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

Draft Evidence Report

April 11, 2018

Prepared for

ICER Staff and Consultants	University of Illinois, Chicago Modeling Group
Alexandra Ellis, MSc, AM 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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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
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

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] and is among the top ten causes of years lived with disability.[3,4] 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 although they may be associated with specific triggers in some patients. 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).[5-7]

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] 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 (pre-headache).[8] Hence, for some patients, the duration of impairment may be longer than the migraine attack itself, which can lead to ongoing disability.[9-11] However, the intensity of pain and other symptoms varies by migraine and by individual, so the burden of migraine may be more severe for some patients than others; in many patients, migraine is a mild intermittent problem controlled with oral analgesics. In patients with more severe disease, migraine also may affect school, employment, choice of leisure activities and foods, or interpersonal relationships.[12-14] In addition, patients with migraine feel stigmatized, which may disrupt quality of life and ability to work.[15]

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.[16] 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.[1,17]

Despite its high prevalence and impairment, migraine is often not recognized or effectively treated.[17,18] Barriers to appropriate care arise when accessing healthcare professionals, obtaining a correct diagnosis, and receiving appropriate therapy.[17,18] 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.[19] 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[9]) 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.[20-23] These agents are relatively safe, available, and inexpensive. If patients do not respond to these agents or 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).[24-27]

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 headaches and chronic daily headaches.[28] Opioids and barbiturates are associated with the highest risk for medication overuse headaches, although frequent use of NSAIDS and triptans can also lead to chronic migraines and medication overuse headaches.[28]

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 current 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).[29] Patients with chronic migraine may also use onabotulinum toxin A (Botox®, Allergan plc) injections for prevention.[30]

Patients who benefit from preventive therapy over at least six months may begin to taper off the therapy.[31] However, patients on preventive therapy frequently discontinue or switch treatments due to lack of efficacy or tolerability.[9] Because of a delayed response in many of these therapies, adequate therapeutic trials of preventive therapies may require two to six months of treatment.[32] Without adequate treatment, patients with episodic migraine are more likely to progress to chronic migraine.[28] About 2.5% of patients with episodic migraine progress to chronic migraine per year.[28]

CGRP Inhibitors

The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation, and CGRP has been observed to increase during a migraine.[33-35] 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.[33,34] 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 CGRPs have been hindered or terminated due to concerns of toxicity.[36] To date, the development of monoclonal antibodies for migraine prevention has seen fewer challenges related to toxicity.

Currently, erenumab (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.[37-39] 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.[40-43] The US Food and Drug Administration (FDA) is currently evaluating erenumab with a decision expected in May 2018;[44] fremanezumab in the first half of 2018 with a possible delay until 2019;[45,46] and galcanezumab in the third quarter of 2018.[47] 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 draft 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 one monthly dose of galcanezumab (120 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.

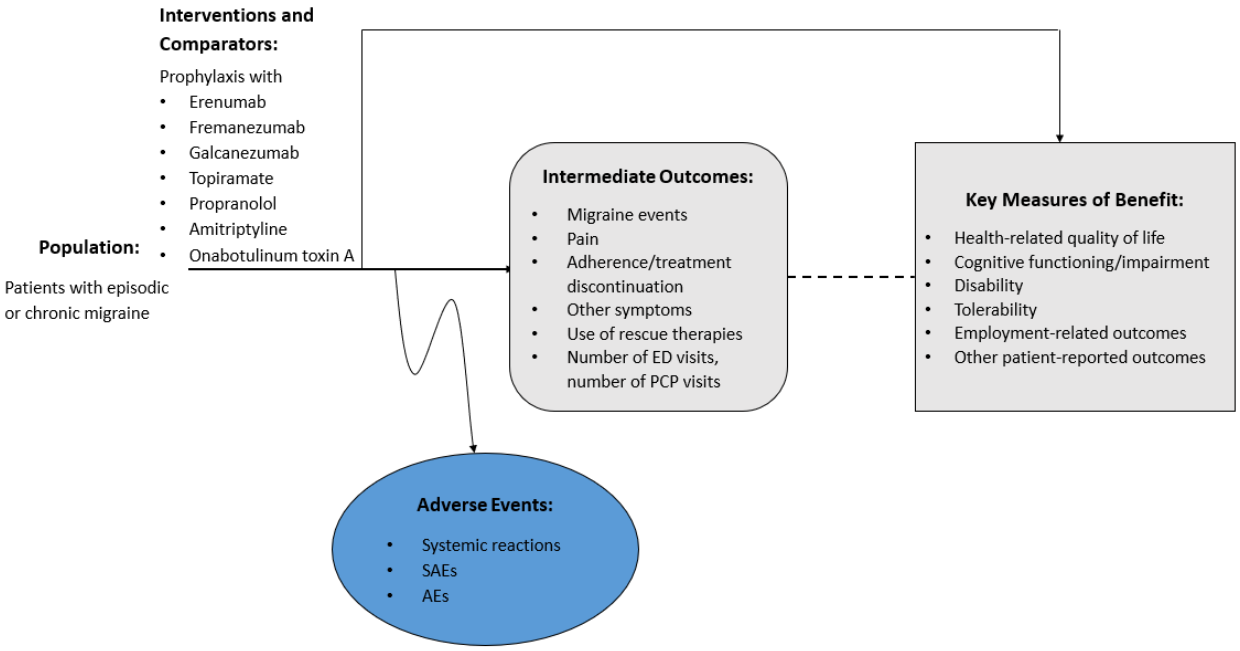
Settings

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.[48]

1.3 Definitions

Select International Classification of Headache Disorders (ICHD) Third Edition Criteria for Migraine Diagnoses[49]

- **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 extensively from 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.
- Patients frequently reported feeling frustrated, depressed, defeated, isolated, or a burden to society; some patients have expressed 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.

- Patient reported paying high co-pays for many treatments; some patients must wait for pre-authorization from their insurer; patients also are concerned about the ability to afford new 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.[50] 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:[51]

- 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.

ICER encourages all stakeholders to suggest any additional services (including treatments and mechanisms of care) currently used for people with migraine that could be reduced, eliminated, or made more efficient.

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]). We were unable to survey policies pertaining to CGRP inhibitors, as none were approved by the FDA at the time this draft report was released.

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.[52] The policy from the California DCHS pertaining to Medi-Cal matches the LCD.[53] California DHCS further covers amitriptyline, propranolol, and topiramate at the lowest formulary tier; we were unable to locate formulary information for onabotulinum toxin A.[54]

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.[55-62]

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.[63-68] 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.[55,69] 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.

American Academy of Neurology (AAN)

Botulinum Neurotoxin for the Treatment of Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache (2016)[30]

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)[29,70]

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[71]

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)[72]

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)
    - 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.[73,74] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[75,76] The PRISMA guidelines include a list of 27 checklist items, which are described further 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. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. For more information on the search algorithms used, methods of study selection, or data extraction, refer to Appendix Tables A2-A3 and Appendix D.

Study Selection

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. 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/).

Data Extraction and Quality Assessment

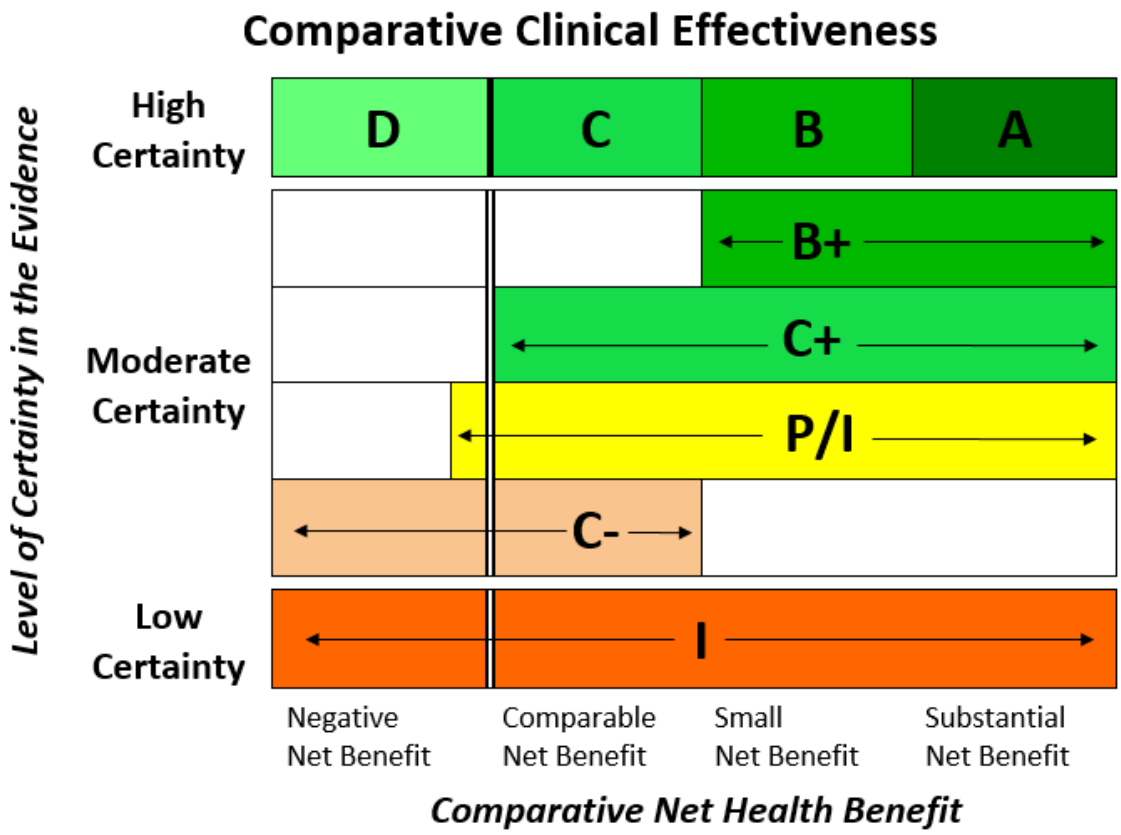
Data were extracted into the Systematic Review Data Repository™ by a single researcher and then verified by at least one other researcher. Quality assessment was based on US Preventive Services Task Force (USPSTF)[77] criteria that included presence of comparable groups, non-differential loss to follow-up, use of blinding, clear definition of interventions and outcomes, control for confounders, appropriate handling of missing data.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3.1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

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
The level of **certainty** in the best point estimate of net health benefit.[78]

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

Assessment of Publication Bias

We assessed the presence of publication bias by utilizing the clinicaltrials.gov database of trials. We searched for registered trials of CGRP inhibitors that were completed more than two years ago that would have met our inclusion criteria but with no available published findings. We identified three Phase III trials on episodic migraine that are still active, but not recruiting; one erenumab trial (NCT03096834, LIBERTY) for episodic migraine patients for whom other preventive treatments had failed; and two galcanezumab trials (NCT02614183, EVOLVE-1; NCT02614196, EVOLVE-2). We also identified one Phase III galcanezumab trial (NCT02614261, REGAIN) in chronic migraine that is still

active, but not recruiting. These trials are described in the Ongoing Studies section in Appendix C and not included in our analyses. One Phase III trial on fremanezumab in episodic migraine was also identified (NCT02629861, HALO-EM), but was completed less than two years ago. We included this trial in our review based on data from conference abstracts and data submitted by the manufacturer. As such, we found no evidence of publication bias for trials of CGRP inhibitors.

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), and the change from baseline in days per month using acute medications. Due to limited data, 50% responders in the chronic 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 a 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 D28-D30. 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 D28-D30.

All NMAs were conducted in a Bayesian framework with random effects on the treatment parameters using the *gemtc* package in R.[79] Continuous outcomes were analysed using a normal likelihood and identity link; binary outcomes were analysed using a binomial likelihood and logit link.[80] 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 trials. Additional details regarding the analysis methods, network diagrams, and league tables with all pairwise results are provided in Appendix D including Appendix Tables D19-D27 and Figures D1-D8.

3.3 Results

Study Selection

Our literature search identified a total of 1,538 potentially relevant references (see Appendix A Figure A1). We included a total of 76 references, of which 69 references were comparative clinical trials, two were OLEs, and five were observational studies. These references consisted of 55 publications (20 in chronic migraine, 34 in episodic migraine) and 21 conference abstracts (seven chronic, 14 episodic). 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 follow-up less than six months), and conference abstracts with duplicate data as the original publications.

The 69 references of comparative trials correspond to 47 trials, of which 13 trials (29 references) assessed a CGRP inhibitor and 36 trials (40 references) assessed one or more 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 did not impute missing data in their primary outcomes. The fremanezumab and galcanezumab trials 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). 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.[81,82]

In both the chronic and episodic migraine populations, trials on the commonly-used preventive therapies had ratings of good, fair, or poor. All five trials on onabotulinum toxin A versus placebo for the chronic migraine population received a good rating except for one which was rated fair due to a lack of reporting of the comparability of the arms at baseline. We considered nine of the 11 topiramate versus placebo trials in both populations to be of good quality. Four of the nine trials of propranolol versus placebo received a rating of good, four received a rating of fair, and one received a poor rating. The head-to-head trials of multiple preventive therapies either received a good or fair rating (six good, four fair). 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 published Phase II RCT assessing erenumab (NCT02066415, Tepper 2017),[83] one published Phase II RCT assessing fremanezumab (NCT02021773, Bigal 2015a),[41] and one published Phase III RCT assessing fremanezumab (NCT02621931, HALO-CM).[43] We also identified one unpublished, ongoing Phase III RCT on galcanezumab (NCT02614261, REGAIN). 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) 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 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, the patients could not have experienced the failure of more than three preventive therapy categories. In the fremanezumab trials, the patients could not have experienced the failure of more than two preventive medication categories or more than three preventive medications across two categories. 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% 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 (9-12 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]).[39] 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]). 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]).

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, one crossover trial,[84] and one OLE[85] were included for onabotulinum toxin A versus placebo, two RCTs for onabotulinum toxin A versus topiramate,[84] and one RCT for onabotulinum toxin A versus amitriptyline.[86] Four RCTs (six publications)[87-92] were included for topiramate versus placebo and one RCT compared topiramate and propranolol combination therapy to topiramate alone.[88]

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 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. 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 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 follow-up periods of a

year. Overall, the trials included predominantly female patients living with migraine since their adolescence or early twenties. When reported, age varied from 30 to 50 years, and mean monthly migraine days from 10 to 25 days at baseline.

Clinical Benefits

Of the 16 included trials that evaluated preventive therapies in chronic migraine, 10 trials reported outcome data on at least one of the efficacy endpoints described below (change from baseline in monthly migraine days, 50% responders, or change from baseline in days per month using acute medication). Two of these trials (Sandrini 2011, Mei 2006) only included patients with medication overuse headache and were excluded from these 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.

The remaining seven trials were placebo-controlled and assessed erenumab (one trial), fremanezumab (two trials), onabotulinum toxin A (two trials), or topiramate (two trials). Both fremanezumab trials and one topiramate trial (Silberstein 2007) permitted concomitant preventive migraine therapy, which was not permitted in the other four trials. Across five of the seven trials, the included patients had a history of chronic migraine for an average of 20 years, which was higher in one topiramate trial (nine years; Silberstein 2007) or not reported (Diener 2007). One topiramate trial (Silberstein 2007) 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 seven trials were deemed sufficiently similar and included in the efficacy analyses below.

Migraine Days per Month

All 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. 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, and the difference in change from baseline for each active therapy versus placebo as reported in the trials. For the arm-level change from baseline, a negative value indicated a reduction in monthly migraine days, and a negative difference in change from baseline indicated a larger reduction for the intervention versus placebo. Reported data were for the last four weeks of the randomized period, except for

PREEMPT 1 and 2, which were for the full 24-week period, and Silberstein 2007, which were for the full 16-week period. 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 (95% CI)	Tx 3	Mean	SE	Difference (95% CI)
Tepper, 2017[83]	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, 2015[41]	12	Placebo	NA	NA	Fremanezumab 675/225 mg*	-1.72	1.01	-1.72 (-3.7, 0.2)				
Silberstein, 2017 (HALO-CM)[43]	12	Placebo	-3.80	0.40	Fremanezumab 675/225 mg	-5.43	0.30	-1.63 (NR)	Fremanezumab 675 mg	-5.08	0.35	-1.28 (NR)
Aurora, 2010 (PREEMPT 1)[93]	24	Placebo	-6.10	0.37	Onabotulinum toxin A 155U	-7.60	0.35	-1.5 (-2.6, -0.6)				
Diener, 2010 (PREEMPT 2)[94]	24	Placebo	-6.30	0.35	Onabotulinum toxin A 155U	-8.70	0.36	-2.4 (-3.3, -1.4)				
Silberstein, 2007[88]	16	Placebo	-4.70	0.49	Topiramate 100 mg/day	-6.40	0.47	-1.7 (NR)				
Diener, 2007[95]	16	Placebo	0.20	0.90	Topiramate 100 mg/day	-3.50	1.11	-3.7 (NR)				

*Results are for difference vs placebo only.

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

Table 3.2 presents the results from a 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 negative values indicating a larger reduction in monthly migraine days versus placebo. The second column provides the corresponding 95% credible intervals (CrIs). 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 0.68 (0.03, 3.02), which led to wide CrIs for the treatment effects. The NMA results suggest patients using CGRP inhibitors experience fewer monthly migraine days than those on placebo, although these results are not statistically significant. Patients using erenumab 70 mg and 140 mg had approximately 2.4 fewer migraine days per month than those on placebo, whereas those on fremanezumab quarterly and monthly had 1.3 and 1.7 fewer migraine days per month versus placebo, respectively. Patients using onabotulinum toxin A had approximately 2.0 fewer migraine days per month versus placebo and those on topiramate 100 mg per day had approximately 2.2 fewer migraine days per month versus placebo, which were both statistically significant. Results comparing active therapies were not statistically significant.

The estimated reduction in monthly migraine days for each active therapy is presented in the third column, with the corresponding 95% CrIs in the last column. Here, the estimates for the CGRP inhibitors ranged from 5.5 fewer migraine days per month with fremanezumab quarterly to 6.6 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 vs. Placebo		Expected Results	
	Estimate	95% CrI	Estimate	95% CrI
Placebo	NA	NA	-4.2	NA
Erenumab 70 mg Monthly	-2.40	(-5.16, 0.38)	-6.60	(-9.36, -3.82)
Erenumab 140 mg Monthly	-2.40	(-5.17, 0.39)	-6.60	(-9.37, -3.81)
Fremanezumab 675 mg Quarterly	-1.29	(-3.88, 1.30)	-5.49	(-8.08, -2.90)
Fremanezumab 675/225 mg Monthly	-1.66	(-3.71, 0.38)	-5.86	(-7.91, -3.82)
Onabotulinum toxin A 155U Quarterly	-1.95	(-3.89, -0.00)	-6.15	(-8.09, -4.20)
Topiramate 100 mg/day	-2.22	(-4.70, -0.24)	-6.42	(-8.90, -4.44)

Standard deviation for treatment effects: 0.68 (0.03, 3.02)

CrI: credible interval, NA: not applicable

In addition, 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]).[85]

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.[96]

50% Responders

Three trials reported the proportion of patients who experienced at least a 50% reduction in the number of migraine days (Tepper 2017, Silberstein 2007, Diener 2007). Four other trials defined 50% response as at least a 50% reduction in moderate-to-severe headache days (Bigal 2015a) or any headache days (HALO-CM, Silvestrini 2003, 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 versus placebo (40% vs. 23%, respectively; OR 2.2 [95% CI 1.5, 3.3]). 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. 22%; OR 1.4). 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.

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]). 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) as did two trials of topiramate (Silvestrini 2003: 71% vs. 7% at 8 weeks OR 32.5 [95% CI 3.1, 337]; Silberstein 2007: 26% vs. 22% at 16 weeks OR 1.2) and one trial of onabotulinum toxin A (58%) versus topiramate (32%) at 24 weeks OR 2.9 (Mathew 2009).

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 3.3. The time point of the analysis was the last four

weeks of the randomization period (nine to 12 weeks) for erenumab trials, 12 weeks for the fremanezumab trial, and 16 weeks for both topiramate trials. The data for the fremanezumab and topiramate trials were days of any acute medication, whereas the erenumab trial were days using migraine-specific acute medication as data on any acute medication was not reported. Overall, the trials reported greater reductions in acute medication use with the active therapies than with placebo.

Table 3.4 presents the results of the random effects NMA in terms of the difference in change from baseline for each intervention versus placebo (columns one and two). Imprecise estimates of the heterogeneity parameter of 0.71 (0.03, 2.32) 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 (2.5 and 2.3 fewer days per month, respectively), which were both statistically significant. Results for topiramate suggested a reduction of 1.3 days per month, 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 3.7 days with fremanezumab quarterly to 4.4 days with erenumab 140 mg.

Table 3.3. 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 (95% CI)	Tx 3	Mean	SE	Difference (95% CI)
Tepper, 2017[83]	12	Placebo	-1.60	0.20	Erenumab 70 mg	-3.50	0.30	-1.9 (-2.6, -1.1)	Erenumab 140 mg	-4.1	0.3	-2.6 (-3.3, -1.8)
Bigal, 2015a[41]	12	Placebo	NA	NA	Fremanezumab 675/225 mg *	-2.15	0.94	-2.15 (-4.0, 0.3)				
Silberstein, 2017 (HALO-CM)[43]	12	Placebo	-1.90	0.30	Fremanezumab 675/225 mg	-4.20	0.30	-2.3 (NR)	Fremanezumab 675 mg	-3.7	0.3	-1.8 (NR)
Silberstein, 2007[90]	16	Placebo	-3.40	0.43	Topiramate 100 mg/day	-4.40	0.47	-1.0 (NR)				
Diener, 2007[95]	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 3.4. NMA Results for Days of Acute Medication Use in Chronic Migraine Patients

	Difference vs. Placebo		Expected Results	
	Estimate	95% CrI	Estimate	95% CrI
Placebo	NA	NA	-1.9	NA
Erenumab 70 mg Monthly	-1.90	(-4.36, 0.58)	-3.80	(-6.26, -1.32)
Erenumab 140 mg Monthly	-2.50	(-4.96, -0.01)	-4.40	(-6.86, -1.91)
Fremanezumab 675 mg Quarterly	-1.78	(-4.13, 0.59)	-3.68	(-6.03, -1.31)
Fremanezumab 675/225 mg Monthly	-2.25	(-4.10, -0.35)	-4.15	(-6.00, -2.25)
Topiramate 100 mg/day	-1.28	(-3.56, 0.68)	-3.18	(-5.46, -1.22)

Standard deviation for treatment effects: 0.71 (0.03, 2.32)

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. Only one of the CGRP inhibitor trials reported total MIDAS in chronic migraine populations. The change from baseline in total MIDAS by week 12 was statistically significant for both doses of erenumab versus placebo (erenumab 140 mg -18.1, erenumab 70 mg -19.5, placebo -9.1). Five trials of onabotulinum toxin A or topiramate also reported MIDAS, which also saw improvements in total MIDAS by weeks 12 to 26.

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. Six 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. 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 9.8, whereas the average improvement across all active therapies ranged from 3.5 to 18.4. 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 and another assessing topiramate reported MSQ data. Across those two trials, both topiramate and erenumab improved quality of life, but the topiramate trial (EF: 26.7; RFR: 23.8; RFP: 16.9) had a larger increase in scores from baseline than the erenumab trial (EF: 19 in both arms; RFR: 17-19 in both arms; RFP: 13-14 in both arms) by 12 weeks in all three domains.

Overview of Observational Studies

In the chronic migraine population, we identified two onabotulinum toxin A studies[97,98] conducted in general clinical practices in Italy or Spain. In both studies, a headache diary was used to assess migraine days, headache days, and acute pain medication use in patients for up to two years. One of the studies (Aicua-Rapan 2016) included patients with other comorbidities such as anxiety, depression, fibromyalgia and other vascular conditions, those with medication overuse, and those for whom at least topiramate previously failed. The authors found that acute pain medication use decreased from an average of 19.1 days per month to 8.6 days per month during the first year. In

addition, 68.7% of 79 patients with chronic migraine at baseline 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. The second study (Negro 2016) found that both doses of onabotulinum toxin A (155U and 195U) were effective in reducing migraine days and headache days with a greater reduction in the 195U dose. After two years of treatment with onabotulinum toxin A 195U, 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 was similar safety for both doses and consistent with the trials on onabotulinum toxin A.

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)[38] with its associated OLE,[99] two Phase III RCTs of erenumab (NCT02456740, STRIVE; and NCT02483585, ARISE),[37,100] one Phase II RCT of fremanezumab (NCT0202556, Bigal 2015b),[40] one completed but unpublished Phase III RCT of fremanezumab (NCT02629861, HALO-EM), and two Phase II RCTs of galcanezumab (NCT01625988, Dodick 2014; and NCT02163993, Skljarevski 2018).[42,101] We also identified two unpublished, ongoing Phase III RCT on galcanezumab (NCT02614183, EVOLVE-1; NCT02614196, EVOLVE-2). Given limited details on their study design and baseline characteristics, we were unable to assess the similarity of these trials to those published in full-text and we did not include the results in any quantitative analysis. Refer to Appendix C for the data available from these trials.

