraine



Dominant: lower costs, improved efficacy vs. the comparator

Fremanezumab



Dominated: higher costs, inferior efficacy vs. the comparator

Table E15. Probabilistic Sensitivity Analysis Results: CGRP Inhibitors versus Onabotulinum Toxin A

Treatment	Comparator	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY
Chronic Migraine				
Erenumab 140 mg monthly	Onabotulinum toxin A	43.4%	79.7%	90.4%
Fremanezumab 625/225 mg monthly	Onabotulinum toxin A	38.1%	49.9%	56.7%

Figure E8. Scatterplot of Costs and Effects Comparing Erenumab 140mg Monthly to Onabotulinum Toxin A in Patients with Chronic Migraine for whom Prior Preventive Therapies Failed

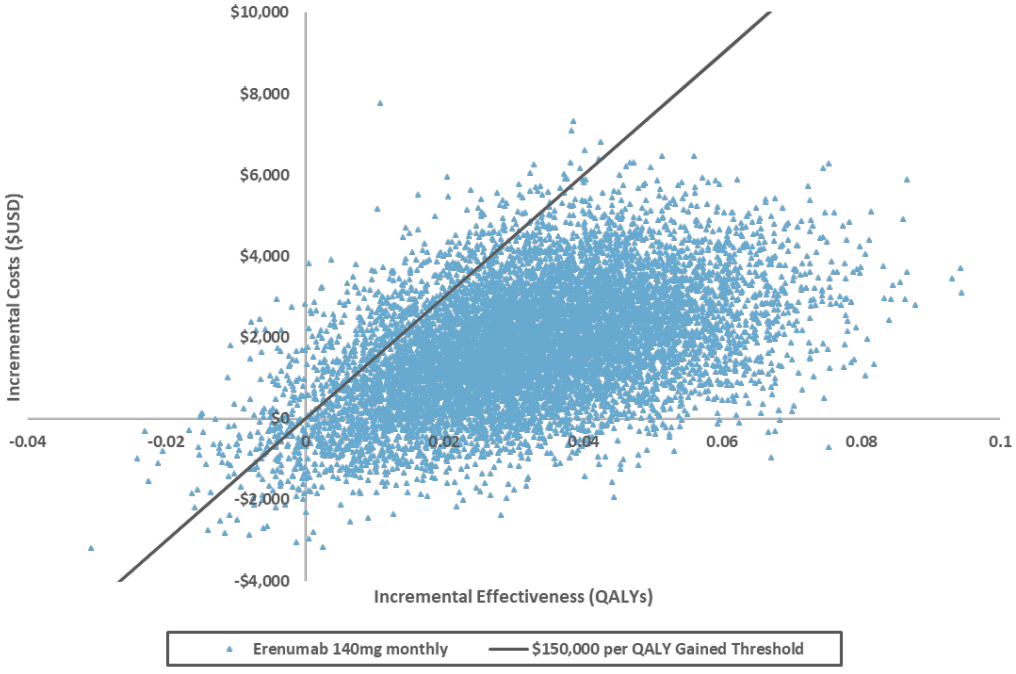


Figure E9. Scatterplot of Costs and Effects Comparing Fremanezumab 625/225mg Monthly to Onabotulinum Toxin A in Patients with Chronic Migraine for whom Prior Preventive Therapies Failed