Appendix Tables D3 and D6 contain the key study design and baseline characteristics of the trials. The seven 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) 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 this 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. The average age of migraine onset was 16 to 22 years. At baseline, the average number of migraine days per month ranged from 6 to 8 per month in the erenumab and galcanezumab trials, and patients in Bigal 2015b (fremanezumab) experienced a higher frequency at

baseline with approximately 12 migraine days per month. The average number of days using an acute migraine-specific medication at baseline was approximately 3 to 4 days per month (Sun 2015, STRIVE, and ARISE, erenumab), and the number of days using any acute medication was approximately 7 (Sun 2015, erenumab) to 10 (Bigal 2015b, fremanezumab). These data were not reported in either galcanezumab trial.

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. Patients in three trials (Sun 2016, Dodick 2014, Skljarevski 2018) were required to discontinue any migraine preventive therapies at baseline, whereas patients in three trials (ARISE, STRIVE, 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 and -1.0 [95% CI -1.6, -0.5] in ARISE). During months three through six, patients on erenumab 140 mg and 170 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]). In the fremanezumab trial, the primary outcome was the mean reduction (change) in migraine days from baseline to the last four weeks of the treatment phase. 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]). For the two 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 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. In Dodick 2014, patients on galcanezumab experienced a greater reduction in monthly migraine days than those on placebo during weeks 9 through 12 (difference in galcanezumab vs. placebo -1.2 [95% CI -1.9, -0.6]).

Overview of Trials Assessing Current Preventive Therapies in Episodic Migraine

Of the 23 trials assessing a comparator of interest in the episodic migraine population, we included 16 trials of an active therapy versus placebo (three RCTs assessed amitriptyline,[102-104] four RCTs[105-108] and one crossover of propranolol,[109] eight RCTs (nine publications) Of the 23 trials assessing a comparator of interest in the episodic migraine population, we included 16 trials of an active therapy versus placebo (three RCTs assessed amitriptyline,[102-104] four RCTs[105-108] and one crossover of propranolol,[109] eight RCTs (10 publications) of topiramate[110-119]) and seven head-to-head studies (three RCTs of topiramate vs. propranolol,[120-122] one RCT of topiramate vs. amitriptyline,[123] one RCT of propranolol vs. amitriptyline,[124] one RCT of topiramate vs. amitriptyline vs. topiramate plus amitriptyline,[125] and one RCT of propranolol vs. amitriptyline vs. propranolol plus amitriptyline).[126]

As with the CGRP inhibitor trials, most trials of the oral preventive therapies were multi-centered, and industry funded. 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 five to 12 days per month. Key study design and baseline patient characteristics are presented in the Appendix Tables D4 and D6. Most trials excluded patients who were currently taking other preventive therapies or had previously 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 30 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 C for the results data available from this trial. Of the remaining 29 trials, 16 trials reported outcome data on at least one of the efficacy endpoints described below (change from baseline in monthly migraine days, 50% responders, or change from baseline in days per month using acute medication). Fourteen of the trials were placebo-controlled and assessed erenumab (three trials), fremanezumab (two trials), galcanezumab (one trial), 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 16 trials were deemed sufficiently similar to include in the efficacy analyses below.

Migraine Days per Month

Twelve of the 16 trials were included in the NMA of change from baseline in monthly migraine days. Ten of the trials were placebo controlled, while two trials compared topiramate with either amitriptyline or propranolol. 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 four hours in Bigal 2015b). The CGRP inhibitor trials also considered a day taking acute migraine-specific medication as a migraine day. Table 3.5 contains the data inputs for the NMA, which included the mean change from baseline and standard error for each arm of the trials, and the difference in change from baseline for each active therapy versus placebo as reported in the trials. Overall, trials reported greater reductions in monthly migraine days for all interventions versus placebo. The head-to-head trials reported slightly larger reductions with topiramate than with amitriptyline (Dodick 2009) or slightly larger reductions with propranolol than with topiramate (Diener 2004).

Table 3.6 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% credible intervals in the second column. Negative values indicated a larger reduction in monthly migraine days versus placebo. Patients using erenumab had approximately 1.3 (70 mg dose) and 1.9 (140 mg dose) fewer migraine days per month than those on placebo, whereas those on fremanezumab had 1.4 (quarterly dose) or 1.9 (monthly dose) fewer migraine days per month; these estimates were statistically significant. Patients on galcanezumab 120 mg had approximately 0.9 fewer migraine days per month than those on placebo, which was not statistically significant. For the oral preventive therapies, patients experienced approximately 1.2 (propranolol 160 mg and topiramate 100 mg), or 1.1 (topiramate 200 mg) fewer migraine days per month, which were statistically significant versus placebo. Neither amitriptyline dose nor the topiramate 50 mg dose were statistically significant versus placebo. Results for erenumab 140 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 column three, with the corresponding 95% credible intervals in column four. Here, the estimates for the CGRP inhibitors ranged from 3.5 fewer migraine days per month with erenumab 70 mg to 4.1 fewer migraine days per month with erenumab 140 mg.

In addition, 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 3.5. Data for Change from Baseline in Monthly Migraine Days in Episodic Migraine Patients

Trial	Week	Tx 1	Mean	SE	Tx 2	Mean	SE	Difference (95% CI)	Tx 3	Mean	SE	Difference (95% CI)	Tx 4	Mean	SE	Difference (95% CI)
Sun 2016[38]	12	Placebo	-2.30	0.30	Erenumab 70 mg	-3.40	0.40	-1.1 (-2.1, -0.2)								
Goadsby 2017 (STRIVE)[37]	24	Placebo	-1.67	0.21	Erenumab 70 mg	-3.26	0.21	-1.59 (NR)	Erenumab 140 mg	-3.76	0.21	-2.09 (NR)				
Dodick 2018 (ARISE)[100]	12	Placebo	-1.80	0.20	Erenumab 70 mg	-2.90	0.20	-1.0 (-1.6, -0.5)								
Bigal 2015b[40]	12	Placebo	-3.46	0.53	Fremanezumab 225 mg	-6.27	0.55	-2.81 (-4.07, -1.55)								
Aycardi 2017 (HALO-EM)[127]	12	Placebo	-2.20	0.28	Fremanezumab 675 mg quarterly	-3.40	0.28	-1.2 (NR)	Fremanezumab 225 mg	-3.70	0.28	-1.5 (NR)				
Skljarevski 2018[101]	12	Placebo	-3.40	0.14	Galcanezumab 120 mg	-4.30	0.21	-0.9 (NR)								
Goncalves 2016[104]	12	Placebo	-1.10	0.37	Amitriptyline 25 mg/day	-2.20	0.33	-1.1 (-1.5, -0.7)								
Lipton 2011 [113]	26	Placebo	-5.30	0.28	Topiramate 100 mg/day	-6.60	0.28	-1.3 (NR)								
Brandes 2004[114]	26	Placebo	-1.30	0.32	Topiramate 50 mg/day	-1.70	0.51	-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 [115]	26	Placebo	-1.10	0.30	Topiramate 50 mg/day	-1.60	0.33	-0.5 (NR)	Topiramate 100 mg/day	-2.70	0.27	-1.6 (NR)	Topiramate 200 mg/day	-2.70	0.31	-1.6 (NR)
Dodick 2009 [123]	26	Topiramate 100 mg/day	-3.20	0.42	Amitriptyline 100 mg/day	-3.10	0.43	-0.1 (-0.9, 0.7)								
Diener 2004[121]	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)

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

Table 3.6. NMA Results for Change from Baseline in Migraine Days in Episodic Migraine Patients

	Difference vs. Placebo		Expected Results	
	Estimate	95% CrI	Estimate	95% CrI
Placebo	NA	NA	-2.2	NA
Erenumab 70 mg monthly	-1.29	(-1.92, -0.65)	-3.49	(-4.12, -2.85)
Erenumab 140 mg monthly	-1.94	(-2.89, -0.98)	-4.14	(-5.09, -3.18)
Fremanezumab 675 mg quarterly	-1.38	(-2.52, -0.28)	-3.58	(-4.72, -2.48)
Fremanezumab 225 mg monthly	-1.87	(-2.88, -0.96)	-4.07	(-5.08, -3.16)
Galcanezumab 120 mg monthly	-0.90	(-1.9, 0.11)	-3.10	(-4.1, -2.09)
Topiramate 50 mg/day	-0.18	(-1.05, 0.66)	-2.38	(-3.25, -1.54)
Topiramate 100 mg/day	-1.19	(-1.78, -0.63)	-3.39	(-3.98, -2.83)
Topiramate 200 mg/day	-1.05	(-1.74, -0.43)	-3.25	(-3.94, -2.63)
Amitriptyline 25 mg/day	-1.11	(-2.38, 0.19)	-3.31	(-4.58, -2.01)
Amitriptyline 100 mg/day	-1.09	(-2.65, 0.46)	-3.29	(-4.85, -1.74)
Propranolol 160 mg/day	-1.24	(-2.22, -0.29)	-3.44	(-4.42, -2.49)

Standard deviation for treatment effects: 0.33 (0.02, 0.88)

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

Sixteen 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 3.7 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.

Table 3.8 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. Both doses of erenumab and both doses of fremanezumab had statistically significant higher odds of response versus placebo (erenumab 70 mg: 1.9, erenumab 140 mg: 2.2, fremanezumab quarterly: 2.1, fremanezumab monthly: 2.4), whereas the results for galcanezumab suggest a higher odds of response versus placebo but were not statistically significant. All three doses of topiramate (50 mg, 100 mg, 200 mg), propranolol 120-160

mg, and amitriptyline 25 mg were also statistically significant versus placebo, whereas amitriptyline 100 mg was not statistically significant versus placebo. 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 45-50%: 45% (erenumab 70 mg), 48% (erenumab 140 mg), 47% (fremanezumab quarterly), 50% (fremanezumab monthly), and 46% (galcanezumab 120 mg). The expected response for the oral therapies ranged from 40% (topiramate 50 mg) to 53% (topiramate 100 mg and propranolol 120-160 mg).

In addition, the OLE of the Phase II erenumab trial followed patients for one year. All patients were given 70 mg of erenumab. After one year, 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 3.7. 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[38]	12	Placebo	43	144	Erenumab 70 mg/month	46	99	2.0 (1.2, 3.4)								
Goadsby 2017 (STRIVE)[37]	24	Placebo	93	316	Erenumab 70 mg/month	147	312	2.13 (1.52, 2.98)	Erenumab 140 mg/month	156	318	2.81 (2.01, 3.94)				
Dodick 2018 (ARISE)[100]	12	Placebo	85	288	Erenumab 70 mg/month	112	282	1.59 (1.12, 2.27)								
Bigal 2015b[40]	12	Placebo	36	104	Fremanezumab 225 mg/month	53	95	2.4 (NR)								
Aycardi 2017 (HALO-EM)[127]	12	Placebo	104	371	Fremanezumab 675 mg/3 months	167	375	2.1 (NR)	Fremanezumab 225 mg/month	179	375	2.3 (NR)				
Skljarevski 2018[101]	12	Placebo	78	126	Galcanezumab 120 mg/month	47	62	1.9 (NR)								
Goncalves 2016[104]	12	Placebo	12	59	Amitriptyline 25 mg/day	23	59	2.5 (NR)								
Diener 1996[105]	12	Placebo	17	55	Propranolol 120 mg/day	33	78	1.6 (NR)								
Mei 2004[112]	16	Placebo	8	37	Topiramate 100 mg/day	22	35	6.1 (NR)								
Lipton 2011[113]	26	Placebo	83	171	Topiramate 100 mg/day	105	159	2.1 (NR)								
Brandes 2004[114]	26	Placebo	26	114	Topiramate 50 mg/day	45	116	2.1 (NR)	Topiramate 100 mg/day	59	120	3.3 (NR)	Topiramate 200 mg/day	55	117	3.0 (NR)
Silberstein 2004 [115]	26	Placebo	26	115	Topiramate 50 mg/day	42	117	1.9 (NR)	Topiramate 100 mg/day	68	125	4.1 (NR)	Topiramate 200 mg/day	59	112	3.8 (NR)
Silberstein 2006 [117]	20	Placebo	25	73	Topiramate 200 mg/day	55	138	1.3 (NR)								
Storey 2001 [116]	16	Placebo	2	21	Topiramate 200 mg/day	5	19	3.4 (NR)								
Dodick 2009 [123]	26	Topiramate 100 mg/day	96	172	Amitriptyline 100 mg/day	73	159	0.7 (NR)								
Diener 2004 [121]	26	Placebo	31	143	Propranolol 160 mg/day	61	143	2.7 (NR)	Topiramate 100 mg/day	51	139	2.1 (NR)	Topiramate 200 mg/day	50	143	1.9 (NR)

NR: not reported, OR: odds ratio, r: responders, Tx: therapy, n: total population

Table 3.8. NMA Results for 50% Response in Episodic Migraine Patients

	Results vs. Placebo		Expected Proportion	
	OR Estimate	95% CrI	Estimate	95% CrI
Placebo	NA	NA	0.30	NA
Erenumab 70 mg monthly	1.89	(1.35, 2.66)	0.45	(0.37, 0.53)
Erenumab 140 mg monthly	2.17	(1.31, 3.59)	0.48	(0.36, 0.61)
Fremanezumab 675 mg quarterly	2.07	(1.24, 3.46)	0.47	(0.35, 0.6)
Fremanezumab 225 mg monthly	2.35	(1.55, 3.63)	0.50	(0.4, 0.61)
Galcanezumab 120 mg monthly	1.97	(0.88, 4.5)	0.46	(0.27, 0.66)
Topiramate 50 mg/day	1.56	(1.02, 2.46)	0.40	(0.3, 0.51)
Topiramate 100 mg/day	2.64	(1.97, 3.67)	0.53	(0.46, 0.61)
Topiramate 200 mg/day	2.28	(1.66, 3.2)	0.49	(0.42, 0.58)
Amitriptyline 25 mg/day	2.54	(1.02, 6.49)	0.52	(0.3, 0.74)
Amitriptyline 100 mg/day	1.76	(0.9, 3.6)	0.43	(0.28, 0.61)
Propranolol 120-160 mg/day	2.64	(1.63, 4.2)	0.53	(0.41, 0.64)

Standard deviation for treatment effects: 0.16 (0.01, 0.46);
CrI: credible interval, NA: not applicable, OR: odds ratio

Days per Month of Acute Medication Use

Ten of the 12 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 3.9 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.

Table 3.10 provides the results from a 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: -1.4, fremanezumab monthly: -1.5). For the oral preventives, the results for topiramate 100 mg, topiramate 200 mg, and propranolol 160 mg also were statistically significant and ranged from 0.8 (topiramate 200 mg) to 1.1 (propranolol 160 mg) fewer days per month using acute medications.

The expected reduction in days per month using acute medications with the CGRP inhibitors was 2.4 (erenumab 70 mg), 3.1 (erenumab 140 mg), 2.9 (fremanezumab quarterly), and 3.0 (fremanezumab monthly). The expected reduction using the oral therapies ranged from 1.7 (topiramate 50 mg) to 2.6 (propranolol 160 mg and amitriptyline 100 mg).

In addition, 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 2.1 fewer days per month using acute medications compared with 2.5 fewer days per month at week 12 among the patients taking erenumab during the double-blind phase.

Table 3.9. 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 (95% CI)	Tx 3	Mean	SE	Difference (95% CI)	Tx 4	Mean	SE	Difference (95% CI)
Sun 2016[38]	12	Placebo	-1.40	0.30	Erenumab 70 mg	-2.50	0.30	-1.2 (-2, -0.3)								
Goadsby 2017 (STRIVE) [128]	24	Placebo	0.01	0.13	Erenumab 70 mg	-1.14	0.13	-1.15 (NR)	Erenumab 140 mg	-1.67	0.13	-1.68 (NR)				
Dodick 2018 (ARISE) [100]	12	Placebo	-0.60	0.10	Erenumab 70 mg	-1.20	0.10	-0.6 (-1.0, -0.2)								
Bigal 2015b[40]	12	Placebo	-3.10	0.45	Fremanezumab 225 mg	-4.86	0.48	-1.76 (-2.86, -0.66)								
Aycardi 2017 (HALO-EM)[129]	12	Placebo	-1.60	0.27	Fremanezumab 675 mg quarterly	-2.90	0.27	-1.3 (NR)	Fremanezumab 225 mg	-3.00	0.27	-1.4 (NR)				
Lipton 2011[113]	26	Placebo	-3.80	0.28	Topiramate 100 mg/day	-4.80	0.28	-1.0 (NR)								
Brandes 2004[114]	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[115]	26	Placebo	-0.90	0.29	Topiramate 50 mg/day	-1.30	0.26	-0.4 (NR)	Topiramate 100 mg/day	-1.90	0.27	-1 (NR)	Topiramate 200 mg/day	-2.10	0.26	-1.2 (NR)
Dodick 2009[123]	26	Topiramate 100 mg/day	-2.60	0.39	Amitriptyline 100 mg/day	-2.80	0.41	-0.2 (NR)								
Diener 2004[121]	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)

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

Table 3.10. NMA Results for Days of Acute Medication Use in Episodic Migraine Patients

	Difference vs. Placebo		Expected Results	
	Estimate	95% CrI	Estimate	95% CrI
Placebo	NA	NA	-1.5	NA
Erenumab 70 mg monthly	-0.89	(-1.46, -0.39)	-2.39	(-2.96, -1.89)
Erenumab 140 mg monthly	-1.55	(-2.37, -0.76)	-3.05	(-3.87, -2.26)
Fremanezumab 675 mg quarterly	-1.36	(-2.39, -0.34)	-2.86	(-3.89, -1.84)
Fremanezumab 225 mg monthly	-1.51	(-2.39, -0.66)	-3.01	(-3.89, -2.16)
Topiramate 50 mg/day	-0.21	(-1.16, 0.71)	-1.71	(-2.66, -0.79)
Topiramate 100 mg/day	-0.92	(-1.46, -0.39)	-2.42	(-2.96, -1.89)
Topiramate 200 mg/day	-0.75	(-1.37, -0.19)	-2.25	(-2.87, -1.69)
Amitriptyline 100 mg/day	-1.11	(-2.58, 0.32)	-2.61	(-4.08, -1.18)
Propranolol 160 mg/day	-1.08	(-1.96, -0.24)	-2.58	(-3.46, -1.74)

Standard deviation for treatment effects: 0.31 (0.05, 0.79)

CrI: credible interval, NA: not applicable

Quality of Life: MIDAS, HIT-6, MSQ

Three quality of life measures were infrequently assessed and reported in nine 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 change from baseline in total MIDAS, there were greater reductions overall in the CGRP inhibitors than placebo although not statistically significant. Scores were assessed over 12 weeks for erenumab and galcanezumab, with one erenumab study reporting results by eight weeks that stayed stable through the 24-week follow-up period. While also not statistically significant, one trial reported an improvement with topiramate versus placebo over 24 weeks, and another trial reported an improvement with amitriptyline over topiramate in 24 weeks.

The STRIVE and ARISE trials reported HIT-6 data. At baseline, patients had values very close to the most severe impact category (severe impact ≥ 60). Reductions in scores with erenumab were small with a change ranging from 1 to 7 and did not substantially differ from placebo throughout the study durations.

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: 2-30; RFP, range: 0-21). The comparator trials (topiramate and amitriptyline only) also reported larger improvements in scores for up to 24 weeks.

In one OLE, patients 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 identified three studies[130-132] 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 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. Another study (Nelles 2010) used the same flexible dosing procedure and reported findings in patients receiving topiramate for six months (optional follow-up of 12 months). Median monthly migraine days decreased from 6.0 days at baseline to 1.2 days at six months with paresthesia and nausea being the most frequently reported adverse events. The third study (Malessa 2010) followed 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, 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. Across the 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 Discontinuations

Thirty-four 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 2% to 18% by 12 weeks. Discontinuations among patients on other preventive therapies ranged from 7% to 50%. Results from the NMA in Table 3.11 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.

For the episodic population, Appendix Table D14 presents the data available from 21 trials. Discontinuations among patients on placebo ranged from 0% to 53% between four and 26 weeks. Discontinuations among patients on a CGRP inhibitor ranged from 3% to 11% between 12 and 24 weeks. Discontinuations among patients on other preventive therapies ranged from 0% to 59%. As with the chronic migraine population, the results from a NMA were not statistically significant (Table 3.12). The point estimates for erenumab 70 mg and 140 mg indicate a lower odds of discontinuation, whereas the point estimates for all other interventions indicate a higher odds.

Table 3.11. NMA Results for All-Cause Discontinuations in Chronic Migraine

	Results vs. Placebo	
	OR Estimate	95% CrI
Placebo	NA	NA
Erenumab 70 mg monthly	0.65	(0.18, 2.21)
Erenumab 140 mg monthly	0.42	(0.09, 1.57)
Fremanezumab 675 mg quarterly	0.84	(0.35, 2)
Fremanezumab 675/225 mg monthly	1.19	(0.61, 2.42)
Onabotulinum toxin A	1.10	(0.63, 1.75)
Topiramate 50 mg/day	NE	NE
Topiramate 100 mg/day	0.91	(0.5, 1.57)
Topiramate 200 mg/day	1.25	(0.28, 5.43)

Standard deviation for treatment effects: 0.24 (0.01, 0.85)
CrI: credible interval, NA: not applicable, NE: not able to be estimated, OR: odds ratio

Table 3.12. NMA Results for All-Cause Discontinuations in Episodic Migraine

	Results vs. Placebo	
	OR Estimate	95% CrI
Placebo	NA	NA
Erenumab 70 mg monthly	0.78	(0.32, 1.75)
Erenumab 140 mg monthly	0.65	(0.23, 1.75)
Fremanezumab 225 mg monthly	2.67	(0.7, 10.87)
Galcanezumab 120 mg monthly	1.47	(0.39, 5.46)
Topiramate 50 mg/day	1.04	(0.52, 1.83)
Topiramate 100 mg/day	1.00	(0.67, 1.58)
Topiramate 200 mg/day	1.70	(1.06, 2.7)
Amitriptyline 75-150 mg/day	1.07	(0.61, 2.06)
Propranolol 60-160 mg/day	1.00	(0.6, 1.85)

Standard deviation for treatment effects: 0.40 (0.15, 0.79);
CrI: credible interval, NA: not applicable, OR: odds ratio

Discontinuations from Adverse Events

Appendix Table D15 contains the data available from 29 trials reporting discontinuations due to AEs. Discontinuations due to AEs among patients on placebo ranged from 0% to 10% between eight 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 44%. The results from a random effects NMA are expressed in terms of an OR for each intervention versus placebo (Table 3.13). 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. The results for all other interventions were not significant and suggested a higher odds of discontinuation, except for fremanezumab quarterly which had a point estimate suggesting a lower odds of discontinuation.

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

Table 3.13. NMA Results for Discontinuations from Adverse Events in Chronic or Episodic Migraine

	Results vs. Placebo	
	OR Estimate	95% CrI
Placebo	NA	NA
Erenumab 70 mg monthly	1.36	(0.51, 3.73)
Erenumab 140 mg monthly	1.38	(0.4, 4.92)
Fremanezumab 675 mg quarterly	0.96	(0.2, 4.53)
Fremanezumab 675/225 mg monthly	2.15	(0.73, 7.47)
Onabotulinum toxin A	2.10	(0.88, 5.07)
Topiramate 50 mg/day	1.60	(0.7, 3.36)
Topiramate 100 mg/day	2.53	(1.63, 4.12)
Topiramate 200 mg/day	3.66	(2.02, 6.58)
Amitriptyline 75-150 mg/day	2.64	(1.3, 5.56)
Propranolol 120-160 mg/day	1.36	(0.57, 3.01)

Standard deviation for treatment effects: 0.50 (0.17, 0.94)
CrI: credible interval, NA: not applicable, OR: odds ratio

Serious Adverse Events

SAEs were reported by 16 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 1% to 2% 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 3.14), with values above one indicating higher odds of SAEs with the active therapy versus placebo. Note that due to sparse data with zero counts,

results for galcanezumab were not able to be estimated. Amitriptyline had a statistically-significant higher odds of SAEs, whereas all other results were not significant. The point estimates favored the erenumab 140 mg and fremanezumab quarterly doses versus placebo, whereas all other interventions had a higher odds of SAEs.

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 randomize portion experienced a SAE after three cycles onabotulinum toxin A by one year.