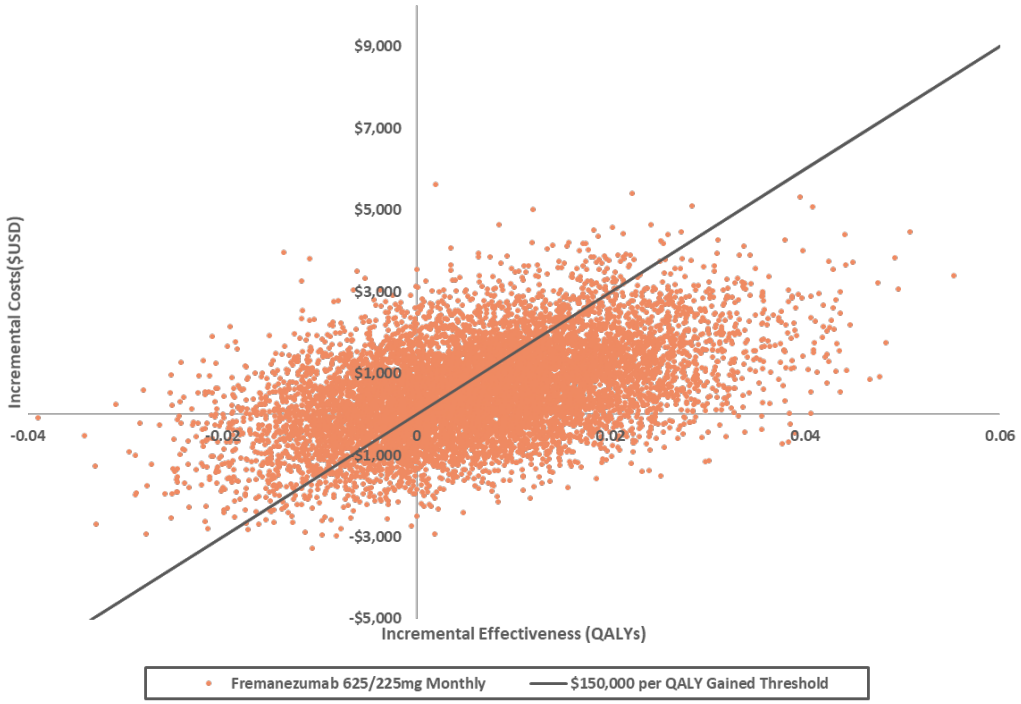


Figure E10. Cost-Effectiveness Acceptability Curves Comparing CGRP Inhibitors to Onabotulinum Toxin A in Chronic Migraine

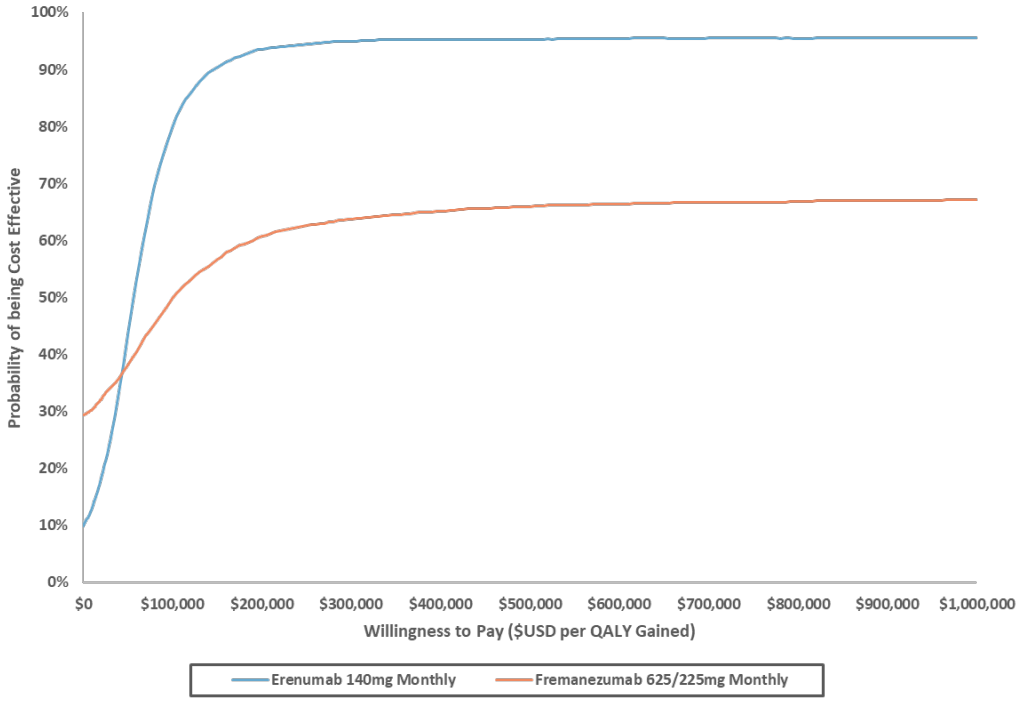


Figure E11. Cost-Effectiveness Acceptability Curves for Scenario Analysis Comparing CGRP Inhibitors to Other Preventive Treatment in Chronic Migraine