Table 3.14. NMA Results for Serious Adverse Events in Chronic or Episodic Migraine

	Results vs. Placebo	
	OR Estimate	95% CrI
Placebo	NA	NA
Erenumab 70 mg monthly	1.11	(0.50, 2.48)
Erenumab 140 mg monthly	0.62	(0.21, 1.67)
Fremanezumab 675 mg quarterly	0.56	(0.09, 2.73)
Fremanezumab 675/225 mg monthly	1.20	(0.37, 4.32)
Galcanezumab 120 mg monthly	NE	NE
Onabotulinum toxin A	2.15	(0.95, 5.02)
Topiramate 100 mg/day	1.06	(0.34, 3.17)
Topiramate 200 mg/day	1.19	(0.15, 10.32)
Amitriptyline 100 mg/day	3.09	(1.17, 8.01)

Standard deviation for treatment effects: 0.23 (0.01,1.00)

CrI: credible interval, NA: not applicable, NE: not able to be estimated, OR: odds ratio

Adverse Events ≥ 5%

AEs reported in ≥ 5% of patients in any 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) at 12 or 24 weeks. One erenumab trial reported injection-site reactions in ≤ 6% of patients taking erenumab. In the fremanezumab trials, 20-24% of patients reported specific injection-site reactions (20-21%, erythema; 20-24% induration for one Phase III trial). For galcanezumab, one trial reported 5% of patients with an injection-site reaction and 17% of patients with injection-site pain and in another trial, 8-14% of patients reported injection-site pain. Nasopharyngitis and upper respiratory tract infection were reported in 5% to 12% of patients in erenumab 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

Although trial results of the CGRP inhibitors show treatment benefits with few harms, there is uncertainty in the durability of the any effects gained from the use of CGRP inhibitors. All the available Phase II and Phase III trials had outcomes assessed by 12 weeks or 24 weeks. Longer-term efficacy and safety remains unknown due the lack of data at this time.

Additionally, while 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 may continue after treatment is discontinued, such data on efficacy after discontinuation were not available. Any discontinuation rates were ascertained from the reported all-cause discontinuations, and discontinuations due to AEs, which were both low in the trials of CGRP inhibitors.

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.[133] 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 few trials, was at most evaluated for 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 generalizability of the results from the trials also poses some problems in clinical practice. The baseline period of four weeks used in the CGRP inhibitor trials required patients to comply with a headache diary. It is unclear how the results from trials would apply to those who did not comply with a headache diary. If the non-compliers were different from those who initiated the randomized phase in ways that affect the treatment effects, then the trial results cannot be generalized. Similarly, patients who were included in trials of current preventive therapies generally were not required to comply with a headache diary at baseline, and these patients may respond differently to treatment than those in trials of CGRP inhibitors.

The efficacy and safety of CGRP inhibitors in patients with comorbidities, particularly cardiovascular diseases, have not been evaluated. As migraine is associated with higher prevalence of comorbidities including cardiovascular disease than in the general population, data on these patients are of particular interest.[134]

From our analyses, we have limited subgroup data on failures of treatment. The CGRP inhibitor trials altogether excluded those who experienced failures in receiving any benefits from two or more previous treatments.

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

- **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 (1.3-2.4 fewer migraine days per month), a modest reduction in days using acute medications (0.9-2.5 fewer days per month), and a greater proportion of patients experiencing a reduction in migraine days by at least 50% (OR 1.9-2.3) 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

- **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 (1.3-1.9 fewer migraine days) and modest reduction in days using acute medications (1.4-2.3 fewer days). Results also suggest a greater proportion of patients experiencing a reduction in migraine days by at least 50% versus placebo (OR 2-2.4 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

- **Number of trials:** In the chronic migraine population, we did not identify any published trials. In the episodic migraine population, we included two placebo-controlled, Phase II, 12-week trials which assessed different regimens of galcanezumab.
- **Efficacy:** Results from one trial in episodic migraine suggest a modest reduction in monthly migraine days (0.9 fewer days per month) and a greater proportion of patients experiencing a reduction in migraine days by at least 50% versus placebo (OR 2.0).
- **Safety:** Galcanezumab 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. In addition, nasopharyngitis was reported by <10% of patients and upper respiratory tract infections were reported by <20% of patients.

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 with oral agents or onabotulinum toxin A, we rated the evidence on the net benefit of erenumab and fremanezumab as insufficient ("I"). 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+"), 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 with oral agents, we rated the evidence on the net benefit of erenumab and fremanezumab as insufficient ("I"). 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"), 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 data currently available, we rated the evidence on net benefit of galcanezumab as insufficient ("I") for all comparisons.

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 treatment and to onabotulinum toxin A in people with chronic migraine for whom previous preventive therapy failed, and compared to no treatment in people with 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 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 that were similar in structure to recent models in migraine treatment.[135-138] 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). Note that although we have rated the evidence comparing erenumab and fremanezumab to onabotulinum toxin A as insufficient ("I") in the clinical section of the report, we have elected to present the results of that analysis here to facilitate public comment on the related economic analyses. If, after reviewing public comments on the clinical section and economic analysis, the evidence rating remains "I", we will consider this comparison to be a secondary analysis and move the corresponding results to the appendix.

4.2 Methods

Model Structure

We developed separate semi-Markov models to assess the cost-effectiveness of erenumab and fremanezumab compared to no 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 two prior preventive treatments result in failure. This subset of patients was selected as the

base-case population to align 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) and because of exclusion criteria in the trials of CGRP inhibitors limiting evidence on patients for whom greater numbers of preventive therapies had failed. For patients with chronic migraine for whom a previous preventive treatment had failed we also created a separate model to compare CGRP inhibitors to onabotulinum toxin A. 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 vs. no 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 a 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 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 a NMA using the subset of patients for whom a previous therapy for episodic migraines had failed.
3. **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 a NMA.

Patients moved through the health states in the model in monthly cycles. In the models, in each of the arms (see Figures 4.1 and 4.2 below), patients start in an initial health state numbered "1" in the figures 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.[135-141] 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)

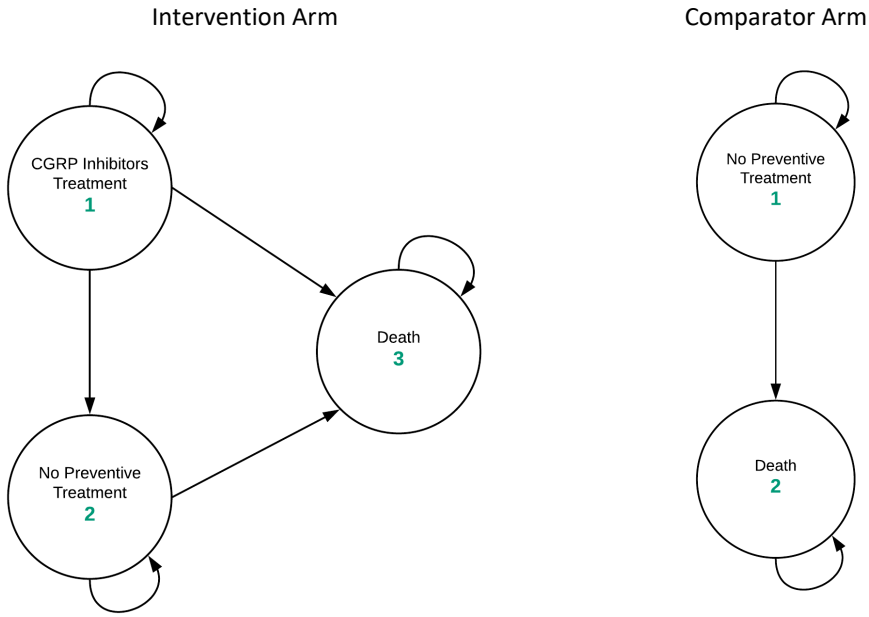
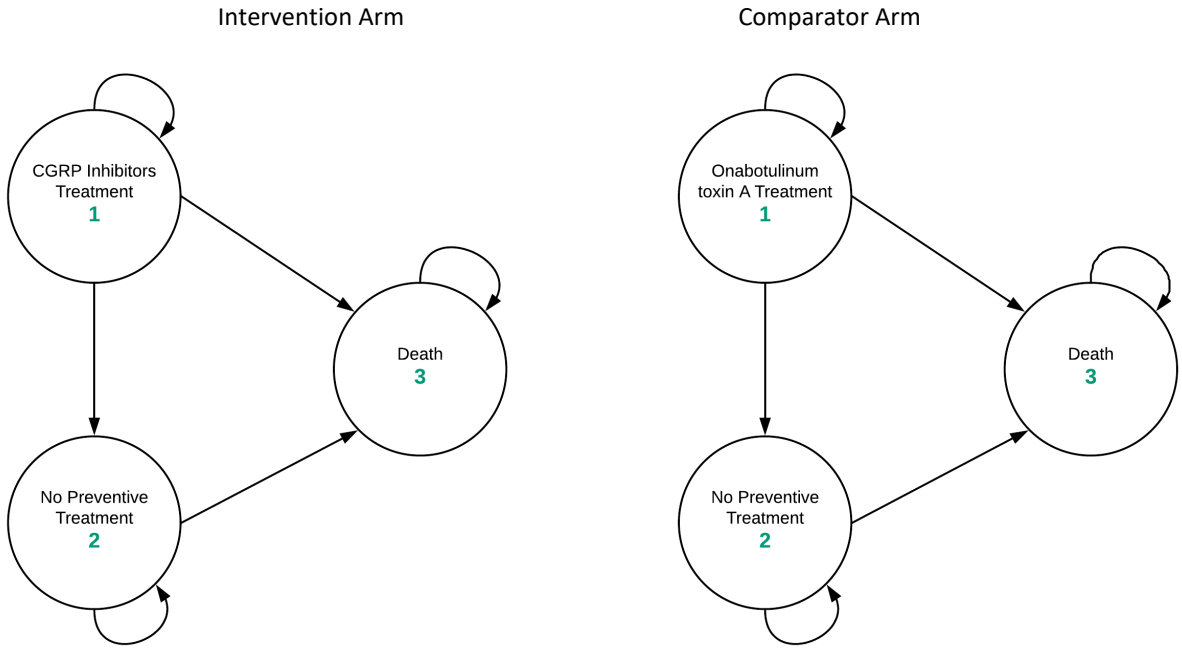


Figure 4.2. Model Framework for CGRP Inhibitors versus Onabotulinum Toxin A (Chronic Migraine)



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[9]
	Female	80.5%	Lipton et al. 2016[142]
	Race/Ethnicity	88.6% - white 11.4% - non-white	Lipton et al. 2016[142]
	Mean Migraine Days per Month	17.7	RCT Population in Network Meta-analysis
Episodic Migraine	Mean age	39.9 years	Ford et al. 2017[9]
	Female	76.4%	Lipton et al. 2016[142]
	Race/Ethnicity	85.0% - white 15.0% - non-white	Lipton et al 2016[142]
	Mean Migraine Days per Month	8.0	RCT Population in Network Meta-analysis

Treatment Strategies

As described above, each of the CGRP inhibitors was compared with no preventive treatment in chronic and episodic migraine patients, separately. An additional comparison was conducted for those with chronic migraine where the CGRP inhibitors were compared to onabotulinum toxin A.

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.[135-138] 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. It was assumed that the treatment effects result in a reduction in migraine days across all severity levels and do not change the distribution of migraine severity.	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. Also, we did not have adequate data to suggest a change in the distribution of severity of migraine days associated with any of the treatments.
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.[143] 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.[143]	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).[144]	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).[145]

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 Network Meta-analysis
Headache Severity (%)	Mild	0.4%	1.4%	Blumenfeld[145]
	Moderate	7.2%	20.5%	Blumenfeld[145]
	Severe	92.4%	78.1%	Blumenfeld[145]

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, with those for the CGRP inhibitors 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 treatment from the NMA among the subset of patients that failed at least one prior preventive therapy.

Table 4.4. Treatment Effects for CGRP Inhibitors and Onabotulinum toxin A 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			
Fremanezumab 675/225 mg monthly			
Onabotulinum toxin A	0.8 (-1.92, 0.22)	1.5 (-2.66, -0.37)	2.0 (-3.18, -0.82)

Black cells indicate confidential data
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			
Fremanezumab 225 mg monthly			

Black cells indicate confidential data
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).[143]

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[143]

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 except for onabotulinum toxin A, where we based the overall reduction on reported reductions in triptan days. The reductions in acute treatments are listed below (Table 4.7).

Table 4.7. Reduction in Days per Month of Acute Treatments for CGRP Inhibitors and Onabotulinum Toxin A

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	-2.50 (-4.30, 0.51)	-1.54 (-2.28, -0.83)
Fremanezumab 225 mg monthly	-2.29 (-4.02, -0.45)	-1.48 (-2.23, -0.76)
Onabotulinum toxin A	-1.10 (-1.74, -0.61)	--

CI: confidence interval

Discontinuation Rates

In each of the models, patients transitioned from the "CGRP Inhibitor Treatment" or "Onabotulinum toxin A Treatment" health states 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 and Onabotulinum Toxin A

Treatment	Chronic Migraine: Discontinuation Rate (95% CI)	Episodic Migraine: Discontinuation Rate (95% CI)
Erenumab 140 mg monthly	0.025 (0.005, 0.089)	0.035 (0.007,0.159)
Fremanezumab 225 mg monthly	0.049 (0.021, 0.116)	0.175 (0.044,0.763)
Onabotulinum toxin A	0.061 (0.034, 0.104)	--

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.[146]

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. Table 4.9 shows the utility values used for a severe, moderate, mild, and pain-free migraine 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.[147] 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. Specifically, the weighted utility for a migraine day for chronic migraines is 0.466 and the weighted utility for a migraine day for episodic migraines is 0.514. To estimate the monthly total quality adjusted days, the migraine day utilities were multiplied by the number of migraine days per month and the non-migraine days per month (calculated as 30 minus the number of migraine days) were multiplied by the pain-free migraine day utility of 0.959 and these two totals were summed. 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. 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[147]
Moderate Migraine Day	0.773	(0.755, 0.789)	EQ-5D	Xu et al 2011[147]
Mild Migraine Day	0.835	(0.790, 0.883)	EQ-5D	Xu et al 2011[147]
Pain-Free Migraine Day	0.959	(0.896, 0.967)	EQ-5D	Xu et al 2011[147]

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 (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 4.10.

Table 4.10. 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[83]	5.6%	Goadsby et al. 2017[37]
Fremanezumab 225 mg monthly	11.5%	Silberstein et al. 2017[43]	6.6%	Bigal et al. 2015[41]
Onabotulinum toxin A	3.5%	Diener et al. 2010[148]	NA	NA

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.[149]

Drug Acquisition Costs

We used Federal Supply Schedule costs for the 200 unit package size of onabotulinum toxin A and assumed that 155 units would be administered per quarter; we assumed wastage for the remaining units (Table 4.11).[150] Because there are currently no publicly-available prices for CGRP inhibitors, we have used an analyst -estimated price of $8,500 per year as a placeholder until the real-world price becomes available.[151]

Table 4.11. Preventive Drug Cost Inputs

Drug	Administration	Unit	Cost per Unit/Dose*	Annual Drug Cost
Erenumab 140 mg monthly	SQ	mg		$8,500†
Fremanezumab 225 mg monthly	SQ	mg		$8,500†
Onabotulinum toxin A	SQ	units	$857.28	$3429.12

*Federal supply schedule price for 200 units as of 3/28/18[150]

† Placeholder price

Administration and Monitoring Costs

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

The administration of onabotulinum toxin A is based on a quarterly cost of administration prorated to the monthly cycles in the model (CPT 64615; 2017 national non-facility price = $149.30).[144]

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.[143] The cost per day for acute treatments was $25 for chronic migraine patients and $21 for episodic migraine patients.

For hospitalization costs, we used 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).[152] The average cost per person per month was $1.10 due to the low rate of hospitalizations (342 per 100,000 migraine patients). Importantly, the Lucado estimate may be an overestimate of the costs of hospitalization associated with migraines as it is an estimate for hospitalizations due to all headache diagnoses. The Mesalli et al. analysis included the costs of emergency department, primary care physician, nurse practitioner, and specialist visits; transcutaneous nerve stimulator use; occipital nerve block procedures; imaging; and blood tests, all of which we included in our model.[143] The resource use costs without medications was $93 per month for chronic migraine and $38 per month for episodic migraine. These resource use costs were reduced proportionately in the treatment arms based on the migraine day treatment effect of the individual CGRP inhibitors and, where relevant, other preventive medications.

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 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:

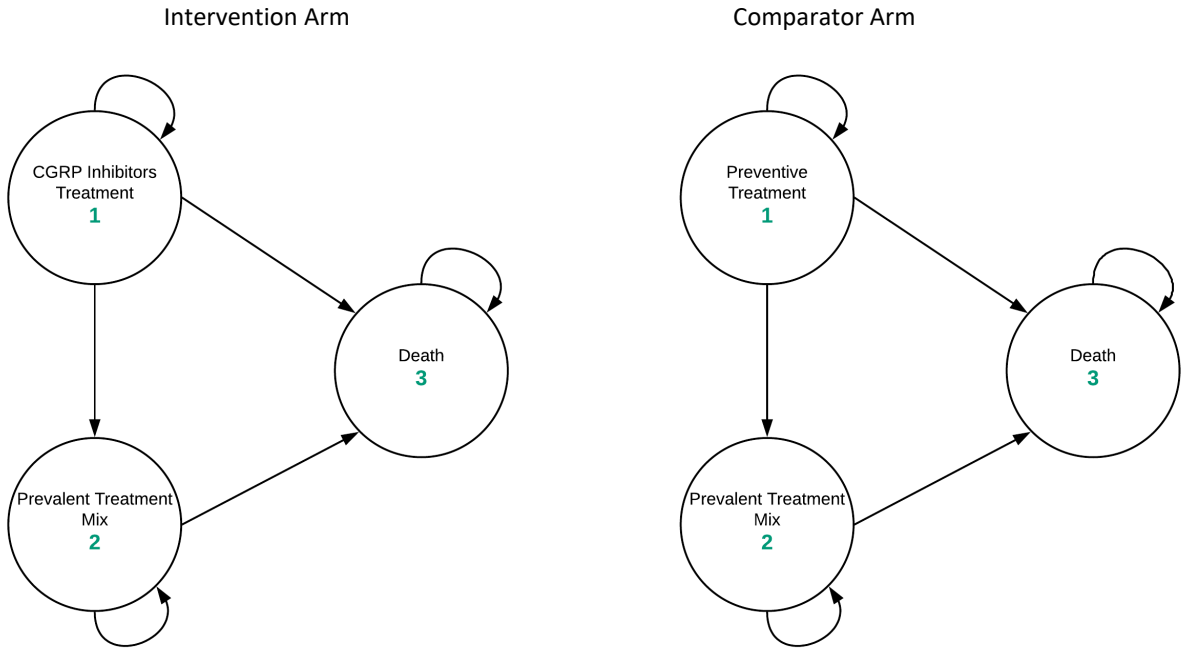
1. CGRP Inhibitors Compared to Current Preventive Treatments

The first scenario analysis evaluated the cost-effectiveness of 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. 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.[9] 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.[9] 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.
2. CGRP inhibitor versus active preventive treatment in episodic migraine (Figure 4.3). In this comparison, CGRP inhibitors 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.[9] 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.[9] 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 4.3. 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. We based the productivity costs from Mesalli et al. 2016, which captured presenteeism productivity loss, days missed, and lack of housework done for full-time employees, part-time employees, and those with other employment status.[143] This study reported on the findings of the International Burden of Migraine Study (IBMS-I) that measured healthcare resource utilization, productivity and quality of life among a sample of patients classified as either episodic or chronic migraine. The total productivity costs for chronic migraines were $858 per month for chronic and $245 per month for episodic migraine. These productivity costs were reduced

proportionately to the migraine day treatment effect from the NMA across all the preventive treatments. In addition, we ran a sensitivity analysis for this scenario using alternative estimates of productivity costs associated with migraines that were supplied by Amgen based on previous studies involving the MIDAS questionnaire and productivity information in patients with episodic and chronic migraine.[153]

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. Changes in Distribution of Severity of Migraine

To evaluate the impact of the distribution of migraine severity used in the base case analysis, a scenario analysis was conducted that utilized an alternative distribution of severity. The distribution used in the base case and this scenario analysis are shown in Table 4.12.

Table 4.12. Distribution of Migraine Severity in the Episodic and Chronic Models in Scenario Analyses

	Base Case		Scenario Analysis	
Headache Severity (%)	Chronic Model	Episodic Model	Chronic Model	Episodic Model*
Mild	0.4%	1.4%	10.3%	11.3%
Moderate	7.2%	20.5%	38.6%	51.9%
Severe	92.4%	78.1%	51.1%	36.8%

*Data were not provided by the manufacturer for distribution of headache severity for patients with episodic migraine. We assumed the same absolute change in the distribution for the episodic model as was observed in the chronic model.

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

Base-Case Results

Treatment with CGRP inhibitors resulted in higher total costs, more migraine-free days, and increased QALYs compared to no treatment in both chronic and episodic migraine among patients for whom at least one but not more than two previous preventive therapies had failed (Table 4.13 and 4.14). Similarly, when compared with onabotulinum toxin A, the CGRP inhibitors were associated with higher costs, increased migraine-free days and slightly more QALYs. 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 Treatment and Onabotulinum Toxin A in Chronic Migraine*

Treatment	Drug Cost	Total Cost	Migraine-Free Days Gained	QALYs
CGRP Inhibitors vs. No Treatment				
Erenumab 140 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 625/225 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment	$0	[redacted]	0	[redacted]
CGRP Inhibitors vs. Onabotulinum Toxin A				
Erenumab 140mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 625/225 mg monthly	[redacted]	[redacted]	[redacted]	[redacted]
Onabotulinum Toxin A	$3,912	$10,084	23.17	1.31

Results in this table are redacted to preserve the confidentiality of certain data inputs used in their generation
*All results presented in this table for the CGRP inhibitors are based on placeholder costs

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

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

Results in this table are redacted to preserve the confidentiality of certain data inputs used in their generation
*All results presented in this table for the CGRP inhibitors are based on placeholder costs.

Using a placeholder price of $8,500 per year, the base case incremental cost-effectiveness ratios for erenumab in chronic migraine for patients among whom prior preventive therapy failed was approximately $135,000 per QALY gained compared to no treatment and approximately $147,000 per QALY gained compared to onabotulinum toxin A (Table 4.15). The comparable results for fremanezumab were approximately $184,000 per QALY gained compared to no treatment and approximately $315,000 per QALY gained compared to onabotulinum toxin A. For patients with episodic migraine among whom prior preventive therapy failed, using a placeholder price of $8,500 per year, the incremental cost-effectiveness ratios for the CGRP inhibitors compared to no treatment were more than $225,000 per QALY gained.

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

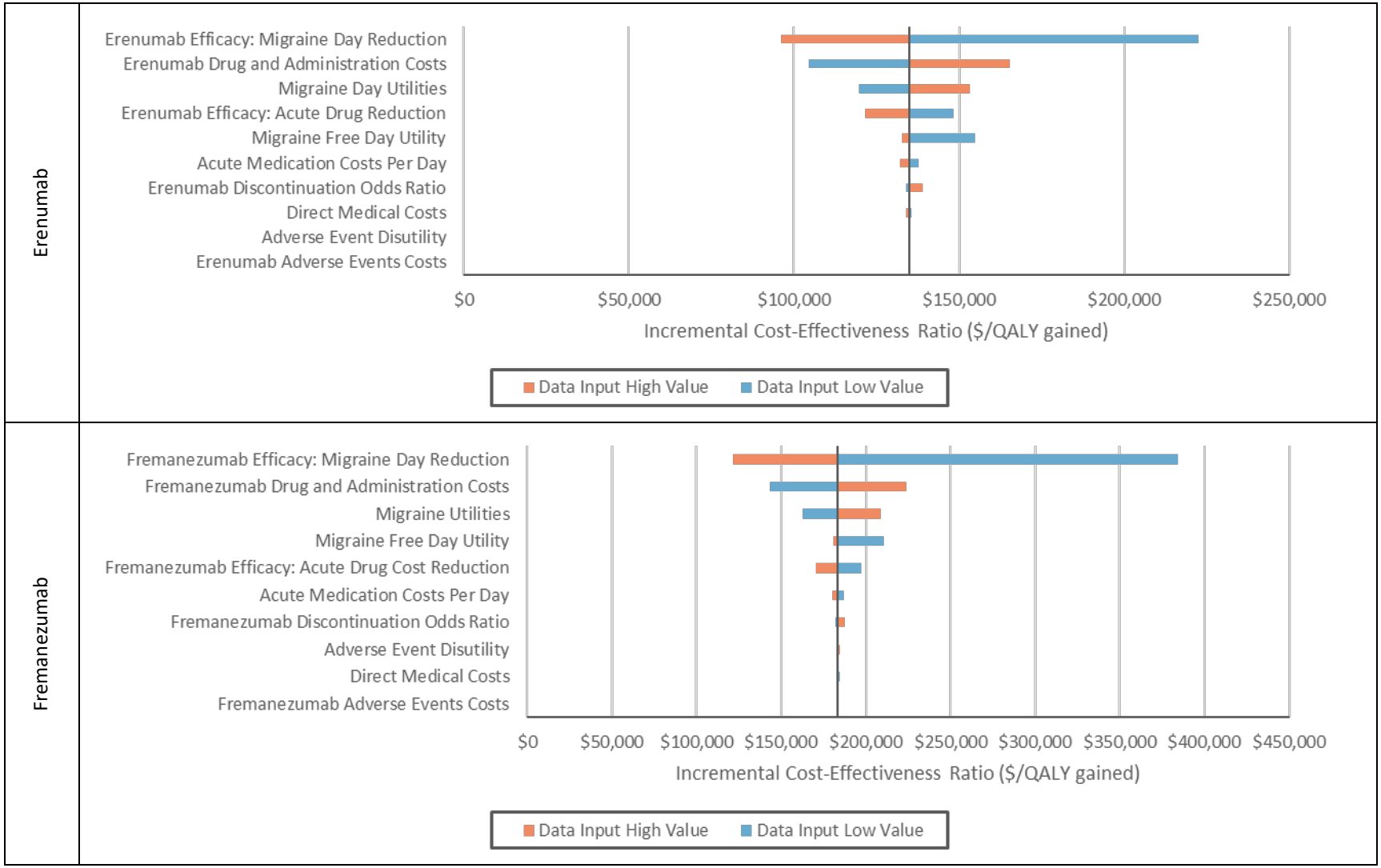
Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-free Day Gained
Chronic Migraine			
Erenumab 140mg monthly	No Treatment	$134,900	$180
Fremanezumab 625/225mg monthly	No Treatment	$183,600	$250
Erenumab 140mg monthly	Onabotulinum Toxin A	$147,200	$200
Fremanezumab 625/225mg monthly	Onabotulinum Toxin A	$315,100	$420
Episodic Migraine			
Erenumab 140mg monthly	No Treatment	$235,600	$290
Fremanezumab 225mg monthly	No Treatment	$225,100	$270

* All results presented in this table for the CGRP inhibitors are based on placeholder costs and, to ensure the confidentiality of the data used to generate the results, are rounded to the nearest hundred for cost per QALY gained and to the nearest ten 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 addition 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).