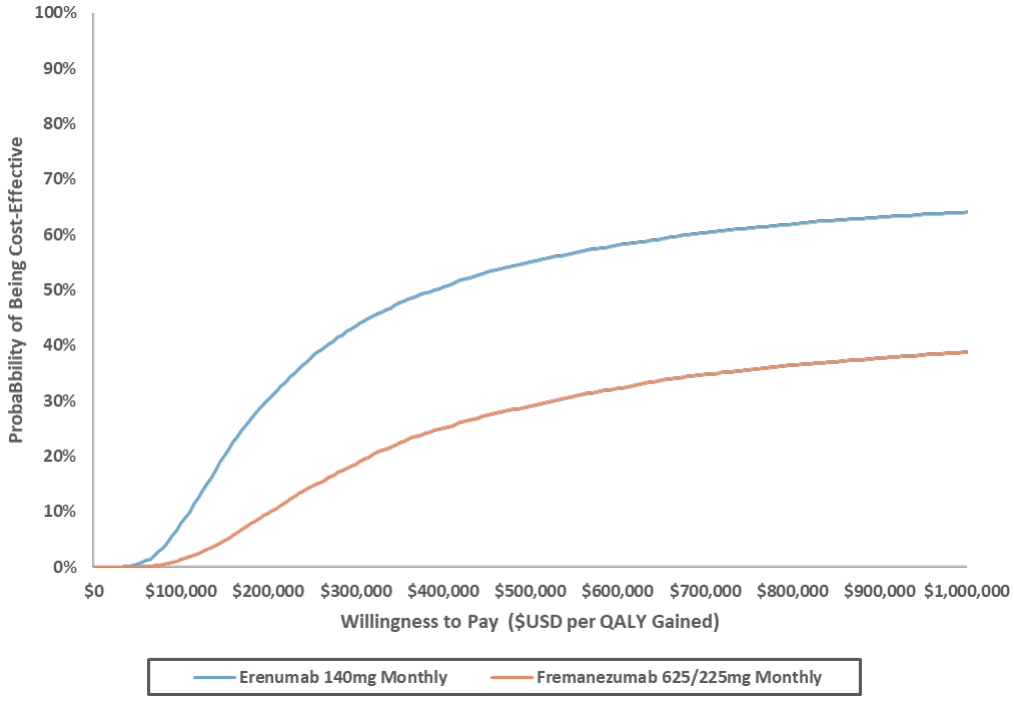


Figure E12. Cost-Effectiveness Acceptability Curves for Scenario Analysis Comparing CGRP Inhibitors to Other Preventive Treatment in Episodic Migraine