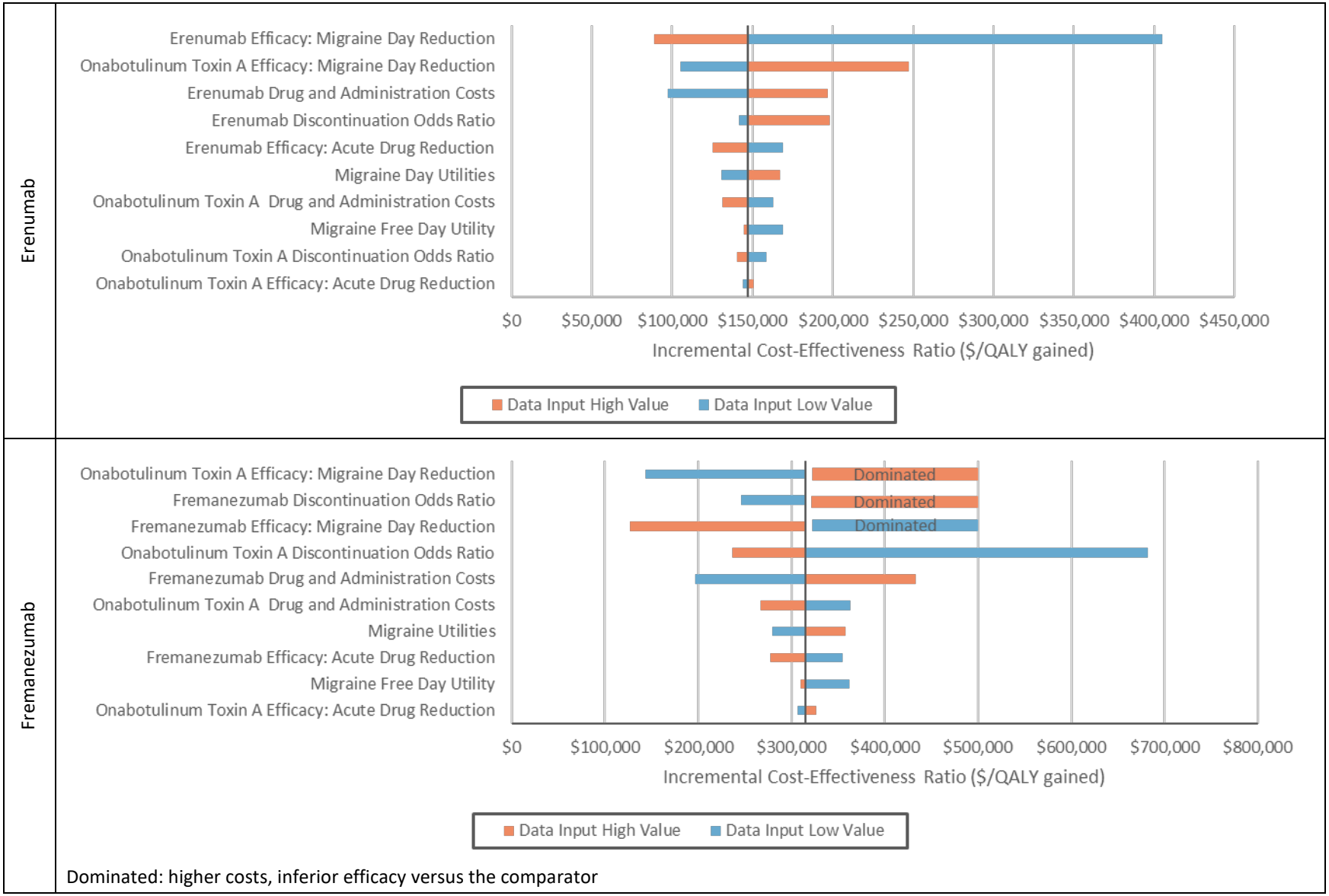
Figure 4.4. Tornado Diagrams for One-Way Sensitivity Analyses of CGRP Inhibitors versus No Treatment in Chronic Migraine



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

Figures 4.5 and 4.6 below show the tornado diagram results for the CGRP inhibitor versus onabotulinum toxin A model followed by the results from the base case model for CGRP inhibitors relative to no treatment in episodic migraine. Those show similar findings in terms of the variables that influence the incremental cost effectiveness ratios from the models. One exception, seen in Figure 4.5, is that fremanezumab and onabotulinum toxin A discontinuation rates had relatively high effects on the incremental cost effectiveness ratio, which happened because the incremental quality adjusted life years associated with fremanezumab relative to onabotulinum toxin A were extremely small. Consequently, small changes in the quality adjusted life years from changing the discontinuation rates of fremanezumab or onabotulinum toxin A resulted in relatively large changes in the incremental cost effectiveness ratio. Also, as shown in figure 4.5, onabotulinum toxin A dominated (i.e., had lower costs and higher quality adjusted life years) fremanezumab over some ranges of the model inputs.

Figure 4.5. Tornado Diagrams for One-Way Sensitivity Analyses of CGRP Inhibitors versus Onabotulinum Toxin A in Chronic Migraine



Dominated: higher costs, inferior efficacy versus the comparator

Figure 4.6. Tornado Diagrams for One-Way Sensitivity Analyses of CGRP Inhibitors versus No Treatment in Episodic Migraine

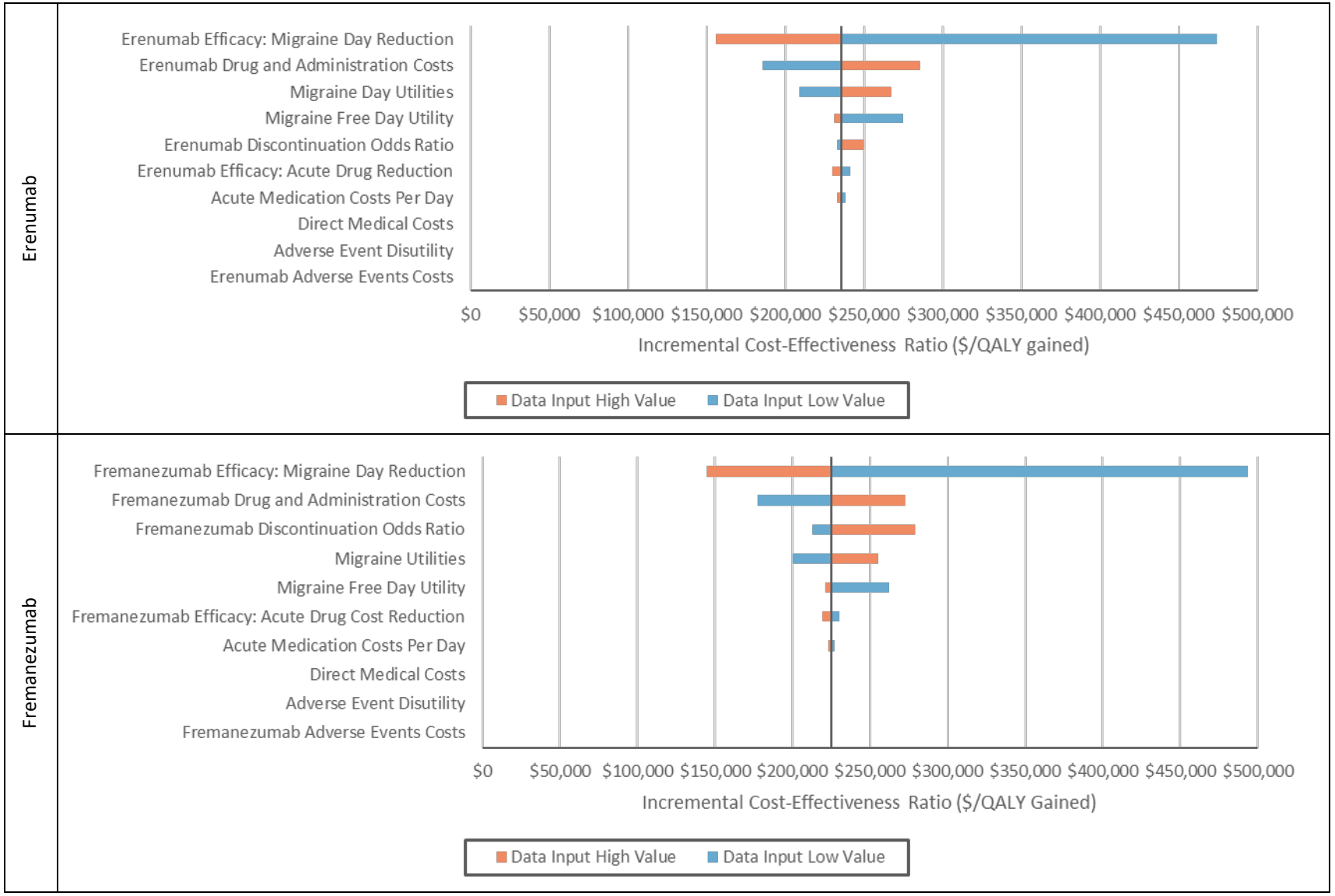


Table 4.16 summarizes the probabilistic sensitivity analyses (see Appendix E including Figures E1-E9 for more details). In chronic migraine, in the simulations reflecting potential variance in the model inputs, erenumab was never associated with an incremental cost effectiveness ratio below $50,000, and infrequently with a ratio below $100,000 (7%), but was associated with an incremental cost effectiveness ratio below $150,000 61.7% of the time versus no treatment and below $150,000 46.7% of the time versus onabotulinum toxin A. Fremanezumab was never below $50,000 or $100,000 and was infrequently (19.1%) associated with a cost effectiveness ratio below $150,000 in chronic migraine relative to no treatment. Relative to onabotulinum toxin A, fremanezumab was associated with an incremental cost effectiveness ratio less than $150,000 12.3% of the time. In addition, both treatments were rarely (less than 2.5%) associated with in incremental cost effectiveness ratio less than $150,000 in episodic migraine relative to no treatment.

Table 4.16. Probabilistic Sensitivity Analysis Results: CGRP Inhibitors versus No Treatment and 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	No treatment	0%	7.0%	61.7%
Fremanezumab 625/225 mg monthly	No treatment	0%	0%	19.1%
Erenumab 140 mg monthly	Onabotulinum toxin A	0.8%	13.5%	46.7%
Fremanezumab 625/225 mg monthly	Onabotulinum toxin A	0.3%	2.7%	12.3%
Episodic Migraine				
Erenumab 140 mg monthly	No treatment	0%	0%	1.7%
Fremanezumab 225 mg monthly	No treatment	0%	0%	2.2%

* All results presented in this table for the CGRP inhibitors are based on placeholder costs

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-E11 and Figures E10-E11. In the chronic migraine population, fremanezumab was dominated by the current preventive treatments while erenumab 140 mg monthly had an incremental cost-effectiveness ratio of $705,000 per QALY gained (Table 4.17). In episodic migraine, erenumab 140 mg monthly had an incremental cost-effectiveness ratio of $584,000 per QALY gained and fremanezumab 225 mg monthly had an incremental cost-effectiveness ratio of $466,000 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	$705,264	$984
Fremanezumab 625/225 mg monthly	Preventive treatment	Dominated	Dominated
Episodic Migraine			
Erenumab 140 mg monthly	Preventive treatment	$584,276	$731
Fremanezumab 225 mg monthly	Preventive treatment	$466,498	$535

* All results presented in this table for the CGRP inhibitors are based on placeholder costs
Dominated: higher costs, inferior efficacy versus the comparator

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 $100,000 per QALY gained for chronic patients relative to no treatment, and the incremental cost of fremanezumab relative to no treatment in chronic patients was below $150,000 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 treatment	$99,000	$130
Fremanezumab 625/225 mg monthly	No treatment	$147,600	$200
Erenumab 140 mg monthly	Onabotulinum toxin A	$111,400	$150
Fremanezumab 625/225 mg monthly	Onabotulinum toxin A	$278,900	$370
Episodic Migraine			
Erenumab 140 mg monthly	No treatment	$210,400	$240
Fremanezumab 225 mg monthly	No treatment	$200,000	$260

* All results presented in this table for the CGRP inhibitors are based on placeholder costs and, to ensure the confidentiality of the data used to generate the results, are rounded to the nearest hundred for cost per QALY gained and to the nearest ten 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 treatment	$132,900	$132,500	$132,400
Fremanezumab 625/225 mg monthly	No treatment	$182,300	$182,200	$182,200
Erenumab 140 mg monthly	Onabotulinum toxin A	$141,100	$139,000	$138,700
Fremanezumab 625/225 mg monthly	Onabotulinum toxin A	$297,900	$292,300	$291,900
Episodic Migraine				
Erenumab 140 mg monthly	No treatment	$232,300	$231,700	$231,700
Fremanezumab 225 mg monthly	No treatment	$224,700	$224,700	$224,700

* All results presented in this table for the CGRP inhibitors are based on placeholder costs and, to ensure the confidentiality of the data used to generate the results, are rounded to the nearest hundred for cost per QALY gained and to the nearest ten for cost per migraine-free day 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 treatment	$119,700	$160
Fremanezumab 625/22 5mg monthly	No treatment	$165,900	$220
Erenumab 140 mg monthly	Onabotulinum toxin A	$137,000	$190
Fremanezumab 625/225 mg monthly	Onabotulinum toxin A	$291,500	$390
Episodic Migraine			
Erenumab 140 mg monthly	No treatment	$206,000	$250
Fremanezumab 225 mg monthly	No treatment	$213,800	$260

* All results presented in this table for the CGRP inhibitors are based on placeholder costs and, to ensure the confidentiality of the data used to generate the results, are rounded to the nearest hundred for cost per QALY gained and to the nearest ten for cost per migraine-free day gained

Changes in Distribution of Severity of Migraine

Table 4.21 shows results from the base case models but incorporating an alternative distribution of migraine severity. With the alternative distribution of severity, the incremental ratios were all higher (i.e., less favorable) and above $150,000 per QALY gained.

Table 4.21. Incremental Cost-Effectiveness Ratios Incorporating Alternative Distribution of Migraine Severity*

Treatment	Comparator	Cost per QALY Gained	Cost per Migraine-Free Day Gained
Chronic Migraine			
Erenumab 140 mg monthly	No Treatment	$190,400	$180
Fremanezumab 625/225 mg monthly	No Treatment	$259,500	$250
Erenumab 140 mg monthly	Onabotulinum Toxin A	$207,500	$200
Fremanezumab 625/225 mg monthly	Onabotulinum Toxin A	$446,100	$420
Episodic Migraine			
Erenumab 140 mg monthly	No Treatment	$348,300	$290
Fremanezumab 225 mg monthly	No Treatment	$332,800	$270

* All results presented in this table for the CGRP inhibitors are based on placeholder costs and, to ensure the confidentiality of the data used to generate the results, are rounded to the nearest hundred for cost per QALY gained and to the nearest ten 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 Treatment	$3,800	$6,600	$9,400
Fremanezumab 625/225 mg vs. no Treatment	$2,900	$5,000	$7,100
Erenumab 140 mg vs. Onabotulinum Toxin A	$5,200	$6,900	$8,600
Fremanezumab 625/225 mg vs. Onabotulinum Toxin A	$4,700	$5,400	$6,100
Episodic Migraine			
Erenumab 140 mg vs. no Treatment	$2,200	$3,900	$5,600
Fremanezumab 225 mg vs. no Treatment	$2,200	$4,000	$5,800

*WAC prices for the two investigational drugs were not available as of the date of this report.
†Placeholder price

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.[154] 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.[154] 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 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 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 similar to the corresponding threshold price for the chronic migraine population in the ICER analysis ($7,400 versus $6,500, respectively).

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 WTP 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, Lipton et al. calculate a value-based price for WTP thresholds between $100,000 and $200,000 per QALY gained, whereas the ICER model

uses a placeholder annual price of $8,500 based on a market analyst estimate, in addition to calculating prices for erenumab at WTP 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.[150]

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.

- 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 for full and part-time employees, as well as housework productivity loss due to migraine, as reported by Mesalli et al.[143]

A model by Yu et al.[138] 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 CGRPs and patients could move to the market basket treatment upon CGRP 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 CGRPs 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.[135] 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 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, applying a fixed distribution of severity across migraine days. 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

CGRP inhibitors are predicted to positively impact the health of patients with both chronic or episodic migraine for whom prior preventive therapy had failed relative to no treatment. In the base-case analyses, which used a placeholder price of $8,500 per year, the incremental cost effectiveness ratio of erenumab is under the $150,000 per QALY gained threshold compared to no treatment and compared to onabotulinum toxin A. At the placeholder price, fremanezumab was above the threshold of $150,000 per QALY gained in patients with chronic migraine compared to no treatment and onabotulinum toxin A. However, the analyses were sensitive to a number of parameters including the costs of the medication, and in 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 than those seen in the trials. Discontinuation rates may be lower in the clinical trials than would be seen in a general patient population. The placeholder price estimate 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. The estimate here is likely an upper bound in terms of severity such that the expected incremental cost effectiveness ratios of the CGRP inhibitors are likely to be higher (i.e., less favorable) in a general 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, CGRP inhibitors may meet the upper bound of common WTP thresholds. In patients with episodic migraine and patients with chronic migraine who have other treatment options available to them, it is likely that CGRP inhibitors will exceed commonly-cited WTP thresholds using the placeholder price.

5. Additional 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 provides significant direct patient health benefits that are not adequately captured by the QALY.
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 CGRPs 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

Value-based price benchmarks will be included in the revised Evidence Report that will be released on/about May 31, 2018.

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 placeholder price used in the cost-effectiveness analyses 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.[155] 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.[156,157] Chronic and episodic migraine were defined as ≥ 15 and < 15 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 F12-F13.

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. The Adelphi Migraine Disease Specific Programme (DSP), a real-world, cross-sectional survey of physicians and their patients with migraine, estimates that 95.6% of people with chronic migraine were on preventive migraine therapy.[9] The study had a sample size of 1,487 people, categorized into episodic and chronic categories based on the ICDH-2 criteria. Applying this estimate to the prevalent chronic migraine population resulted in approximately 2.3 million individuals on preventive therapy. In the episodic migraine population, a study by Lipton et al. found that only 12.4% of people with episodic migraine are on preventive therapy.[156] Applying this estimate to the

prevalent episodic migraine population resulted in approximately 3.2 million people with migraine on preventive therapy. There are currently no published real-world estimates on the percentage of people with either chronic or episodic migraine for whom at least one preventive therapy has failed. However, we heard from clinical experts and relevant stakeholders that people with migraine cycle through preventive therapy at a relatively high rate due to treatment failure. We therefore assumed that 50% of patients had experienced the failure of at least one preventive therapy. 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 1.2 million people with chronic migraine and approximately 1.6 million people with episodic migraine who were eligible to be treated with CGRPs.

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 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. 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 CGRPs would replace no treatment since patients had already experienced the failure of other preventive therapy.

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 prices (placeholder and the three WTP threshold prices) weighted by the size of the prevalent population. Unweighted population-specific per-patient budget impact results can be found in Appendix Tables E14-E17.

The combined annual average potential budget impact per patient for erenumab when using the placeholder WAC ($8,500 annually) was approximately $6,000 versus no current preventive treatment. The per-patient annual budget impact ranged from approximately $1,700 using the price to reach $50,000 per QALY ($2,831) to approximately $5,000 using the price to reach $150,000 per QALY ($7,161) threshold (Table 7.2). The total potential annual budget impact across the entire eligible migraine populations when using erenumab relative to no active preventive treatment ranged from approximately $1.7 billion using the price to reach the $50,000 per QALY threshold ($2,831 annually) to approximately $5.8 billion using the placeholder WAC ($8,500 annually). As shown in Figure 7.1, approximately 16% of the total annual eligible migraine population could be treated with erenumab at its placeholder WAC without crossing the ICER annual budget impact threshold of $915 million. Between 19% and 55% of the entire eligible

migraine population could be treated annually at the prices to reach the $150,000 per QALY ($7,161 annually) and $50,000 per QALY ($2,831 annually) thresholds.

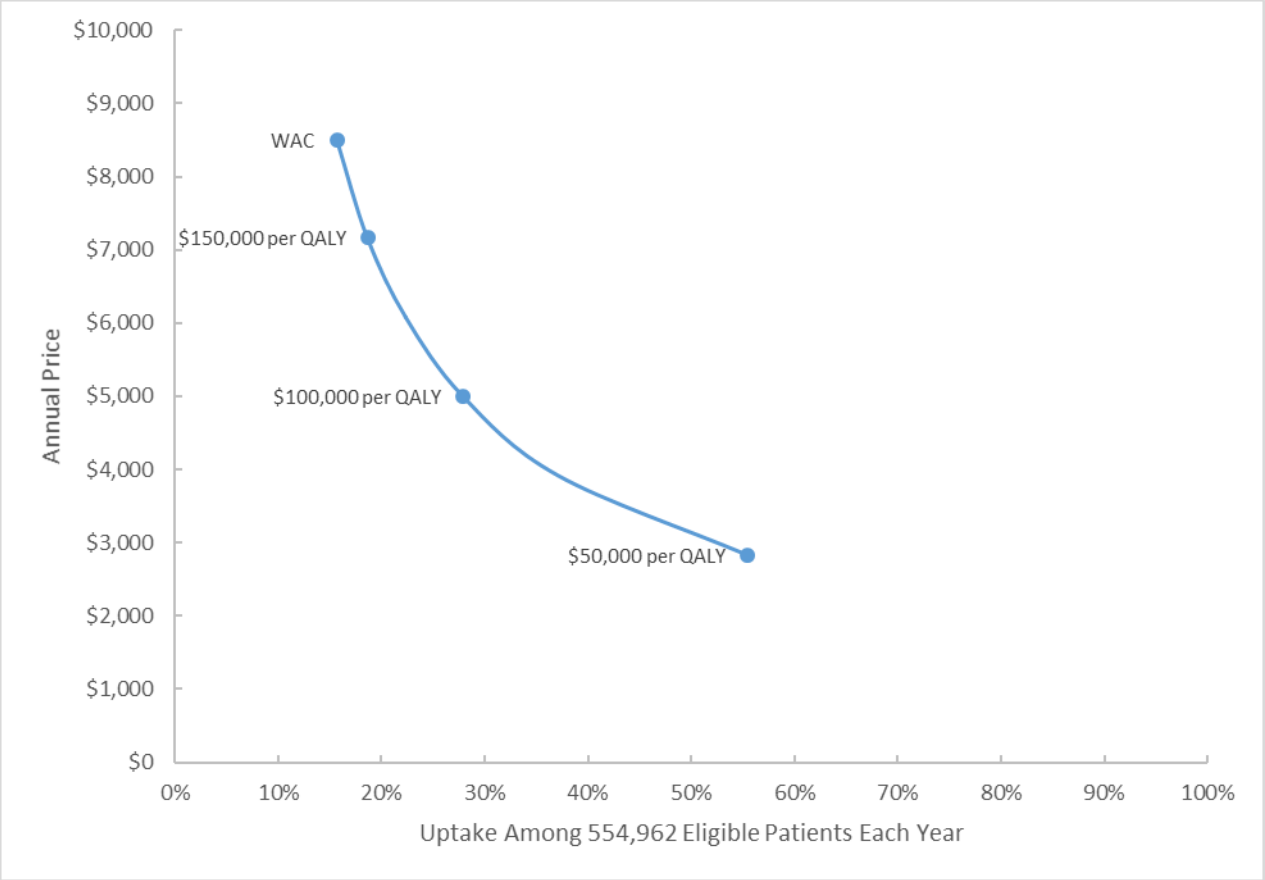
Table 7.2. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Erenumab in Migraine Patients For Whom Other Preventive Therapy Has Failed

	Average Annual Per Patient Budget Impact			
	Placeholder WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$8,142	$7,202	$5,541	$3,880
No Active Preventive Treatment	$2,191			
Difference	$5,951	$5,011	$3,350	$1,690

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 After Previously Failing At Least One Preventive Therapy



The combined annual average potential budget impact per patient for fremanezumab when using the placeholder WAC ($8,500 annually) was approximately $3,600 relative no current preventive

treatment. The per patient annual budget impact ranged from approximately $900 using the price to reach $50,000 per QALY ($2,475) to approximately $2,700 using the price to reach $150,000 per QALY ($6,340) threshold (Table 7.3). The total potential annual budget impact across the entire eligible migraine populations when using erenumab relative to no active preventive treatment ranged from approximately $887 million using the price to reach the $50,000 per QALY threshold ($2,475 annually) to approximately $3.5 billion using the placeholder WAC ($8,500 annually). As shown in Figure 7.2, approximately 27% of the total annual eligible migraine population could be treated with fremanezumab at its placeholder WAC without crossing the ICER annual budget impact threshold of $915 million. Between 35% and 52% of the entire eligible migraine population could be treated annually at the prices to reach the $150,000 per QALY ($6,340 annually) and $100,000 per QALY ($4,407 annually) thresholds. The entire eligible population could be treated at the price to reach the $50,000 per QALY threshold ($2,475 annually), with the total budget impact for the entire population reaching 97% of the ICER annual budget impact threshold.