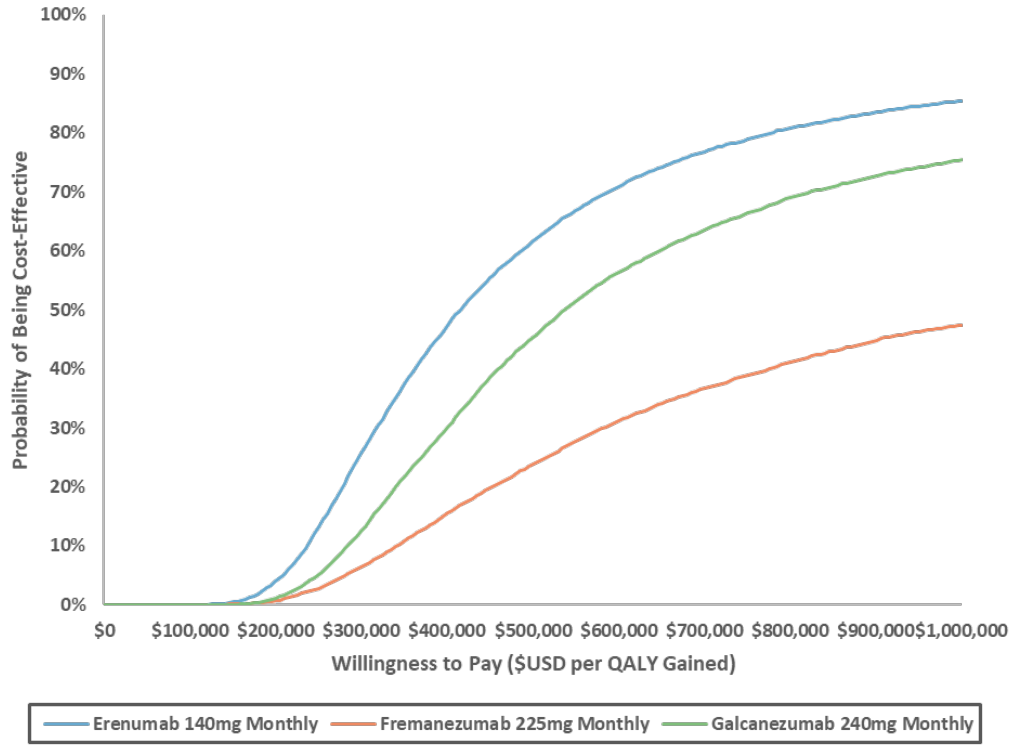


Table E16. Prevalence of Chronic Migraine by Age and Gender in the United States

Age Group	Male	Female
12-17 years	0.24%	0.46%
18-29 years	0.39%	1.86%
30-39 years	0.69%	1.77%
40-49 years	0.79%	1.89%
50-59 years	0.59%	1.33%
≥60 years	0.26%	0.56%

Sources: Lipton et al., 2007 ; Buse et al., 2012

Table E17. Prevalence of Episodic Migraine by Age and Gender in the United States

Age Group	Male	Female
12-17 years	4.00%	6.40%
18-29 years	5.00%	17.30%
30-39 years	7.40%	24.40%
40-49 years	6.50%	22.20%
50-59 years	5.00%	16.00%
≥60 years	1.60%	5.00%

Source: Lipton et al., 2007

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on June 14, 2018 in Los Angeles, California. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Four speakers did not submit summaries of their public comments.

A video recording of all comments can be found here (https://youtu.be/rEzVgZahSsI?t=1h19m55s), beginning at minute 1:19:55. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Sandhya Sapra, PhD, Amgen
Director, Global Health Economics, Global Product Lead, Erenumab

Migraine patients need options, and Amgen and Novartis believe Aimovig brings high value to patients, payers and providers. While we appreciate the positive aspects to this review (such as the appropriate population and dose for the base case), we urge ICER to incorporate the below recommendations to more accurately capture Aimovig's efficacy and value in the Final Report, without which AIMOVIG is undervalued:

- Of most importance is to incorporate patient work productivity costs into the base-case. Excluding costs associated with missed workdays and lost time at work underestimates the impact to patients and employers. Including these costs better reflects real-world impact and more accurately represents Aimovig's value as seen in the Revised Report modified societal perspective scenario.
- The Revised Report underestimates hospitalization and ER rates by using the entire prevalent migraine population. The Final Report should correctly utilize only patients who need prevention (less than 1/3 of the full migraine population).
- Utility data in the Revised Report comes from the incorrect patient population (those who do not need preventives). These patients with 2-3 migraines over a 3-month period can be treated with over-the-counter therapy. The Final Report should accurately reflect the quality-of-life of patients with much higher migraine frequency ranging from 4-30 monthly migraine days; similar to CGRP trial patients.
- The Revised Report underestimates the benefit Aimovig delivers by subtracting placebo numbers from Aimovig's efficacy. This misaligns with clinical practice, where patients do not receive placebo. At minimum, we request the Final Report include non-placebo subtracted efficacy alongside placebo-subtracted efficacy.

Dr. Sapra is a full-time employee of Amgen.

Joshua Cohen, MD, MPH, FAHS, Teva Pharmaceuticals
Therapeutic Area Lead, Migraine and Headache, Global Medical Affairs

Teva fully agrees with ICER's assessment that the CGRP inhibitor therapies including fremanezumab demonstrate clinically meaningful benefits in patients with chronic and episodic migraine. The ICER analysis reports the pooled efficacy data on some of the key outcome measures (e.g., reduction in migraine days) across trials with wide confidence intervals around these pooled estimates for included CGRP inhibitor therapies. Therefore, we would like to encourage the decision makers to focus more on the overall value these CGRP inhibitors bring for migraine patients and avoiding over-interpretation of numerical differences in results between included CGRP inhibitors.