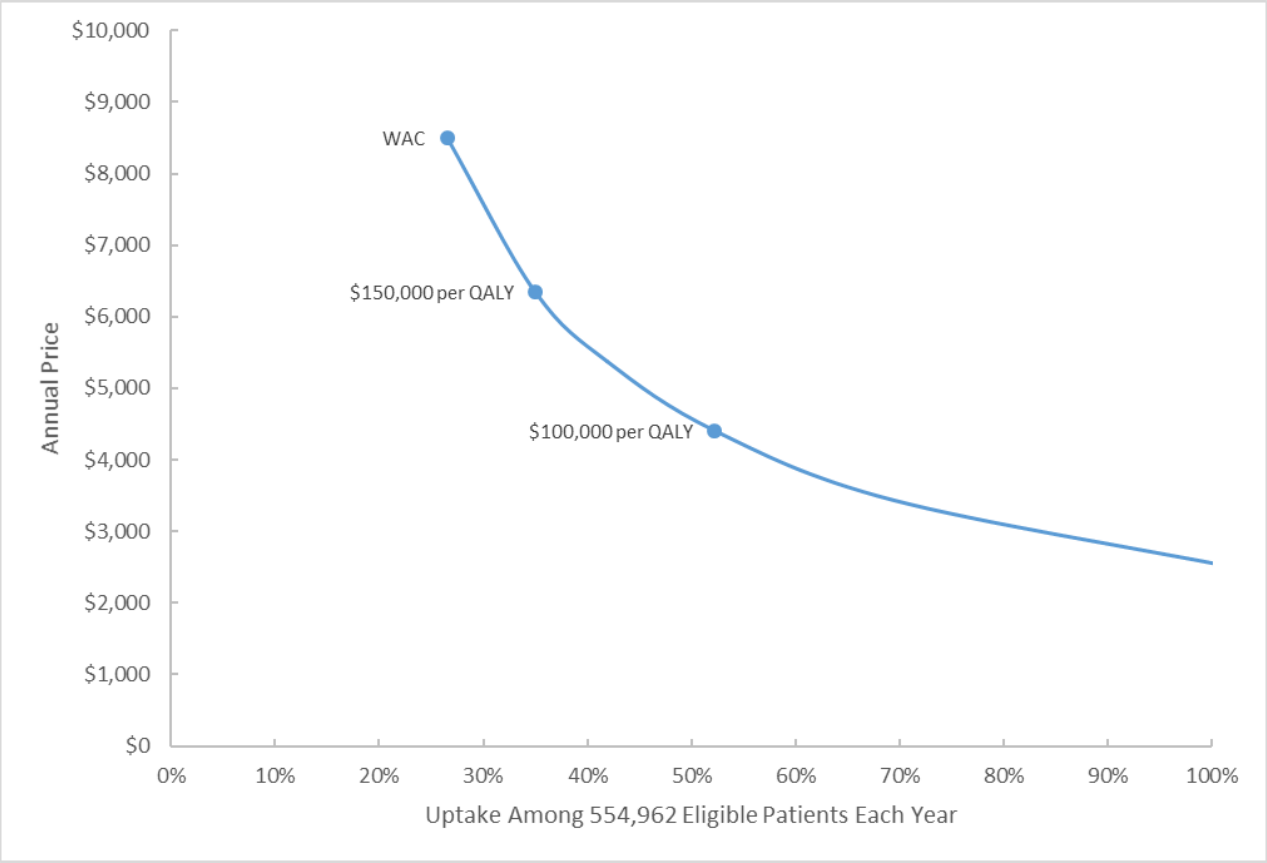
Table 7.3. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Fremanezumab in Migraine Patients For Whom Other Preventive Therapy Has Failed

	Average Annual Per Patient Budget Impact			
	Placeholder WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Fremanezumab	$5,798	$4,291	$4,020	$3,118
No Active Preventive Treatment	$2,191			
Difference	$3,607	$2,730	$1,829	$927

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 After Previously Failing At Least One Preventive Therapy



In summary, the annual budget impact of using erenumab (using the placeholder price) in the eligible migraine population relative to no preventive therapy resulted in an additional $6,000 in costs per patient to the health system. At this price, only 16% of the eligible migraine population could be treated before total costs exceed the ICER potential budget impact threshold. The annual budget impact of using fremanezumab (again using the placeholder price) in the eligible migraine population relative to no preventive therapy resulted in an additional $3,600 in costs per patient to the health system. At this price, only 27% of the eligible migraine population could be treated with fremanezumab before total costs exceed the ICER potential budget impact threshold.

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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, January 9, 2018.

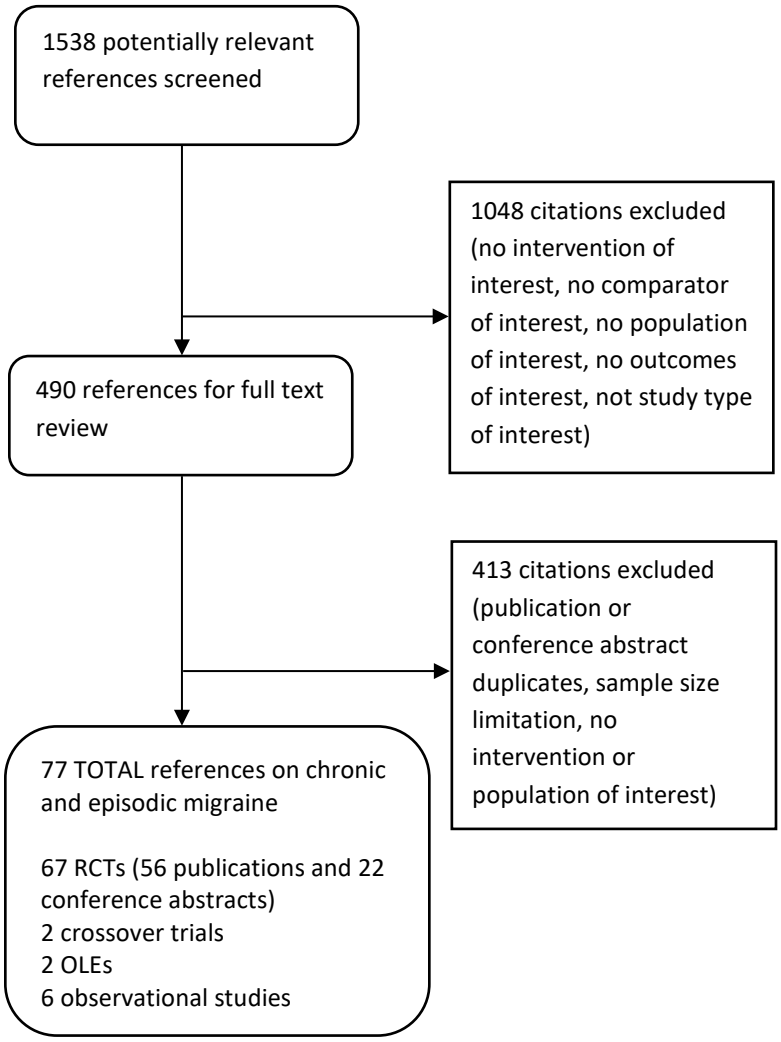
#	Search Terms
1	exp migraine/
2	(migrain* or headache* or cephalgi* or cephalalgi*).ti,ab.
3	(migrain* disorder* or headache disorder*).mp.
4	1 or 2 or 3
5	(AMG-334 or AMG 334 or AMG334 or erenumab).mp.
6	(TEV-48125 or TEV 48125 or TEV48125 or fremanezumab).mp.
7	(LY2951742 or LY 2951742 or galcanezumab).mp.
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, January 9, 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) CGRPs 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 in Chronic Migraine

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 2/3, randomize, parallel assignment, quadruple blinded trial Estimated enrollment: 540	1.Fremanezumab 225 mg subcutaneous injection once monthly after 675 mg loading dose 2. Fremanezumab 675mg subcutaneous injection at month 1 followed by placebo 3. Placebo	Inclusion: 18-70 years Diagnosis of chronic migraine (≥15 headache days per month, at least 8 of which are migraine days) Exclusion: Older than 50 at time of migraine onset Use of migraine-related medicine within 2 months prior to study start Evidence or history of other major disease Known history of HIV, TB, or chronic hepatitis B or C	Primary: Change from baseline in monthly headache days of at least moderate severity during 12-week period Secondary: Change from baseline in monthly acute migraine-specific medication treatment days, monthly headache days of at least moderate severity, and monthly migraine days at week 12 50% reduction in monthly headache days of at least moderate severity at week 12	April 2019

Table C2. Ongoing Trials of CGRP Inhibitors in Episodic Migraine

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Erenumab					
Study of Efficacy and Safety of AMG 334 in Adult Episodic Migraine Patients (EMPOwER), Novartis NCT03333109	Phase 3, randomized, parallel assignment, quadruple-blinded trial Estimated enrollment: 880	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 Diagnosis of 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
A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies (LIBERTY), Novartis NCT03096834	Phase 3, randomized, parallel assignment, double-blinded trial Estimated enrollment: 246	1. Erenumab subcutaneous injection once monthly 2. Placebo	Inclusion: 18-65 years History of migraine for at least 12 months Diagnosis of 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 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Galcanezumab					
Evaluation of LY2951742 in the Prevention of Episodic Migraine (EVOLVE-1), Eli Lilly NCT02614183	Phase 3, randomized, parallel assignment, double-blinded trial Estimated enrollment: 862	1.Galcanezumab 120 mg subcutaneous injection once monthly after 240 mg loading dose 2.Galcanezumab 240 mg subcutaneous injection once monthly 3. Placebo	Inclusion: 18-65 years Diagnosis of episodic migraine (4-14 migraine days per month) History of migraine for at least 12 months Exclusion: Older than 50 at time of migraine onset Exposure to CGRP treatment Hsitory of persistent daily headache, cluster headache, or migraine subtypes	Primary: Change from baseline in monthly migraine days at week 24 Secondary: Change from baseline in monthly acute medication treatment days, MSQ score, MIDAS score, and headache hours at week 24 50%, 75%, and 100% reduction in monthly migraine days at week 24	October 2018
Evaluation of Galcanezumab in the Prevention of Episodic Migraine (EVOLVE-2), Eli Lilly NCT02614196	Phase 3, randomized, parallel assignment, double-blinded trial Estimated enrollment: 922	1.Galcanezumab 120 mg subcutaneous injection once monthly after 240 mg loading dose 2.Galcanezumab 240 mg subcutaneous injection once monthly 3. Placebo	See EVOLVE-1	See EVOLVE-1	April 2019

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

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)[77] 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.*

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

Study/ Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month (SD)	Days of Acute Medication Use per Month (SD)
Tepper, 2017 [83] 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
Bigal, 2015a [41] 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)
	Fremanezumab 900 mg/month	86	41.5 (12.9)	38	18.8 (12.2)	16.4 (5.3)	15.9 (6.5)	16.2 (6.7)
	Placebo	89	40.7 (11.5)	43	20.4 (13.1)	16.8 (5.0)	16.5 (6.3)	15.7 (6.2)
Silberstein, 2017 (HALO-CM)[43] Phase III	Fremanezumab 675 mg/3 months	376	42.0 (12.4)	20	19.7 (12.8)	16.2 (4.9)	13.2 (5.5)	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)	12.8 (5.8)	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)	13.3 (5.8)	13.0 (6.9) headache-specific 10.7 (6.3) migraine-specific

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

Study/Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month (SD)	Days of Acute Medication Use per Month (SD)
Onabotulinum Toxin A								
Aurora, 2010, (PREEMPT 1)[93]	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) [94]	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
Freitag, 2008 [158]	Onabotulinum toxin A 100U	20	42.2 (NR)	NR	NR	NR	NR	NR
	Placebo	21	42.4 (NR)	NR	NR	NR	NR	NR
Cady, 2014 [159]	Onabotulinum toxin A 155U	10	48.5 (12.87)	NR	NR	23.4 (1.9)	NR	NR
	Placebo	10	48.5 (12.87)	NR	NR	24.8 (1.9)	NR	NR
Sandrini, 2011 [160]	Onabotulinum toxin A 100U	27	48.5 (9.2)	0	19.7 (NR)	NR	24.2 (5.0)	22.7 (6.4)
	Placebo	29	49.0 (10.1)	0	20.3 (NR)	NR	25.5 (5.6)	23.6 (6.6)
Topiramate								
Mei, 2006 [87]	Topiramate 100 mg/day	21	45.80 (9.07)	0	5.00 (1.93)	NR	24.38 (3.93)	NR
	Placebo	14	45.93 (8.41)	0	4.95 (2.19)	NR	23.50 (3.70)	NR
Silberstein, 2007 [88]	Topiramate 100 mg/day	153	37.8 (12.38)	0	9.3 (10.5)	17.1 (5.4)	20.4 (4.8)	11.9 (7.0)
	Placebo	153	38.6 (11.80)	0	9.1 (10.6)	17.0 (5.0)	20.8 (4.6)	11.4 (6.6)
Diener, 2007 [95]	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

Study/Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month (SD)	Days of Acute Medication Use per Month (SD)
Silvestrini, 2003 [92]	Topiramate 50 mg/day	14	43 (NR)	0	3 (NR)	NR	20 (NR)	NR
	Placebo	14	44 (NR)	0	3 (NR)	NR	20 (NR)	NR
Head-to-Head Trials								
Cady, 2011[84]	Onabotulinum toxin A 200 U	29	NR	NR	NR	11.9 (NR)	21.8 (NR)	13.9 (NR)
	Topiramate 200 mg/day	30	NR	NR	NR	10.3 (NR)	20.5 (NR)	15.1 (NR)
	Total	59	39.6	NR	Median 16	11.1 (NR)	21.1 (NR)	14.5 (NR)
Magalhaes, 2010 [86]	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 [161]	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
	Total	60	36.8 (10.3)	0	NR	NR	NR	NR
Silberstein, 2012 [162]	Topiramate 100 mg/day	95	Median 42 [18-67]	0	NR	NR	NR	NR
	Topiramate + propranolol 240 mg/day	96	Median 39 [18-62]	100	NR	NR	NR	NR

NR: not reported, SD: standard deviation

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

Study/ Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month (SD)	Days of Acute Medication Use per Month (SD)
Sun 2016 [38] 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) [37] 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) [100] 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
Bigal 2015b [40] 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); 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); 6.9 (3.5) triptans
	Placebo	104	42 (11.6)	27	21.1 (14.1)	11.5 (2.24)	12.4 (2.3)	10.4 (3.6); 8.5 (3.4) triptans

Study/ Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month (SD)	Days of Acute Medication Use per Month (SD)
Aycardi 2017 [129] (HALO-EM) Phase III	Fremanezumab 675 mg/3 months	NR	NR	NR	NR	8.9	NR	NR
	Fremanezumab 225 mg/month	NR	NR	NR	NR	9.2	NR	NR
	Placebo	NR	NR	NR	NR	9.1	NR	NR
Dodick 2014 [42] Phase II	Galcanezumab 150 mg/2 weeks	107	40.9 (11.4)	0	NR	6.7 (2.4)	8.1 (2.9)	NR
	Placebo	110	41.9 (11.7)	0	NR	7.0 (2.5)	8.8 (2.9)	NR
Skljarevski 2018 [101] Phase II	Galcanezumab (5, 50, 120, 300 mg)	273	40.6 (11.9)	0	NR	6.7 (2.6)	NR	NR
	Placebo	137	39.5 (12.1)	0	NR	6.6 (2.7)	NR	NR

NR: not reported, SD: standard deviation

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

Study/Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month	Days of Acute Medication Use per Month (SD)
Amitriptyline								
Couch 1979 [102]	Amitriptyline 100 mg/day	47	NR	NR	NR	NR	NR	NR
	Placebo	53	NR	NR	NR	NR	NR	NR
Couch 2011 [103]	Amitriptyline 100 mg/day	194	34.1 (NR)	0	NR	NR	NR	NR
	Placebo	197	35.7 (NR)	0	NR	NR	NR	NR
Goncalves 2016 [104] Phase III	Amitriptyline 25 mg/day	66	37.2 (11.2)	0	24.1 (9.1)	NR	7.2 (2.5)	NR
	Placebo	65	36.6 (13.7)	0	20.2 (10.6)	NR	7.3 (3.1)	NR
Propranolol								
Diener 1996 [105]	Propranolol 120 mg/day	78	40 (13)	NR	21 (13)	NR	NR	NR
	Placebo	55	39 (11)	NR	19 (11)	NR	NR	NR
Jafarpour 2016 [106]	Propranolol 60 mg/day	26	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 [107]	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 [108]	Total	161	30 (NR)	0	20 (NR)	NR	NR	NR
Weber 1972 [109]	Total	25	40.6 (NR)	NR	NR	NR	NR	NR
Topiramate								
Gode 2010 [110]	Topiramate 50 mg/day	15	37.1	0	NR	NR	NR	NR
	Topiramate 100 mg/day	15	40	0	NR	NR	NR	NR
Lo 2010 [111]	Topiramate 25 mg/day	10	NR	NR	NR	NR	10.2 (5.1)	NR
	Topiramate 50 mg/day	10	NR	NR	NR	NR	6.9 (2.6)	NR
	Topiramate 75 mg/day	10	NR	NR	NR	NR	8.8 (4.4)	NR
	Topiramate 100 mg/day	10	NR	NR	NR	NR	8.0 (2.5)	NR
	Total	40	38	NR	NR	NR	NR	NR
Mei 2004 [112]	Topiramate 100 mg/day	35	39.74 (12.02)	NR	NR	NR	NR	6.17 (1.8)
	Placebo	37	38.7 (11.04)	NR	NR	NR	NR	6.49 (1.29)

Study/Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month	Days of Acute Medication Use per Month (SD)
Lipton 2011 [113]	Topiramate 100 mg/day	159	39.6 (10.6)	0	NR	11.6 (2.0)	13.0 (2.5)	8.6 (3.2) headache-specific
	Placebo	171	40.9 (11.2)	0	NR	11.8 (2.2)	13.1 (2.6)	8.6 (3.5) headache-specific
Brandes 2004[114] Phase III	Topiramate 50 mg/day	117	39 (12.09)	0	NR	6.4 (2.88)	NR	5.7 (2.72)
	Topiramate 100 mg/day	120	39.1 (12.58)	0	NR	6.9 (3)	NR	6.2 (2.13)
	Topiramate 200 mg/day	117	39.1 (12.71)	0	NR	6.1 (2.54)	NR	5.8 (2.52)
	Placebo	114	38.3 (11.96)	0	NR	6.7 (2.84)	NR	5.8 (2.67)
Silberstein 2004 [115] Phase III	Topiramate 50 mg/day	117	40.2 (11.5)	0	NR	6.4 (2.7)	NR	5.8 (2.5)
	Topiramate 100 mg/day	125	40.6 (11.0)	0	NR	6.4 (2.7)	NR	5.9 (2.5)
	Topiramate 200 mg/day	112	40.5 (11.4)	0	NR	6.6 (3.1)	NR	6.1 (2.6)
	Placebo	115	40.4 (11.5)	0	NR	6.4 (2.6)	NR	6.1 (3.0)
Silberstein 2006 [117]	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 [116]	Topiramate 200 mg/day	19	38.3	63	NR	NR	NR	NR
	Placebo	21	38.1	43	NR	NR	NR	NR
Head-to-Head Trials								
Ashtari 2008 [120]	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 [123]	Topiramate 100 mg/day	172	39.7 (10.7)	0	NR	NR	8.7 (3.1)	6.5 (3.0)
	Amitriptyline 100 mg/day	159	37.9 (11.3)	0	NR	NR	8.4 (2.9)	6.1 (3.1)
Dogan 2015 [124]	Propranolol 80 mg/day	24	32.0 (11.8)	0	NR	NR	NR	NR
	Topiramate 50 mg/day	25	34.2 (8.7)	0	NR	NR	NR	NR

Study/Phase	Arm	N	Age (SD)	% Add-On Preventive Therapy	Mean Years Since Onset (SD)	Migraine Days per Month (SD)	Headache Days per Month	Days of Acute Medication Use per Month (SD)
Diener 2004 [121]	Propranolol 160 mg/day	139	40.6 (11.13)	0	NR	6.1 (2.70)	NR	5.4 (2.54)
	Topiramate 100 mg/day	143	39.8 (10.88)	0	NR	5.8 (2.21)	NR	5.0 (2.21)
	Topiramate 200 mg/day	143	42.6 (11.29)	0	NR	6.2 (2.76)	NR	5.5 (2.62)
	Placebo	143	40.4 (10.11)	0	NR	6.1 (2.60)	NR	5.3 (2.52)
Duman 2015 [122]	Total	147	34.2 (9.3)	0	NR	NR	NR	NR
Keskinbora 2008 [125]	Topiramate 200 mg/day	20	35.25 (9.39)	0	NR	NR	6.3 (3.25)	NR
	Amitriptyline 150 mg/day	22	37.86 (8.67)	0	NR	NR	6.09 (2.56)	NR
	Topiramate+amitriptyline	21	39.14 (9.13)	0	NR	NR	6.05 (2.75)	NR
Mathew 1981 [126]	Propranolol 160 mg/day	44	35	NR	NR	NR	NR	NR
	Amitriptyline 75 mg/day	42	36	NR	NR	NR	NR	NR
	Amitriptyline+propranolol	41	31	NR	NR	NR	NR	NR
	Placebo	45	32	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[83]	Multicenter	North America, Europe	Industry	4	12	24	≥15 headache days per month, of which ≥8 of those days were migraine day	Previously failed >3 preventive medications	Not allowed
Fremanezumab									
Bigal, 2015a[41]	Multicenter	US	Industry	4	12	12	ICHD	Previously failed >2 preventive medication categories or >3 preventive medications	Allowed
Silberstein, 2017 (HALO-CM)[43]	Multicenter	Global	Industry	4	12	12	ICHD	Previously failed ≥2 preventive medication categories	Allowed
Galcanezumab									
Detke, 2017[163]	Multicenter	Global	Industry	NR	12	NR	ICHD		NR
Onabotulinum toxin A									
Aurora, 2010 (PREEMPT 1) [93]	Multicenter	North America	Industry	4	24	56	ICHD		Not allowed
Diener, 2010 (PREEMPT 2)[94]	Multicenter	North America, Europe	Industry	4	24	56	ICHD		Not allowed
Freitag, 2008[158]	Multicenter	US	Industry	4	16	16	ICHD		Allowed
Cady, 2014[159]	Multicenter	US	Industry		16	28	ICHD		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
Sandrini, 2011[160]	Multicenter	Italy	Industry	4	12	24	ICHD		Not allowed
Topiramate									
Mei, 2006[87]	Unclear	Italy	NR	4	12	12	ICHD		Not allowed
Silberstein, 2007[88]	Multicenter	US	Industry	4	16	18	≥15 headache days per month, of which ≥8 of those days were migraine day	Previously failed >2 preventive medications	Not allowed
Diener, 2007[95]	Multicenter	Europe	Industry	4	16	23	ICHD		Allowed
Silvestrini, 2003[92]	Single center	Italy	NR	8	9	9	NS	Previously failed <4 preventive medications	Not allowed
Head-to-head									
Cady, 2011[84]	Multicenter	US	Industry	4	12	12	ICHD		NR
Magalhães, 2010[86]	Single center	Brazil	Government/non-profit	4	12	12	ICHD		Not allowed
Mathew, 2009[161]	Single center	US	Industry	4	36	42	ICHD		Not allowed
Silberstein, 2012[162]	Multicenter	US	Industry	4	24	24	ICHD		Not allowed

US: United States; ICHD: International Classification of Headache Disorders; NR: not reported; NS: not specified

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[38]	Multicenter	North America, Europe	Industry	4	12	280	ICHD	Previously failed >2 preventive medications	Not allowed
Goadsby, 2017 (STRIVE) [37]	Multicenter	North America, Europe	Industry	4	24	64	ICHD	Previously failed >2 preventive medications	Allowed
Dodick, 2018 (ARISE)[100]	Multicenter	North America, Europe	Industry	4	12	40	ICHD	Previously failed >2 preventive medication categories	Allowed
Fremanezumab									
Bigal, 2015b[40]	Multicenter	US	Industry	4	12	12	ICHD	Previously failed >2 preventive medication categories or >3 preventive medications	Allowed
Aycardi, 2017 (HALO-EM)[127]	Multicenter	Global	Industry	4	12	12	NR		NR

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[42]	Multicenter	US	Industry	4	12	24	ICHD	Previously failed >2 preventive medications	Not allowed
Skljarevski, 2018[101]	Multicenter	US	Industry	4-5	12	12	4-14 MHD per month	Previously failed >2 preventive medications	Not allowed
Skljarevski, 2017 (EVOLVE-1)[164]	Multicenter	North America	Industry	NR	24	24	ICHD		NR
Skljarevski, 2017 (EVOLVE-2)[164]	Multicenter	Global	Industry	NR	24	24	ICHD		NR
Amitriptyline									
Couch, 1979[102]	Single center	US	NR	4	4	8	≥2 disabling or severe migraines in prior month		NR
Couch, 2011[103]	Multicenter	US	Industry	4	16	20	≥2 moderate or severe MHD per month		Not allowed
Gonçalves, 2016[104]	Multicenter	Brazil	Government/non-profit	4	12	12	ICHD		Not allowed
Propranolol									
Diener, 1996[105]	Multicenter	NR	NR	4	14	16	ICHD		Not allowed
Jafarpour, 2016[106]	Single center	Iran	NR	NR	4	4	ICHD		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
Pradalier, 1989[107]	Multicenter	NR	NR	4	12	12	ICHD	Previously failed ≥2 preventive medications	Not allowed
Sargent, 1985[108]	Multicenter	NR	NR	NA	14	17	Average of 12 migraine days per six migraine attacks		Not allowed
Weber, 1972[109]	Unclear	US	NR	NR	12	24	NIH Ad Hoc Committee on Classification of Headache, 1962		Not allowed
Head-to-head									
Gode, 2010[110]	Single center	Turkey	NR	4	24	24	ICHD		Not allowed
Lo, 2010[111]	Single center	Singapore	NR	4	12	12	ICHD		Not allowed
Mei, 2004[112]	Single center	Italy	NR	4	16	16	ICHD		Not allowed
Lipton, 2011[113]	Multicenter	US	Industry	4	26	26	ICHD	Previously failed >2 preventive medications	Not allowed
Brandes, 2004[114]	Multicenter	US	Industry	4	26	33	ICHD	Previously failed >2 preventive medications	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
Silberstein, 2004[115]	Multicenter	US	Industry	4	26	26	ICHD	Previously failed >2 preventive medications	Not allowed
Silberstein, 2006[117]	Multicenter	US	Industry	4	20	20	ICHD	Previously failed >2 preventive medications	Not allowed
Storey, 2001[116]	Single center	US	Industry	4	16	16	ICHD		Allowed
Ashtari, 2008[120]	Single center	Iran	NR	NR	8	8	ICHD		Not allowed
Dodick, 2009[123]	Multicenter	US	Industry	4	26	26	ICHD	Previously failed >2 preventive medications	Not allowed
Dogan, 2015[124]	Single center	Turkey	NR	NR	4	4	ICHD		Not allowed
Duman, 2015[122]	Single center	Turkey	NR	4	12	12	ICHD		Not allowed
Keskinbora, 2008[125]	Single center	Turkey	NR	NR	12	12	ICHD		Not allowed
Mathew, 1981[126]	Unclear	US	NR	4	24	24	NS		NR
Diener, 2004[121]	Multicenter	Global	Industry	4	26	52	ICHD	Previously failed >2 preventive medications	Not allowed

US: United States; ICHD: International Classification of Headache Disorders; NR: not reported; NS: not specified

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[83]	Yes	Yes	Yes	Yes	Yes	No	Good
Bigal, 2015a[41]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Silberstein, 2017 (HALO-CM)[43]	Yes	Yes	Yes	Yes	Yes	NR	Good
Onabotulinum Toxin A							
Aurora, 2010 (PREEMPT 1)[93]	Yes	Yes	Yes	Yes	Yes	mLOCF	Good
Diener, 2010 (PREEMPT 2)[94]	Yes	Yes	Yes	Yes	Yes	mLOCF	Good
Sandrini, 2011[160]	Yes	Yes	Yes	Yes	Yes	NR	Good
Freitag, 2008[158]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Cady, 2014[159]	NR	Yes	Yes	Yes	Yes	NR	Fair
Topiramate							
Mei, 2006[87]	Yes	Yes	Yes	Yes	Yes	NR	Good
Dodick, 2007[89]	Yes	Yes	Yes	Yes	Yes	NR	Good
Diener, 2007[95]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Silvestrini, 2003[92]	Yes	Yes	Yes	Yes	Yes	NR	Good
Head-to Head							
Cady, 2011[84]	NR	Yes	Yes	Yes	Yes	NR	Fair
Magalhães, 2010[86]	Yes	NR	NR	Yes	Yes	NR	Fair
Mathew, 2009[161]	NR	Yes	Yes	Yes	Yes	NR	Fair
Silberstein, 2012[162]	Yes	Yes	Yes	Yes	Yes	No	Good

LOCF: last observation carried forward (single imputation), mLOCF: modified last observation carried forward (single imputation), MI: multiple imputation, non-responders: non-responders imputation, NR: not reported; 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[38]	Yes	Yes	Yes	Yes	Yes	No	Good
Goadsby, 2017 (STRIVE)[37]	Yes	Yes	Yes	Yes	Yes	No	Good
Dodick, 2018 (ARISE)[100]	Yes	Yes	Yes	Yes	Yes	No	Good
Bigal, 2015b[40]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Dodick, 2014[42]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Skljarevski, 2018[101]	Yes	Yes	Yes	Yes	Yes	Continuous: LOCF Categorical: Non-Responders	Good
Topiramate							
Gode, 2010[110]	NR	Yes	No	Yes	Yes	NR	Fair
Lo, 2010[111]	Yes	Yes	NR	Yes	No	NR	Fair
Mei, 2004[112]	Yes	Yes	Yes	Yes	Yes	NR	Good
Lipton, 2011[113]	Yes	Yes	Yes	Yes	Yes	NR	Good
Brandes, 2004[114]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Silberstein, 2004[115]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Silberstein, 2006[117]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Propranolol							
Storey, 2001[116]	Yes	Yes	Yes	Yes	Yes	NR	Good
Weber, 1972[109]	NR	Yes	Yes	Yes	Yes	NR	Fair
Jafarpour, 2016[106]	Yes	Yes	Yes	Yes	Yes	NR	Good
Sargent, 1985[108]	Yes	NR	Yes	Yes	Yes	NR	Fair
Pradalier, 1989[107]	Yes	Yes	Yes	Yes	No	NR	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
Diener, 1996[105]	Yes	Yes	Yes	Yes	Yes	Continuous: LOCF	Good
Goncalves, 2016[104]	Yes	NR	Yes	Yes	Yes	Single Imputation	Fair
Couch, 1979[102]	Yes	No	Yes	Yes	No	NR	Poor
Couch, 2011[103]	Yes	Yes	Yes	Yes	Yes	NR	Good
Head-to-Head							
Ashtari, 2008[120]	Yes	Yes	Yes	Yes	Yes	NR	Good
Dodick, 2009[123]	Yes	Yes	Yes	Yes	Yes	LOCF	Good
Dogan, 2015[124]	Yes	Yes	Yes	Yes	Yes	NR	Good
Duman, 2015[122]	Yes	NR	Yes	No	Yes	NR	Fair
Keskinbora, 2008[125]	Yes	Yes	Yes	Yes	Yes	NR	Good
Diener, 2004[121]	Yes	Yes	Yes	Yes	Yes	NR	Good

LOCF: last observation carried forward (single imputation), MI: multiple imputation, non-responders: non-responders imputation, NR: not reported

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

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
Tepper, 2017[83]	4	Erenumab 70 mg/month	-5.03 (SE: 0.42)	-3.1 (SE: 0.3)	45/188 (24%)
		Erenumab 140 mg/month	-5.1 (SE: 0.42)	-3.5 (SE: 0.3)	53/187 (28%)
		Placebo	-2.67 (SE: 0.34)	-1.3 (SE: 0.2)	32/281 (11%)
	8	Erenumab 70 mg/month	-6.21 (SE: 0.42)	-3.4 (SE: 0.3)	73/188 (39%)
		Erenumab 140 mg/month	-6.45 (SE: 0.42)	-4.2 (SE: 0.3)	75/187 (40%)
		Placebo	-3.56 (SE: 0.35)	-1.5 (SE: 0.2)	53/281 (19%)
	12	Erenumab 70 mg/month	-6.6 (SE: 0.4)	-3.5 (SE: 0.3)	75/188 (40%)
		Erenumab 140 mg/month	-6.6 (SE: 0.4)	-4.1 (SE: 0.3)	77/187 (41%)
		Placebo	-4.2 (SE: 0.4)	-1.6 (SE: 0.2)	66/281 (23%)
Bigal, 2015a[41]	4	Fremanezumab 675/225 mg/month	-2.07 (95%CI: -3.7, -0.5)*	NR	NR
		Fremanezumab 900 mg/month	-2.99 (95%CI: -4.6, -1.4)*	NR	NR
		Placebo	NR	NR	NR
	8	Fremanezumab 675/225 mg/month	-1.64 (95%CI: -3.4, 0.13)*	NR	NR
		Fremanezumab 900 mg/month	-1.73 (95%CI: -3.49, 0.03)*	NR	NR
		Placebo	NR	NR	NR
	12	Fremanezumab 675/225 mg/month	-1.72 (95%CI: -3.7, 0.2)*	NR	NR
		Fremanezumab 900 mg/month	-2.00 (95%CI: -3.9, -0.1)*	NR	NR
		Placebo	NR	NR	NR
Silberstein, 2017 (HALO-CM)[43]	4	Fremanezumab 675 mg/3 months	-4.80 (SE: 0.32)	NR	NR
		Fremanezumab 675/225 mg/month	-4.73 (SE: 0.27)	NR	NR
		Placebo	-2.67 (SE: 0.33)	NR	NR
	8	Fremanezumab 675 mg/3 months	-4.87 (SE: 0.31)	NR	NR
		Fremanezumab 675/225 mg/month	-5.27 (SE: 0.30)	NR	NR
		Placebo	-3.33 (SE: 0.41)	NR	NR
	12	Fremanezumab 675 mg/3 months	-5.08 (SE: 0.35)	-3.7 (SE: 0.3)†	NR
		Fremanezumab 675/225 mg/month	-5.43 (SE: 0.30)	-4.2 (SE: 0.3)†	NR
		Placebo	-3.80 (SE: 0.4)	-1.9 (SE: 0.3)†	NR

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
Sandrini, 2011[160]	4	Onabotulinum toxin A 100U	NR	-10.7 (SD: 8.02)	NR
		Placebo	NR	-8.3 (SD: 8.88)	NR
	8	Onabotulinum toxin A 100U	NR	-10.6 (SD: 8.39)	NR
		Placebo	NR	-8.5 (SD: 8.96)	NR
	12	Onabotulinum toxin A 100U	NR	-12 (SD: 8.85)	NR
		Placebo	NR	-9.3 (SD: 8.14)	NR
Silberstein, 2009[90]	16	Topiramate 100 mg/day	NR	-4.4 (SD: 5.8)	NR
		Placebo	NR	-3.4 (SD: 5.3)	NR
Diener, 2007[95]	16	Topiramate 100 mg/day	NR	-3.0 (SD: 5.9)	NR
		Placebo	NR	-0.7 (SD: 6.2)	NR
Detke, 2017[163]	12	Placebo	-2.74 (NR)	NR	NR
		Galcanezumab 120 mg/month	-4.83 (NR)	NR	NR
		Galcanezumab 240 mg/month	-4.62 (NR)	NR	NR
Aurora, 2010 (PREEMPT 1)[93]	4	Onabotulinum toxin A 155U	-6.7 (SD: 5.64)	NR	NR
		Placebo	-4 (SD: 5.4)	NR	NR
	8	Onabotulinum toxin A 155U	-7 (SD: 6.24)	NR	NR
		Placebo	-5.6 (SD: 5.6)	NR	NR
	12	Onabotulinum toxin A 155U	-7 (SD: 6.24)	NR	NR
		Placebo	-5.9 (SD: 6.05)	NR	NR
	16	Onabotulinum toxin A 155U	-7 (SD: 6.34)	NR	NR
		Placebo	-5.9 (SD: 6.09)	NR	NR
	20	Onabotulinum toxin A 155U	-7.9 (SD: 6.5)	NR	NR
		Placebo	-6.2 (SD: 6.66)	NR	NR
	24	Onabotulinum toxin A 155U	-7.6 (SD: 6.51)	NR	NR
		Placebo	-6.1 (SD: 6.78)	NR	NR

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
Diener, 2010 (PREEMPT 2)[94]	4	Onabotulinum toxin A 155U	-5.8 (SD: 5.97)	NR	NR
		Placebo	-4.3 (SD: 5.46)	NR	NR
	8	Onabotulinum toxin A 155U	-7.4 (SD: 6.33)	NR	NR
		Placebo	-5.2 (SD: 5.73)	NR	NR
	12	Onabotulinum toxin A 155U	-7.3 (SD: 6.2)	NR	NR
		Placebo	-5.6 (SD: 6.1)	NR	NR
	16	Onabotulinum toxin A 155U	-8.1 (SD: 6.61)	NR	NR
		Placebo	-6.5 (SD: 6.21)	NR	NR
	20	Onabotulinum toxin A 155U	-8.8 (SD: 6.71)	NR	NR
		Placebo	-6.6 (SD: 6.2)	NR	NR
	24	Onabotulinum toxin A 155U	-8.7 (SD: 6.64)	NR	NR
		Placebo	-6.3 (SD: 6.71)	NR	NR
Cady, 2014[159]	4	Onabotulinum toxin A 155U	-7.7 (SD: 6.935)	NR	NR
		Placebo	-6.4 (SD: 7.596)	NR	NR
	8	Onabotulinum toxin A 155U	-9.7 (SD: 5.595)	NR	NR
		Placebo	-5.6 (SD: 8.068)	NR	NR
	12	Onabotulinum toxin A 155U	-10.1 (SD: 5.595)	NR	NR
		Placebo	-5.1 (SD: 8.313)	NR	NR
	16	Onabotulinum toxin A 155U	-9.5 (SD: 6.173)	NR	NR
		Placebo	-6.8 (SD: 7.596)	NR	NR
Silberstein, 2007[88]	16	Topiramate 100 mg/day	-6.4 (SD: 5.8)	NR	57/153 (37%)
		Placebo	-4.7 (SD: 6.1)	NR	44/153 (29%)
Diener, 2007[95]	16	Topiramate 100 mg/day	-3.5 (SD: 6.3)	NR	9/32 (29%)
		Placebo	0.2 (SD: 4.7)	NR	0/27 (0%)

MMD: monthly migraine days; CFB: change from baseline; SD: standard deviation; SE: standard error; NR: not reported

*difference versus placebo; † measured over 1-12 weeks

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

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
Sun, 2016[38]	4	Erenumab 7 mg/month	-1.27 (SE: 0.35)	NR	NR
		Erenumab 21 mg/month	-1.56 (SE: 0.38)	NR	NR
		Erenumab 70 mg/month	-2.59 (SE: 0.37)	NR	39/103 (38%)
		Placebo	-1.63 (SE: 0.29)	NR	34/151 (23%)
	8	Erenumab 7 mg/month	-1.33 (SE: 0.35)	NR	NR
		Erenumab 21 mg/month	-2.65 (SE: 0.37)	NR	NR
		Erenumab 70 mg/month	-3.31 (SE: 0.36)	NR	47/103 (46%)
		Placebo	-2.29 (SE: 0.31)	NR	48/144 (33%)
	12	Erenumab 7 mg/month	-2.2 (SE: 0.4)	NR	30/104 (29%)
		Erenumab 21 mg/month	-2.4 (SE: 0.4)	NR	32/93 (34%)
		Erenumab 70 mg/month	-3.4 (SE: 0.4)	-2.5 (SE: 0.3)	46/99 (46%)
		Placebo	-2.3 (SE: 0.3)	-1.4 (SE: 0.3)	43/144 (30%)
Goadsby, 2017 (STRIVE)[37]	4	Erenumab 70 mg/month	-2.32 (95%CI: -2.73, -1.92)	-0.78 (95%CI: -1.03, -0.53)	102/312 (33%)
		Erenumab 140 mg/month	-2.72 (95%CI: -3.12, -2.32)	-1.40 (95%CI: -1.65, -1.15)	113/318 (36%)
		Placebo	-0.90 (95%CI: -1.30, -0.50)	-0.03 (95%CI: -0.28, 0.22)	49/316 (16%)
	8	Erenumab 70 mg/month	-2.93 (95%CI: -3.34, -2.52)	-1.1 (95%CI: -1.35, -0.85)	124/312 (40%)
		Erenumab 140 mg/month	-3.10 (95%CI: -3.50, -2.70)	-1.56 (95%CI: -1.81, -1.31)	143/318 (45%)
		Placebo	-1.39 (95%CI: -1.80, -0.99)	-0.34 (95%CI: -0.59, -0.09)	77/316 (24%)
	12	Erenumab 70 mg/month	-2.97 (95%CI: -3.38, -2.56)	-1.12 (95%CI: -1.37, -0.87)	129/312 (41%)
		Erenumab 140 mg/month	-3.50 (95%CI: -3.91, -3.10)	-1.56 (95%CI: -1.81, -1.31)	153/318 (48%)
		Placebo	-1.71 (95%CI: -2.12, -1.30)	-0.33 (95%CI: -0.58, -0.08)	83/316 (26%)
	16	Erenumab 70 mg/month	-3.09 (95%CI: -3.50, -2.67)	-1.08 (95%CI: -1.33, -0.82)	128/312 (41%)
		Erenumab 140 mg/month	-3.52 (95%CI: -3.93, -3.11)	-1.56 (95%CI: -1.81, -1.31)	158/318 (50%)
		Placebo	-1.94 (95%CI: -2.35, -1.52)	-0.19 (95%CI: -0.45, -0.06)	91/316 (29%)
	20	Erenumab 70 mg/month	-3.34 (95%CI: -3.75, -2.93)	-1.17 (95%CI: -1.43, -0.92)	147/312 (47%)
		Erenumab 140 mg/month	-3.74 (95%CI: -4.15, -3.33)	-1.61 (95%CI: -1.87, -1.36)	153/318 (48%)
		Placebo	-1.88 (95%CI: -2.29, -1.46)	-0.4 (95%CI: -0.66, -0.14)	92/316 (29%)

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
	24	Erenumab 70 mg/month	-3.26 (95%CI: -3.67, -2.84)	-1.14 (95%CI: -1.40, -0.89)	147/312 (47%)
		Erenumab 140 mg/month	-3.76 (95%CI: -4.17, -3.35)	-1.67 (95%CI: -1.92, -1.41)	156/318 (49%)
		Placebo	-1.67 (95%CI: -2.08, -1.25)	0.01 (95%CI: -0.25, 0.26)	93/316 (29%)
Dodick, 2018 (ARISE)[100]	4	Erenumab 70 mg/month	-1.99 (95%CI: -2.41, -1.59)	-0.890 (95%CI: -1.15, -0.626)	76/282 (27.0%)
		Placebo	-0.959 (95%CI: -1.37, -0.567)	-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)	-1.07 (95%CI: -1.34, -0.809)	101/282 (35.8%)
		Placebo	-1.8 (95%CI: -2.19, -1.40)	-0.502 (95%CI: -0.766, -0.243)	77/288 (26.7%)
	12	Erenumab 70 mg/month	-2.9 (SE: 0.2)	-1.2 (SE: 0.1)	112/282 (39.7%)
		Placebo	-1.8 (SE: 0.2)	-0.6 (SE: 0.1)	85/288 (29.5%)
Bigal, 2015b[40]	4	Fremanezumab 225 mg/month	-4.27 (SD: 5.23)	NR	42/95 (44%)
		Fremanezumab 675 mg/month	-4.57 (SD: 5.11)	NR	50/96 (52%)
		Placebo	-2.14 (SD: 5.33)	NR	20/104 (19%)
	8	Fremanezumab 225 mg/month	-5.38 (SD: 5.45)	NR	52/95 (55%)
		Fremanezumab 675 mg/month	-5.55 (SD: 5.32)	NR	53/96 (55%)
		Placebo	-2.89 (SD: 5.50)	NR	36/104 (35%)
	12	Fremanezumab 225 mg/month	-6.27 (SD: 5.38)	-4.86 (SD: 4.64)	53/95 (56%)
		Fremanezumab 675 mg/month	-6.09 (SD: 5.22)	-4.80 (SD: 4.50)	55/96 (57%)
		Placebo	-3.46 (SD: 5.40)	-3.10 (SD: 4.64)	36/104 (35%)
Dodick, 2014[42]	4	Galcanezumab 150 mg/2 weeks	-4.3 (90%CI: -4.97, -3.97)	NR	NR
		Placebo	-2.5 (90%CI: -3.0, -1.98)	NR	NR
	8	Galcanezumab 150 mg/2 weeks	-4.7 (90%CI:-5.29, -3.98)	NR	NR
		Placebo	-3.5 (90%CI:-4.18, -2.88)	NR	NR
	12	Galcanezumab 150 mg/2 weeks	-4.8 (SD: 4.1)	NR	69/98 (70%)
		Placebo	-3.5 (SD: 4.2)	NR	47/104 (45%)
Aycardi, 2017[127]	12	Fremanezumab 225 mg/month	-3.7 (NR)*	-3.0 (NR)*	179/375 (47.7%)*
		Fremanezumab 675 mg/3 months	-3.4 (NR)*	-2.9 (NR)*	167/375 (44.4%)*
		Placebo	-2.2 (NR)*	-1.6 (NR)*	104/371 (27.9%)*

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
Skljarevski, 2018[101]	4	Galcanezumab 5 mg/month	-3.8 (SE: 0.32)	NR	NR
		Galcanezumab 50 mg/month	-4.0 (SE: 0.32)	NR	NR
		Galcanezumab 120 mg/month	-3.76 (SE: 0.35)	NR	NR
		Galcanezumab 300 mg/month	-4.2 (SE: 0.35)	NR	NR
		Placebo	-3.0 (SE: 0.24)	NR	NR
	8	Galcanezumab 5 mg/month	-3.84 (SE: 0.37)	NR	NR
		Galcanezumab 50 mg/month	-4.16 (SE: 0.34)	NR	NR
		Galcanezumab 120 mg/month	-4.19 (SE: 0.41)	NR	NR
		Galcanezumab 300 mg/month	-4.5 (SE: 0.33)	NR	NR
		Placebo	-3.6 (SE: 0.29)	NR	NR
	12	Galcanezumab 5 mg/month	-4.30 (SE: 0.44)	NR	NR
		Galcanezumab 50 mg/month	-3.85 (SE: 0.43)	NR	NR
		Galcanezumab 120 mg/month	-4.3 (SE: 0.21)	NR	47/62 (75.8%)
		Galcanezumab 300 mg/month	-4.3 (SE: 0.52)	NR	NR
		Placebo	-3.4 (SE: 0.14)	NR	78/126 (61.9%)
Skljarevski, 2017 (EVOVLE-1)[164]	26	Galcanezumab 120 mg/month	-4.73 (NR)	NR	NR
		Galcanezumab 240 mg/month	-4.57 (NR)	NR	NR
		Placebo	-2.81 (NR)	NR	NR
Skljarevski, 2017 (EVOVLE-2)[164]	26	Galcanezumab 120 mg/month	-4.29 (NR)	NR	NR
		Galcanezumab 240 mg/month	-4.18 (NR)	NR	NR
		Placebo	-2.28 (NR)	NR	NR
Gonçalves, 2016[104]	4	Amitriptyline 25 mg/day	-1.4 (SD: 2.33)	NR	NR
		Placebo	-0.3 (SD: 3.01)	NR	NR
	8	Amitriptyline 25 mg/day	-1.9 (SD: 2.45)	NR	NR
		Placebo	-0.7 (SD: 2.88)	NR	NR
	12	Amitriptyline 25 mg/day	-2.2 (SD: 2.5)	NR	23/59 (39.1%)
		Placebo	-1.1 (SD: 2.85)	NR	12/59 (20.4%)