ICER's cost-effectiveness analyses highlight the overall value of CGRP inhibitors as preventive therapy in patients who have failed at least one prior preventive therapy. We believe that the full value of fremanezumab would be better reflected if comparative effectiveness estimates account for differences in baseline migraine days, real-world discontinuation rates for current therapies, and potential for improved adherence with CGRP inhibitor therapies.

ICER noted that the budget impact analysis likely over-estimates the actual number of treatment eligible patients by including patients who do not actively seek treatment. We suggest that ICER carefully weigh the implications of overestimating the potential budget impact of CGRP inhibitor therapies, as this may influence payers to impose unwarranted restrictions to patient access for those who are otherwise appropriate for therapy.

Teva is excited to work with payers to ensure healthcare professionals and patients have access and choice to tailor preventive migraine treatment to meet individual patient needs for improved treatment outcomes.

Dr. Cohen is a full-time employee of Teva Pharmaceuticals.

Mary Franklin, National Headache Foundation
Executive Director

My journey into headache medicine began in 1970, and I was able to observe the evolution of migraine therapy, as a member of the staff of the Diamond Headache Clinic in Chicago. Throughout those years, I witnessed frustration in patients unable to find the appropriate therapy and, frustration on the part of the health care providers seeking to help those patients.

Each attack varies and the disease affects individuals differently. How do you find therapies appropriate for the headaches and the associated symptoms? And how do you find therapies that will help and not exacerbate the comorbidities associated with migraine?

Until 1976, the only drugs approved for migraine use were the ergotamine preparations with their many side effects and contraindications. The antidepressants were also used off-label. And then, propranolol was approved and many patients responded well. The side effect profile of the beta blockers proved a great obstacle to many patients and patients with comorbid asthma could not use these agents.

During the early 1990s, the introduction of the triptans for acute therapy of migraine brought relief to many patients. Yet, many patients did not respond or the drugs became less effective over the years of therapy. The use of the anticonvulsants, such as topiramate, was also heralded but its undesirable side effects limit its use.

The enthusiasm and anticipation of the anti-CGRPs are felt by patients, the advocacy organizations, and the health care professionals who treat headache patients. It is important that these agents be accessible to patients with chronic and episodic migraine.

The National Headache Foundation receives over 25% of its funding from life sciences companies, including Allergan, Allergan Foundation, Amgen, DepoMed, Diamond Headache Clinic (Chicago), Eli Lilly, Novartis, Presence Saint Joseph Hospital, Chicago, Promius, Supernus, Ter Sera Therapeutics, and Teva

Shirley Kessel, Miles for Migraine
Executive Director

My mother, myself and 2 of my three daughters has migraine. This disease not only effects the affected but is also a financial burden to both patients and their families. My mother was disabled by migraine and could not work so my father took a second job. In addition when she was so sick from vomiting and needed to go to the ER she usually did not because of the expenses so instead I learned to give her shots at age 16. What is the financial burden of lost income and reduced medical care? Losing 25 years of work is about 1,000,000.

I left an MBA 4 classes into the program. The cost? Priceless.

My youngest daughter left private school in 11th grade. The cost was 15,000. We had to pay for homeschooling and tutors. The cost was 25,000. She entered a CGRP trial and got better! She went to GWU. Once the trial ended she regressed and went part time. We lost 15,000. She can't work summers and she has to attend summer classes. More lost income and we are supposed to support her until graduating hopefully at age 26. The cost? Approximately 80,000 and this doesn't include additional medical treatment she needs.

My middle daughter left a graduate school program 6 months ago and we lost 15,000. She went to school online but couldn't handle that either so we lost another 9,000. She can't work so we are supporting her. The cost? I may never know.

Miles for Migraine receives sponsorship for programs from the organizations below. Less than 30% of Ms. Kessel's compensation comes from these funds. Companies that sponsor MFM salaries include, Allergan Foundation, Depomed, eNeura, Companies that support MFM programs include Alder Biopharmaceuticals, Amgen, Eli Lilly, Novartis, Teva, and Supernus Pharmaceuticals.

Brian Gifford, PhD, Integrated Benefits Institute (IBI)
Director, Research and Analytics

In the recent ICER report, patients described how migraine interferes with their ability to consistently attend work and put in their best performance on the job. The Integrated Benefit Institute's (IBI) research corroborates their stories and estimates the economic impact to their employers.