Study	Week	Arm	MMD, CFB	Acute medication (days), CFB	≥50% responders
Diener, 1996[105]	12	Propranolol 120 mg/day	NR	NR	33/78 (42%)
		Placebo	NR	NR	17/55 (31%)
Mei, 2004[112]	16	Topiramate 100 mg/day	NR	NR	22/35 (63%)
		Placebo	NR	NR	8/37 (21%)
Lipton, 2011[113]	26	Topiramate 100 mg/day	-6.6 (SD: 3.5)	-4.8 (SD: 3.5)	105/159 (65.8%)
		Placebo	-5.3 (SD: 3.6)	-3.8 (SD: 3.7)	83/171 (48.5%)
Brandes, 2004[114]	26	Topiramate 50 mg/day	-1.7 (NR)	NR	45/116 (39%)
		Topiramate 100 mg/day	-2.6 (SE: 0.31)	-2.1 (SE: 0.29)	59/120 (49%)
		Topiramate 200 mg/day	-2.9 (SE: 0.32)	-2.2 (SE: 0.29)	55/117 (47%)
		Placebo	-1.3 (SE: 0.32)	-1.0 (SE: 0.29)	26/114 (23%)
Silberstein, 2004[115]	26	Topiramate 50 mg/day	-1.6 (SD: 3.534)	-1.3 (SD: 2.85)	42/117 (35.9%)
		Topiramate 100 mg/day	-2.7 (SD: 3.045)	-1.9 (SD: 3.05)	68/125 (54.0%)
		Topiramate 200 mg/day	-2.7 (SD: 3.26)	-2.1 (SD: 2.71)	59/112 (52.3%)
		Placebo	-1.1 (SD: 3.219)	-0.9 (SD: 3.16)	26/115 (22.6%)
Silberstein, 2006[117]	20	Topiramate 200 mg/day	NR	NR	55/138 (39.9%)
		Placebo	NR	NR	25/73 (34.2%)
Storey, 2001[116]	16	Topiramate 200 mg/day	NR	NR	5/19 (26.3%)
		Placebo	NR	NR	2/21 (9.5%)
Dodick, 2009[123]	26	Topiramate 100 mg/day	-3.2 (NR)	-2.6 (NR)	96/172 (55.6%)
		Amitriptyline 100 mg/day	-3.1 (NR)	-2.8 (NR)	73/159 (45.9%)
Diener, 2004[121]	26	Propranolol 160 mg/day	-1.9 (SE: 0.25)	-1.6 (SE: 0.21)	61/143 (43%)
		Topiramate 100 mg/day	-1.8 (SE: 0.25)	-1.5 (SE: 0.21)	51/139 (37%)
		Topiramate 200 mg/day	-1.3 (SE: 0.25)	-0.9 (SE: 0.21)	50/143 (35%)
		Placebo	-1.1 (SE: 0.24)	-0.8 (SE: 0.20)	31/143 (22%)

MMD: monthly migraine days; CFB: change from baseline; NR: not reported; SD: standard deviation; SE: standard error

*measured over 1-12 weeks

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

Study	Arm	Week	MIDAS total, CFB	HIT-6 total, CFB	MSQ-RFR, CFB	MSQ-RFP, CFB	MSQ-EF, CFB
Lipton, 2017[165]	Erenumab 70 mg/month	12	-19.4 (95%CI: -25.2, -13.6)	-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		-19.8 (95%CI: -25.6, -14.0)	-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		-7.5 (95%CI: -12.4, -2.7)	-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)
Dodick, 2007[89]	Topiramate 100 mg/day	4	NR	NR	21.7 (NR)	14 (NR)	25.7 (NR)
	Placebo		NR	NR	12.7 (NR)	10.1 (NR)	15.2 (NR)
	Topiramate 100 mg/day	8	NR	NR	23.6 (NR)	15.7 (NR)	25.9 (NR)
	Placebo		NR	NR	17.4 (NR)	11.8 (NR)	19 (NR)
	Topiramate 100 mg/day	12	NR	NR	23.8 (NR)	16.9 (NR)	26.7 (NR)
	Placebo		NR	NR	19.5 (NR)	13.1 (NR)	20.5 (NR)
	Topiramate 100 mg/day	16	NR	NR	24.3 (NR)	16.9 (NR)	26.9 (NR)
	Placebo		NR	NR	18.5 (NR)	12.5 (NR)	20 (NR)
Silberstein, 2017 (HALO-CM)[43]	Fremanezumab 675 mg/3 months	12	NR	-6.4 (SE: 0.5)	NR	NR	NR
	Fremanezumab 675/225 mg/month		NR	-6.8 (SE: 0.4)	NR	NR	NR
	Placebo		NR	-4.5 (SE: 0.5)	NR	NR	NR
Aurora, 2010 (PREEMPT 1) [93]	Onabotulinum toxin A 155U	24	NR	-4.7 (NR)	NR	NR	NR
	Placebo		NR	-2.4 (NR)	NR	NR	NR
Diener, 2010 (PREEMPT 2)[94]	Onabotulinum toxin A 155U	24	NR	-4.9 (NR)	NR	NR	NR
	Placebo		NR	-2.4 (NR)	NR	NR	NR
Sandrini, 2011[160]	Onabotulinum toxin A 100U	4	22.9 (SE: 10.3)*	50.2 (SE: 5.6)*	NR	NR	NR
	Placebo		42.1 (SE: 6.6)*	60.7 (SE: 2.5)*	NR	NR	NR
	Onabotulinum toxin A 100U	12	13.6 (SE: 10.6)*	49.3 (SE: 5.6)*	NR	NR	NR
	Placebo		36.5 (SE: 6.6)*	58.3 (SE: 2.5)*	NR	NR	NR
Silberstein, 2009[90]	Topiramate 100 mg/day	16	-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)

Study	Arm	Week	MIDAS total, CFB	HIT-6 total, CFB	MSQ-RFR, CFB	MSQ-RFP, CFB	MSQ-EF, CFB
Diener, 2007[95]	Topiramate 100 mg/day	16	-26 (SD: 61)	NR	NR	NR	NR
	Placebo		3 (SD: 21)	NR	NR	NR	NR
Cady, 2011[84]	Onabotulinum toxin A 200 U	4	NR	-4.84 (NR)	NR	NR	NR
	Topiramate 200 mg/day		NR	-5.87 (NR)	NR	NR	NR
	Onabotulinum toxin A 200 U	12	-38.48 (NR)	-6.29 (NR)	NR	NR	NR
	Topiramate 200 mg/day		-26.67 (NR)	-6.00 (NR)	NR	NR	NR
Mathew, 2009[161]	Onabotulinum toxin A 200 U	12	-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
	Onabotulinum toxin A 200 U	24	-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
	Onabotulinum toxin A 200 U	36	NR	-3.47 (SD: 5.23)	NR	NR	NR
	Topiramate 100 mg/day		NR	-8.76 (SD: 7.44)	NR	NR	NR
Silberstein, 2012[162]	Topiramate 100 mg/day + propranolol 240 mg/day	12	-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)
	Topiramate 100 mg/day + propranolol 240 mg/day	24	-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)

CFB: change from baseline; MIDAS: Migraine Disability Assessment; MSQ: Migraine-Specific Quality of Life Questionnaire; RFR: role function restrictive; RFP: rolefunction preventive; EF: emotional function; HIT-6: Headache Impact Test; mg: milligram; NR: not reported; SD: standard deviation; SE: standard error; CI: credible interval
*mean score, not change from baseline

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

Study	Arm		MIDAS total, CFB	HIT-6 total, CFB	MSQ-RFR, CFB	MSQ-RFP, CFB	MSQ-EF, CFB
Buse, 2017 (STRIVE) [166]	Erenumab 70 mg/month	4	-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)
	Erenumab 70 mg/month	8	-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)
	Erenumab 70 mg/month	12	-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)
	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)
	Erenumab 70 mg/month	16	-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)
	Erenumab 70 mg/month	20	-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)
	Erenumab 70 mg/month	24	-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)[100]	Erenumab 70 mg/month	4	NR	-3.20 (95%CI: -3.90, -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, -1.60)	8.48 (95%CI: 6.57, 10.4)	7.64 (95%CI: 5.98, 9.43)	7.61 (95%CI: 5.47, 9.54)
	Erenumab 70 mg/month	8	NR	-5.00 (95%CI: -5.71, -4.30)	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: -3.50, -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)
	Erenumab 70 mg/month	12	-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)
Lipton, 2017[167]	Fremanezumab 225 mg/month	12	NR	NR	7 (SE: 1.4)	17.92 (SD: 21.68)	NR

Study	Arm		MIDAS total, CFB	HIT-6 total, CFB	MSQ-RFR, CFB	MSQ-RFP, CFB	MSQ-EF, CFB
	Fremanezumab 675 mg/3 months		NR	NR	4.1 (SE: 1.4)	20.52 (SD: 23.98)	NR
	Placebo		NR	NR	NR	NR	NR
Dodick, 2014[42]	Galcanezumab 150 mg/2 weeks	12	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)†
Bigal, 2015b[40]	Fremanezumab 225 mg/month	12	-24.33 (SD: 54.56)	NR	NR	NR	NR
	Fremanezumab 675 mg/month		-24.93 (SD: 62.68)	NR	NR	NR	NR
	Placebo		-9.73 (SD: 55.67)	NR	NR	NR	NR
Aycardi, 2017[127]	Fremanezumab 225 mg/month	12	-24.6 (NR) ‡	NR	NR	NR	NR
	Fremanezumab 675 mg/3 months		-23.0 (NR) ‡	NR	NR	NR	NR
	Placebo		-17.5 (NR) ‡	NR	NR	NR	NR
Lipton, 2011[113]	Topiramate 100 mg/day	26	-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[118]	Topiramate 50 mg/day	26	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[117]	Placebo	26	NR	NR	65.8 (SE: 1.8)†	80.6 (SE: 1.5)†	72.9 (SE: 2.0)†
	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)†
Dodick, 2009[123]	Amitriptyline 100 mg/day	26	-14.2 (SD: 20.7)	NR	18.4 (NR)	12.5 (NR)	57.8 (NR)
	Topiramate 100 mg/day		-12.1 (SD: 23.4)	NR	23.7 (NR)	16.7 (NR)	55.9 (NR)

CFB: change from baseline; MIDAS: Migraine Disability Assessment; MSQ: Migraine-Specific Quality of Life Questionnaire; RFR: Role Function Restrictive; RFP: Role Function Preventive; EF: Emotional Function; HIT-6: Headache Impact Test; mg: milligram; NR: not reported; SD: standard deviation; SE: standard error; CI: credible interval *modified MIDAS: modified for 1-month recall period; †mean score, not change from baseline; ‡measured over weeks 1-12

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

Trial	Week	Tx 1	R	n	Tx 2	R	n	Tx 3	R	n
Tepper, 2017[83]	12	Placebo	13	282	Erenumab 70 mg/month	6	190	Erenumab 140 mg/month	4	188
Bigal, 2015a[41]	12	Placebo	12	89	Fremanezumab 675/225 mg/month	16	88			
Silberstein, 2017 (HALO-CM)[43]	12	Placebo	33	375	Fremanezumab 675 mg/3 months	27	376	Fremanezumab 675/225 mg/month	36	379
Aurora, 2010 PREEMPT 1[93]	24	Placebo	43	338	Onabotulinum toxin A 155U	45	341			
Diener, 2010 PREEMPT 2[94]	24	Placebo	24	358	Onabotulinum toxin A 155U	36	347			
Freitag, 2008[158]	16	Placebo	3	21	Onabotulinum toxin A 100U	2	20			
Sandrini, 2011[160]	12	Placebo	6	35	Onabotulinum toxin A 100U	6	33			
Mei, 2006[87]	12	Placebo	6	20	Topiramate 100 mg/day	9	30			
Silberstein, 2007[88]	16	Placebo	73	163	Topiramate 100 mg/day	73	165			
Dodick, 2007[89]	16	Placebo	13	27	Topiramate 100 mg/day	8	32			
Silvestrini, 2003[92]	8	Placebo	0	14	Topiramate 50 mg/day	1	14			
Cady, 2011[84]	12	Topiramate 200 mg/day	8	30	Onabotulinum toxin A 200 U	7	29			
Mathew, 2009[161]	39	Topiramate 100 mg/day	15	30	Onabotulinum toxin A 200 U	12	30			

r: responders, Tx: therapy, n: total population

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

Trial	Week	Tx 1	r	n	Tx 2	r	n	Tx 3	r	n	Tx 4	r	n
Sun 2016[38]	12	Placebo	10	153	Erenumab 70 mg/month	4	106						
Goadsby 2017 (STRIVE)[128]	24	Placebo	37	319	Erenumab 70 mg/month	33	314	Erenumab 140 mg/month	27	319			
Bigal 2015b[40]	12	Placebo	6	104	Fremanezumab 225 mg/month	13	96						
Skljarevski 2018[101]	12	Placebo	11	137	Galcanezumab 120 mg/month	8	70						
Couch 2011[103]	16	Placebo	106	197	Amitriptyline 100 mg/day	93	194						
Diener 1996[105]	12	Placebo	8	55	Propranolol 120 mg/day	12	78						
Jafarpour 2016[106]	4	Placebo	0	30	Propranolol 60 mg/day	5	30						
Pradalier 1989[107]	12	Placebo	5	24	Propranolol 160 mg/day	9	31						
Gode 2010[110]	24	Topiramate 100 mg/day	4	15	Topiramate 50 mg/day	0	15						
Mei 2004[112]	16	Placebo	20	57	Topiramate 100 mg/day	23	58						
Lipton 2011[113]	26	Placebo	86	197	Topiramate 100 mg/day	69	188						
Brandes 2004[114]	26	Placebo	51	114	Topiramate 50 mg/day	58	117	Topiramate 100 mg/day	57	120	Topiramate 200 mg/day	47	117
Silberstein 2004[115]	26	Placebo	46	115	Topiramate 50 mg/day	49	117	Topiramate 100 mg/day	42	125	Topiramate 200 mg/day	67	112
Silberstein 2006[117]	20	Placebo	13	73	Topiramate 200 mg/day	43	138						
Storey 2001 [116]	16	Placebo	2	21	Topiramate 200 mg/day	3	19						

Trial	Week	Tx 1	r	n	Tx 2	r	n	Tx 3	r	n	Tx 4	r	n
Ashtari 2008 [120]	8	Topiramate 50 mg/day	1	31	Propranolol 80 mg/day	1	31						
Dodick 2009 [123]	26	Topiramate 100 mg/day	75	177	Amitriptyline 100 mg/day	74	169						
Dogan 2015 [124]	4	Topiramate 50 mg/day	0	25	Propranolol 80 mg/day	2	26						
Keskinbora 2008 [168]	12	Topiramate 200 mg/day	4	24	Amitriptyline 150 mg/day	6	28						
Mathew 1981 [126]	24	Placebo	12	45	Amitriptyline 75 mg/day	10	42	Propranolol 160 mg/day	6	44			
Diener 2004 [121]	26	Placebo	44	143	Propranolol 160 mg/day	41	143	Topiramate 100 mg/day	45	139	Topiramate 200 mg/day	78	143

R: responders, Tx: therapy

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

Trial	Week	Tx 1	r	n	Tx 2	r	n	Tx 3	r	n	Tx 4	r	n
Tepper, 2017[83]	12	Placebo	2	282	Erenumab 70 mg/month	0	190	Erenumab 140 mg/month	2	188			
Sun 2016 [38]	12	Placebo	2	153	Erenumab 70 mg/month	3	106						
Goadsby 2017 (STRIVE) [128]	24	Placebo	8	319	Erenumab 70 mg/month	7	314	Erenumab 140 mg/month	7	319			
Dodick 2018 (ARISE) [100]	12	Placebo	1	289	Erenumab 70 mg/month	5	283						
Bigal, 2015a[41]	12	Placebo	1	89	Fremanezumab 675/225 mg/month	4	88						
Silberstein, 2017 (HALO-CM)[43]	12	Placebo	8	375	Fremanezumab 675 mg/3 months	5	376	Fremanezumab 675/225 mg/month	7	379			
Bigal 2015b[40]	12	Placebo	0	104	Fremanezumab 225 mg/month	4	96						
Aurora, 2010 PREEMPT 1[93]	24	Placebo	3	334	Onabotulinum toxin A 155U	14	340						
Diener, 2010 PREEMPT 2[94]	24	Placebo	5	358	Onabotulinum toxin A 155U	12	347						
Sandrini, 2011[160]	12	Placebo	2	29	Onabotulinum toxin A 100U	2	27						
Mathew, 2009[161]	39	Topiramate 100 mg/day	8	30	Onabotulinum toxin A 200 U	3	30						
Mei, 2006[87]	12	Placebo	6	14	Topiramate 100 mg/day	9	21						
Silberstein, 2007[88]	16	Placebo	10	163	Topiramate 100 mg/day	18	165						
Diener, 2007[95]	16	Placebo	3	27	Topiramate 100 mg/day	6	32						
Mei 2004 [112]	16	Placebo	2	37	Topiramate 100 mg/day	17	35						
Lipton 2011 [113]	26	Placebo	18	185	Topiramate 100 mg/day	21	176						

Trial	Week	Tx 1	r	n	Tx 2	r	n	Tx 3	r	n	Tx 4	r	n
Brandes 2004[114]	26	Placebo	14	120	Topiramate 50 mg/day	20	120	Topiramate 200 mg/day	25	122	Topiramate 100 mg/day	32	122
Silberstein 2004 [115]	26	Placebo	11	115	Topiramate 50 mg/day	21	117	Topiramate 200 mg/day	38	112	Topiramate 100 mg/day	24	125
Silberstein 2006 [117]	20	Placebo	4	73	Topiramate 200 mg/day	21	140						
Storey 2001 [116]	16	Placebo	0	21	Topiramate 200 mg/day	2	19						
Couch 1979 [102]	8	Placebo	2	61	Amitriptyline 100 mg/day	5	55						
Couch 2011 [103]	16	Placebo	13	197	Amitriptyline 100 mg/day	23	194						
Diener 1996 [105]	12	Placebo	1	55	Propranolol 120 mg/day	6	78						
Pradalier 1989 [107]	12	Placebo	1	24	Propranolol 160 mg/day	0	31						
Gode 2010 [110]	24	Topiramate 50 mg/day	0	15	Topiramate 100 mg/day	4	15						
Dodick 2009 [123]	26	Topiramate 100 mg/day	35	178	Amitriptyline 100 mg/day	38	168						
Keskinbora 2008 [168]	12	Topiramate 200 mg/day	2	20	Amitriptyline 150 mg/day	3	22						
Mathew 1981 [126]	24	Placebo	4	45	Amitriptyline 75 mg/day	4	42	Propranolol 160 mg/day	1	44			
Diener 2004 [121]	26	Placebo	15	143	Topiramate 200 mg/day	63	143	Topiramate 100 mg/day	37	139	Propranolol 160 mg/day	29	143

R: responders, Tx: therapy

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

Trial	Week	Tx 1	R	n	Tx 2	R	n	Tx 3	R	n
Tepper, 2017 [83]	12	Placebo	7	282	Erenumab 70 mg/month	6	190	Erenumab 140 mg/month	2	188
Sun 2016[38]	12	Placebo	0	153	Erenumab 70 mg/month	1	106			
Goadsby 2017 (STRIVE)[128]	24	Placebo	7	319	Erenumab 70 mg/month	8	314	Erenumab 140 mg/month	6	319
Dodick 2018 (ARISE) [100]	12	Placebo	5	289	Erenumab 70 mg/month	3	283			
Bigal, 2015a[41]	12	Placebo	1	89	Fremanezumab 675/225 mg/month	1	88			
Silberstein, 2017 (HALO-CM)[43]	12	Placebo	6	375	Fremanezumab 675 mg/3 months	3	376	Fremanezumab 675/225 mg/month	5	379
Bigal 2015b[40]	12	Placebo	0	104	Fremanezumab 225 mg/month	2	96			
Skljarevski 2018 [101]	12	Placebo	0	137	Galcanezumab 120 mg/month	1	70			
Aurora, 2010 (PREEMPT 1)[93]	24	Placebo	8	334	Onabotulinum toxin A 155U	18	340			
Diener, 2010 (PREEMPT 2)[94]	24	Placebo	8	358	Onabotulinum toxin A 155U	15	347			
Diener, 2007[91]	16	Placebo	1	27	Topiramate 100 mg/day	1	32			
Lipton 2011[113]	26	Placebo	5	185	Topiramate 100 mg/day	4	176			
Silberstein 2006[117]	20	Placebo	1	73	Topiramate 200 mg/day	2	140			
Storey 2001[116]	16	Placebo	1	21	Topiramate 200 mg/day	1	19			
Couch 2011[103]	16	Placebo	10	197	Amitriptyline 100 mg/day	30	194			
Dodick 2009[123]	26	Topiramate 100 mg/day	4	177	Amitriptyline 100 mg/day	8	169			

R: responders, Tx: therapy

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

Study	Treatment	N	Wks	% Dizziness	% Injection Pain	% Injection Reaction	% Nasopharyngitis	% Nausea	% Paresthesia	% Sinusitis	% Upper Respiratory Tract Infection
Erenumab											
Dodick 2018 (ARISE) [100]	Erenumab 70 mg	283	12		6		5.3				6.4
	Placebo	289	12		4.2		5.9				4.8
Goadsby 2017 (STRIVE) [128]	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 [38]	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 [83]	Erenumab 70 mg	190	12								
	Erenumab 140 mg	188	12								
	Placebo	282	12								
Fremanezumab											
Bigal, 2015 [41]	Fremanezumab 675/225 mg	88	12		7	5(P)			5	5	
	Fremanezumab 900 mg	86	12		9	2(P)			0	0	
	Placebo	89	12		3	0(P)			0	1	
Bigal 2015b [41]	Fremanezumab 225 mg	96	12	5	4					5	
	Fremanezumab 675 mg	96	12	1	9					0	
	Placebo	104	12	0	6					3	
Silberstein, 2017 (HALO-CM)[43]	Fremanezumab 675 mg*	376	12		30	21(Er) 20(I)	5				5
	Fremanezumab 675/225 mg	379	12		26	20(Er) 24(I)	4				4
	Placebo	375	12		28	16 (Er) 18(I)	5				4

Study	Treatment	N	Wks	% Dizziness	% Injection Pain	% Injection Reaction	% Nasopharyngitis	% Nausea	% Paresthesia	% Sinusitis	% Upper Respiratory Tract Infection
Galcanezumab											
Dodick 2014 [169]	Galcanezumab 150 mg†	107	12	5	17	5					17
	Placebo	110	12	3	6	0					9
Skljarevski 2018 [101]	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

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	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Amitriptyline											
Couch 2011 [103]	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[170]	Amitriptyline 25 mg	59	12			10.17	40.68(Sp)				
	Placebo	59	12			1.69	11.86(Sp)				
Propranolol											
Pradalier 1989 [107]	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 [162]	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			
Topiramate											
Brandes 2004[114]	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 [95]	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	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Lipton 2011 [113]	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 [111]	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 [112]	Topiramate 100 mg	35	16	8(Cd)			11(F) 6(S)		23	6	23(WI)
	Placebo	37	16	0(Cd)			0(F) 23(S)		6	0	0(WI)
Mei, 2006 [87]	Topiramate 100 mg	21	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(WI)
	Placebo	14	12	14.29(Cx) 14.29(M) 0(L)			7.14(F) 0(S)		14.29	0	0(A) 0(WI)
Silberstein 2004 [115]	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(WI)
	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(WI)
	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(WI)
	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(WI)

Study	Treatment	N	Wks	% Cognitive Symptoms	% GI Symptoms	% Dry Mouth	% Fatigue	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Silberstein 2006 [117]	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 [88]	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 [92]	Topiramate 50 mg	14	8				14.29(S)		14.29		
	Placebo	14	8				0(S)		7.14		
Storey 2001 [116]	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)
Head-to-Head Trials											
Cady, 2011[84]	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 [86]	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)				11.8(Wg)
Ashtari 2008 [120]	Topiramate 50 mg	31	8				12.90(S)	22.58			16.13(Wl)
	Propranolol		8								
Diener 2004 [121]	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)

Study	Treatment	N	Wks	% Cognitive Symptoms	% GI Symptoms	% Dry Mouth	% Fatigue	% Nausea	% Paresthesia	% Taste Perversion	% Weight Change
Dodick 2009 [123]	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 [168]	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; Onabotulinum toxin A injections are given every three months.