Our most recent migraine analysis show that employees with migraines use more health care services and have more sick days than employees without migraines. Short-term disability leaves for migraine are relatively rare but costly, particularly if they become long-term disability episodes. All told, IBI estimates that companies with paid sick day, health care, and disability benefits can expect about $84,000 in annual migraine-related costs for every 1,000 people they employ—nearly one-third of which are for migraine-related lost work time.

Another IBI study found that migraineurs report more difficulties functioning on the job—but that their productivity was just as high as that of other employees' when they were symptom free. These findings suggest that interventions which help migraineurs avoid and mitigate attacks can improve their value to employers, as well as their quality of life.

Employers should recognize that migraine in the workforce presents sizable productivity losses. Considering that migraine is both underdiagnosed and undertreated, the potential to reduce those losses is also sizable.

As employers consider how to incorporate promising new treatment options into their healthcare benefit plans, we urge them to take into account the business value that these therapies can deliver as well as their costs.

Several health plans or life sciences companies serve on the IBI board, including United HealthCare, Health Care Service Corporation, and Teladoc. IBI receives membership dues from pharmaceutical manufacturers, including Abbot, AbbVie, Amgen, GlaxoSmithKline, Johnson &

Johnson, Merck, National Pharmaceutical Council, Novo Nordisk, Pfizer, PhRMA, Sanofi, and Walgreens.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the June 14, 2018 Public meeting of CTAF.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Laura Cianciolo, BA	ICER	None
Alexandra Ellis, PhD	ICER	None
Ifeoma Otuonye, MPH	ICER	None
Steven Pearson, MD, MSc	ICER	None
David Rind, MD, MSc	ICER	None
Matt Seidner, BS	ICER	None
Surrey Walton, PhD	University of Illinois, Chicago	None

Table G2. CTAF Panel Member COI Disclosures

Name	Organization	Disclosures
Felicia Cohn, PhD	Kaiser Permanente, Orange County	*
Robert Collyar	Patient Advocate	*
Luanda Grazette, MD, MPH, FACC	USC Keck School of Medicine	*
Kimberly Gregory, MD, MPH	Cedars-Sinai Medical Center	*
Jeffrey Hoch, PhD	UC Davis	*
Jeffrey Klingman, MD	The Permanente Medical Group	*
Sei Lee, MD	UCSF	*
Joy Melnikow, MD, MPH	UC Davis	*
Patricia E. Powers, MPA	Center for Healthcare Decisions (UC Davis)	*
William Remak, BSc MT, BPH	California Hepatitis C Task Force	*
Robert E. Rentschler, MD	Retired, Beaver Medical Group	*
Alexander Smith, MD, MPH	UCSF	*
Michael Steinberg, MD	UCLA	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participant COI Disclosures

Name	Title and Affiliation	Disclosures
Amy Benavente, BA	Executive Director, Reimbursement, Access, and Value, Neuroscience, Amgen	Full-time employee of Amgen
Jill Dehlin, RN, MA, MPH, CHES	Migraine Patient, Former President of American Headache and Migraine Association	None
Aaron Deves, BS	Global Disease Lead, Migraine and Headache, Teva Pharmaceuticals	Full-time employee of Teva
Kevin Lenaburg, MA	Executive Director, Coalition for Headache and Migraine Patients (CHAMP), Caregiver for Person With Migraine	CHAMP receives funding from Alder, Amgen, Eli Lilly, MigraineAgain, migraine.com, Novartis, Teva, The Migraine World Summit, Supernus
Everett Neville, RPh	Executive Vice President, Strategy, Supply Chain, and Specialty, Express Scripts	Full-time employee of Express Scripts
Sonja Potrebic, MD, PhD	Residency Program Director, Headache Specialist, and Co-Assistant Chief of Neurology, Southern California Permanente Medical Group, Kaiser Permanente	None
Richard KP Sun, MD, MPH	Medical Consultant and Chief, Clinical Programs and Appeals Section, Health Plan Administration Division, California Public Employees' Retirement System (CalPERS)	None
Yvette Yeung, MD	Neurologist, Clinical Pod Lead, HealthCare Partners Medical Group	None