Cognitive symptoms include cognitive difficulties (Cd), difficulty with memory (M), concentration (Cx), 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) tiredness (T). Weight change 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]).[171,172]

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.[80] 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.[80] 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.[173] 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.[79] In the report, results are presented for each treatment versus placebo. 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.

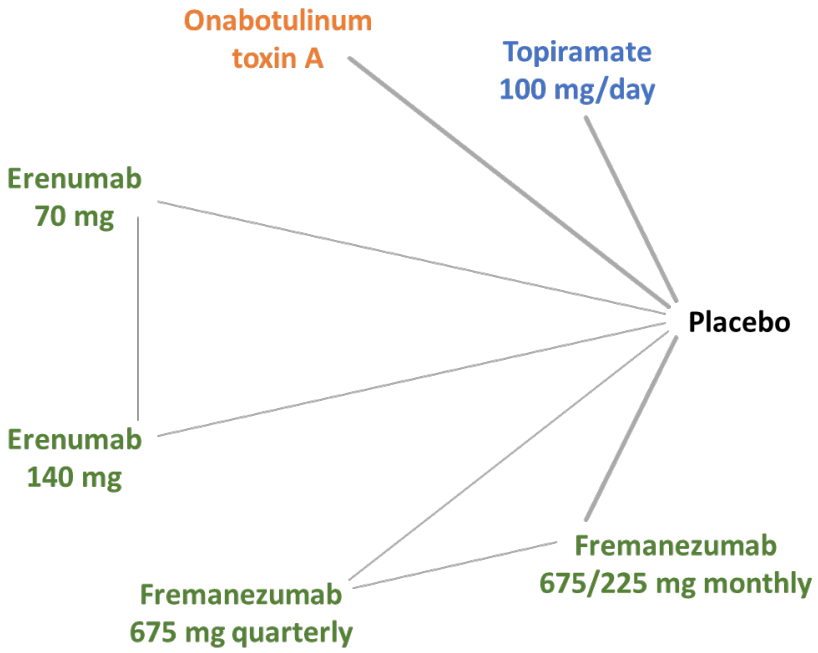
Supplemental NMA Results

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 width of the connecting lines are related to the number of trials available for each pair of treatments.

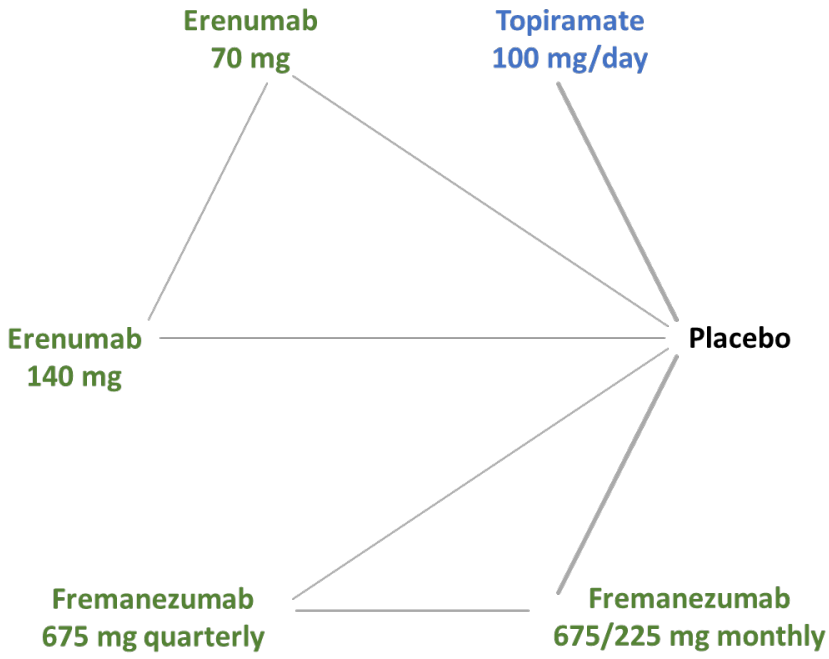
Table D19. Network Meta-Analysis Results for Change from Baseline in Monthly Migraine Days in Chronic Migraine

Erenumab 140 mg/month						
0 (-2.78, 2.77)	**Erenumab 70 mg/month**					
-0.19 (-3.43, 3.63)	-0.18 (-3.46, 3.66)	**Topiramate 100 mg/day**				
-0.45 (-3.82, 2.93)	-0.45 (-3.83, 2.94)	-0.26 (-3.49, 2.39)	**Onabotulinum toxin A 155U**			
-0.75 (-4.17, 2.72)	-0.74 (-4.18, 2.73)	-0.56 (-3.85, 2.19)	-0.29 (-3.11, 2.52)	**Fremanezumab 675/225 mg/month**		
-1.11 (-4.9, 2.69)	-1.1 (-4.89, 2.68)	-0.92 (-4.63, 2.2)	-0.66 (-3.89, 2.57)	-0.36 (-2.94, 2.2)	**Fremanezumab 675 mg/3 months**	
-2.4 (-5.17, 0.39)	-2.4 (-5.16, 0.38)	**-2.22 (-4.7, -0.24)**	-1.95 (-3.89, 0)	-1.66 (-3.71, 0.38)	-1.29 (-3.88, 1.3)	**Placebo**

Tau: 0.68 (0.03, 3.02); DIC: 28.2

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 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 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 width of the connecting lines are related to the number of trials available for each pair of treatments.

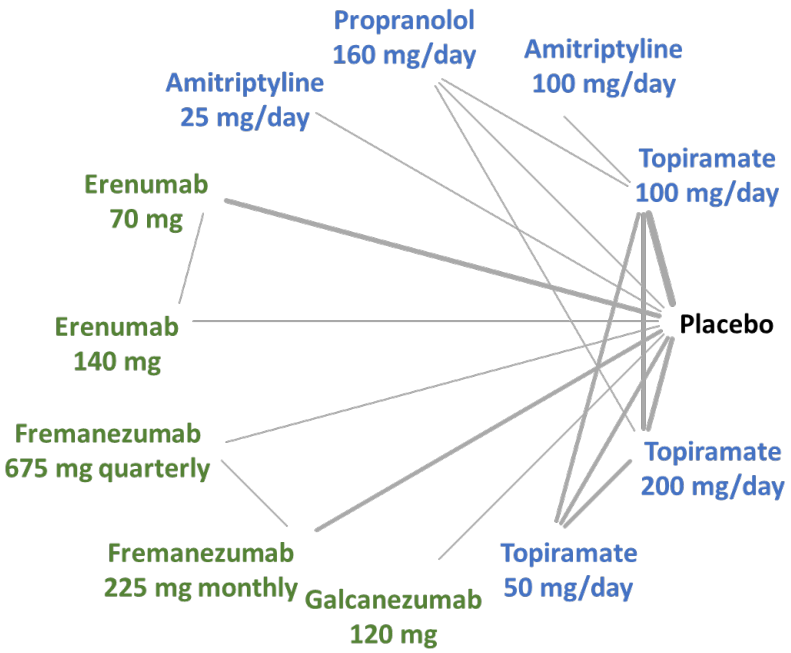
Table D20. Network Meta-Analysis Results for Change from Baseline in Days Using Acute Medication per Month in Chronic Migraine

Erenumab 140 mg/month					
-0.25 (-3.35, 2.86)	**Fremanezumab 675/225 mg/month**				
-0.61 (-3.08, 1.89)	-0.36 (-3.44, 2.76)	**Erenumab 70 mg/month**			
-0.73 (-4.11, 2.72)	-0.47 (-2.82, 1.91)	-0.12 (-3.53, 3.29)	**Fremanezumab 675 mg/3 months**		
-1.24 (-4.27, 2.21)	-0.98 (-3.61, 2.04)	-0.62 (-3.68, 2.81)	-0.5 (-3.47, 2.85)	**Topiramate 100 mg/day**	
-2.5 (-4.96, -0.01)	**-2.25 (-4.1, -0.35)**	-1.9 (-4.36, 0.58)	-1.78 (-4.13, 0.59)	-1.28 (-3.56, 0.68)	**Placebo**

Tau: 0.71 (0.03, 2.32); 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 D3. Network of Studies Assessing Monthly Migraine Days in Episodic Migraine Patients



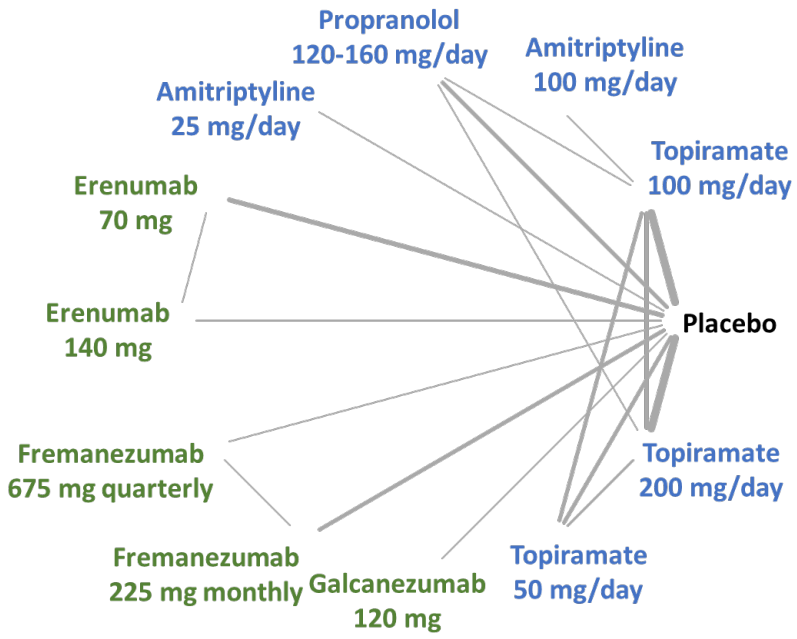
Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, and placebo in black. The width of the connecting lines are related to the number of trials available for each pair of treatments.

Table D21. Network Meta-Analysis Results for Change from Baseline in Monthly Migraine Days in Episodic Migraine

Erenumab 140 mg/month											
-0.08 (-1.36, 1.36)	**Fremanezumab 225 mg/month**										
-0.56 (-1.98, 0.95)	-0.49 (-1.62, 0.59)	**Fremanezumab 675 mg/3 months**									
-0.65 (-1.61, 0.30)	-0.57 (-1.79, 0.51)	-0.09 (-1.41, 1.15)	**Erenumab 70 mg/month**								
-0.69 (-2.04, 0.69)	-0.62 (-2.03, 0.69)	-0.14 (-1.63, 1.31)	-0.05 (-1.18, 1.13)	**Propranolol 160 mg/day**							
-0.75 (-1.85, 0.39)	-0.68 (-1.84, 0.4)	-0.2 (-1.46, 1.07)	-0.11 (-0.93, 0.77)	-0.05 (-1.02, 0.91)	**Topiramate 100 mg/day**						
-0.83 (-2.43, 0.77)	-0.76 (-2.43, 0.79)	-0.28 (-2.02, 1.43)	-0.18 (-1.62, 1.25)	-0.13 (-1.76, 1.46)	-0.08 (-1.51, 1.31)	**Amitriptyline 25 mg/day**					
-0.85 (-2.66, 0.99)	-0.78 (-2.65, 1.02)	-0.29 (-2.22, 1.59)	-0.2 (-1.86, 1.5)	-0.16 (-1.89, 1.58)	-0.1 (-1.55, 1.35)	-0.02 (-2.02, 2.02)	**Amitriptyline 100 mg/day**				
-0.89 (-2.01, 0.31)	-0.81 (-2, 0.31)	-0.34 (-1.61, 0.95)	-0.25 (-1.11, 0.72)	-0.2 (-1.16, 0.81)	-0.14 (-0.77, 0.53)	-0.06 (-1.46, 1.43)	-0.04 (-1.62, 1.57)	**Topiramate 200 mg/day**			
-1.04 (-2.42, 0.35)	-0.96 (-2.42, 0.35)	-0.48 (-2.01, 1.01)	-0.39 (-1.57, 0.8)	-0.34 (-1.75, 1.03)	-0.29 (-1.46, 0.85)	-0.21 (-1.82, 1.43)	-0.19 (-2.05, 1.65)	-0.14 (-1.39, 1)	**Galcanezumab 120 mg/month**		
-1.76 (-3.02, -0.46)	**-1.69 (-3.01, -0.44)**	-1.21 (-2.61, 0.21)	**-1.11 (-2.15, -0.02)**	-1.06 (-2.25, 0.13)	**-1.01 (-1.86, -0.16)**	-0.93 (-2.45, 0.65)	-0.91 (-2.59, 0.78)	**-0.87 (-1.76, -0.01)**	-0.72 (-2.01, 0.61)	**Topiramate 50 mg/day**	
-1.94 (-2.89, -0.98)	**-1.87 (-2.88, -0.96)**	**-1.38 (-2.52, -0.28)**	**-1.29 (-1.92, -0.65)**	**-1.24 (-2.22, -0.29)**	**-1.19 (-1.78, -0.63)**	-1.11 (-2.38, 0.19)	-1.09 (-2.65, 0.46)	**-1.05 (-1.74, -0.43)**	-0.9 (-1.9, 0.11)	-0.18 (-1.05, 0.66)	**Placebo**

Tau: 0.33 (0.02, 0.88); DIC: 59.3 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 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 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 width of the connecting lines are related to the number of trials available for each pair of treatments.

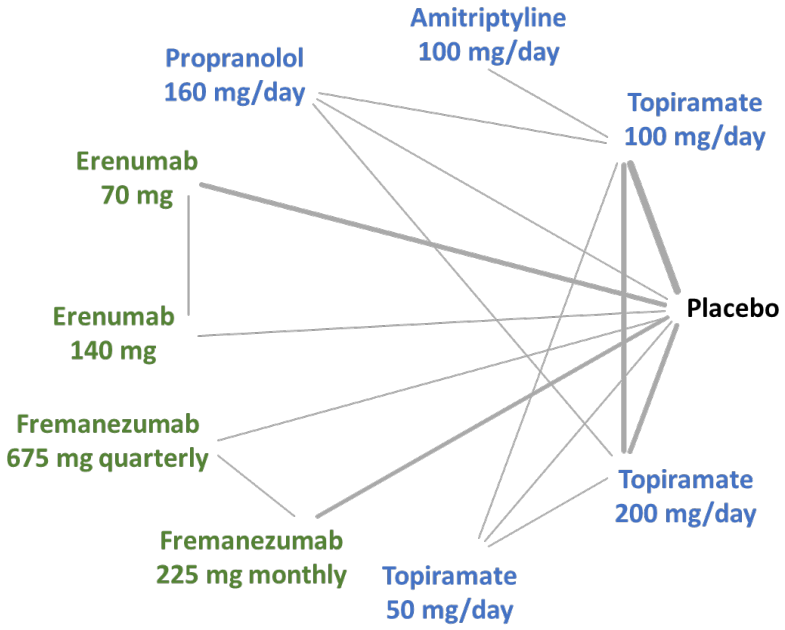
Table D22. Network Meta-Analysis Results for 50% Response in Episodic Migraine

Topiramate 100 mg/day											
1 (0.62, 1.7)	**Propranolol 120-160 mg/day**										
1.04 (0.39, 2.77)	1.03 (0.36, 2.88)	**Amitriptyline 25 mg/day**									
1.12 (0.67, 1.93)	1.12 (0.58, 2.08)	1.08 (0.39, 2.99)	**Fremanezumab 225 mg/month**								
1.16 (0.82, 1.66)	1.16 (0.69, 1.89)	1.12 (0.42, 2.98)	1.04 (0.6, 1.76)	**Topiramate 200 mg/day**							
1.21 (0.69, 2.25)	1.22 (0.6, 2.39)	1.18 (0.41, 3.4)	1.09 (0.56, 2.12)	1.05 (0.58, 1.93)	**Erenumab 140 mg/month**						
1.27 (0.72, 2.36)	1.27 (0.63, 2.52)	1.23 (0.43, 3.55)	1.14 (0.69, 1.9)	1.1 (0.61, 2.04)	1.05 (0.51, 2.15)	**Fremanezumab 675 mg/3 months**					
1.34 (0.56, 3.22)	1.34 (0.51, 3.38)	1.29 (0.37, 4.49)	1.2 (0.47, 2.99)	1.16 (0.47, 2.79)	1.1 (0.42, 2.86)	1.06 (0.4, 2.72)	**Galcanezumab 120 mg/month**				
1.39 (0.9, 2.25)	1.39 (0.77, 2.47)	1.35 (0.51, 3.64)	1.25 (0.72, 2.15)	1.2 (0.76, 1.94)	1.15 (0.69, 1.89)	1.09 (0.59, 2.02)	1.04 (0.43, 2.54)	**Erenumab 70 mg/month**			
1.49 (0.81, 2.77)	1.49 (0.65, 3.2)	1.44 (0.45, 4.57)	1.33 (0.58, 2.95)	1.29 (0.63, 2.59)	1.23 (0.51, 2.83)	1.17 (0.49, 2.71)	1.11 (0.38, 3.21)	1.07 (0.48, 2.27)	**Amitriptyline 100 mg/day**		
1.69 (1.1, 2.62)	1.69 (0.9, 3.01)	1.63 (0.58, 4.54)	1.51 (0.81, 2.74)	1.46 (0.93, 2.26)	1.39 (0.7, 2.66)	1.33 (0.67, 2.55)	1.26 (0.5, 3.22)	1.21 (0.69, 2.07)	1.13 (0.53, 2.42)	**Topiramate 50 mg/day**	
2.64 (1.97, 3.67)	2.64 (1.63, 4.2)	2.54 (1.02, 6.49)	2.35 (1.55, 3.63)	2.28 (1.66, 3.2)	2.17 (1.31, 3.59)	2.07 (1.24, 3.46)	1.97 (0.88, 4.5)	1.89 (1.35, 2.66)	1.76 (0.9, 3.6)	1.56 (1.02, 2.46)	**Placebo**

Tau: 0.16 (0.01, 0.46); DIC: 72.7

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 D5. 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 width of the connecting lines are related to the number of trials available for each pair of treatments.

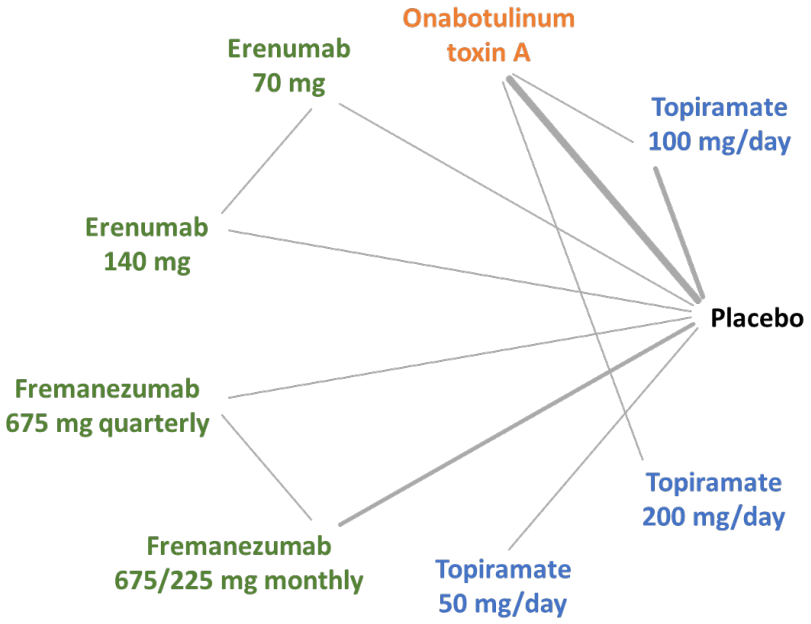
Table D23. Network Meta-Analysis Results for Change from Baseline in Days Using Acute Medication per Month in Episodic Migraine

Erenumab 140 mg/month									
-0.04 (-1.21, 1.15)	**Fremanezumab 225 mg/month**								
-0.19 (-1.49, 1.1)	-0.15 (-1.19, 0.86)	**Fremanezumab 675 mg/3 months**							
-0.47 (-1.64, 0.71)	-0.43 (-1.65, 0.79)	-0.28 (-1.6, 1.07)	**Propranolol 160 mg/day**						
-0.44 (-2.08, 1.22)	-0.4 (-2.09, 1.29)	-0.24 (-2.02, 1.54)	0.03 (-1.56, 1.63)	**Amitriptyline 100 mg/day**					
-0.63 (-1.6, 0.33)	-0.59 (-1.62, 0.42)	-0.44 (-1.59, 0.72)	-0.17 (-1.02, 0.69)	-0.2 (-1.55, 1.15)	**Topiramate 100 mg/day**				
-0.66 (-1.45, 0.16)	-0.62 (-1.63, 0.4)	-0.47 (-1.6, 0.7)	-0.19 (-1.19, 0.83)	-0.22 (-1.76, 1.32)	-0.03 (-0.77, 0.74)	**Erenumab 70 mg/month**			
-0.8 (-1.77, 0.22)	-0.76 (-1.8, 0.3)	-0.61 (-1.77, 0.6)	-0.34 (-1.19, 0.55)	-0.36 (-1.83, 1.12)	-0.17 (-0.74, 0.44)	-0.14 (-0.93, 0.66)	**Topiramate 200 mg/day**		
-1.35 (-2.56, -0.1)	**-1.31 (-2.58, -0.02)**	-1.15 (-2.53, 0.25)	-0.88 (-2.05, 0.31)	-0.91 (-2.55, 0.75)	-0.71 (-1.64, 0.23)	-0.69 (-1.76, 0.39)	-0.54 (-1.49, 0.39)	**Topiramate 50 mg/day**	
-1.55 (-2.37, -0.76)	**-1.51 (-2.39, -0.66)**	**-1.36 (-2.39, -0.34)**	**-1.08 (-1.96, -0.24)**	-1.11 (-2.58, 0.32)	**-0.92 (-1.46, -0.39)**	**-0.89 (-1.46, -0.39)**	**-0.75 (-1.37, -0.19)**	-0.21 (-1.16, 0.71)	**Placebo**

Tau: 0.31 (0.05, 0.79); DIC: 49.3

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 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 D6. 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 width of the connecting lines are related to the number of trials available for each pair of treatments.

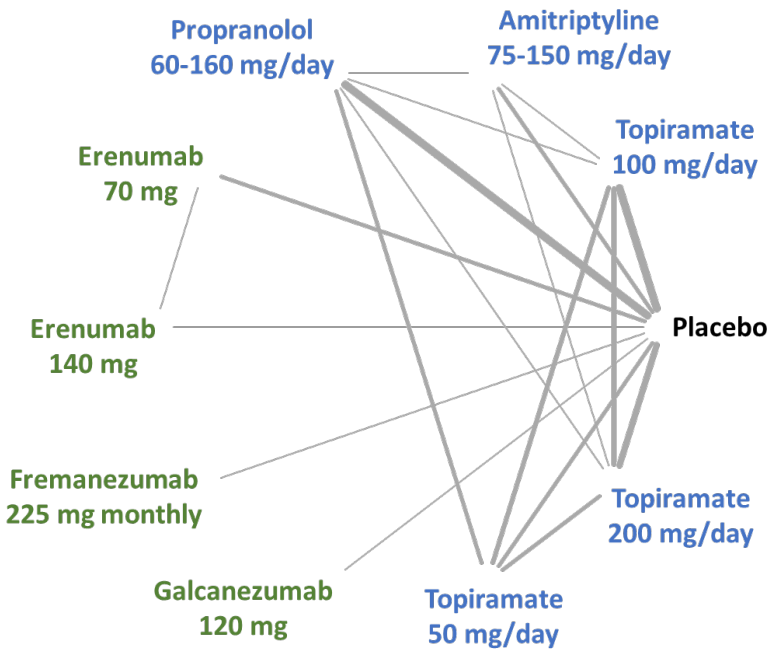
Table D24. Network Meta-Analysis Results for All-Cause Discontinuations in Chronic Migraine

Erenumab 140 mg/month								
0.65 (0.13, 2.83)	**Erenumab 70 mg/month**							
0.5 (0.09, 2.4)	0.78 (0.16, 3.44)	**Fremanezumab 675 mg/3 months**						
0.46 (0.09, 1.98)	0.71 (0.18, 2.78)	0.92 (0.34, 2.67)	**Topiramate 100 mg/day**					
0.42 (0.09, 1.57)	0.65 (0.18, 2.21)	0.84 (0.35, 2)	0.91 (0.5, 1.57)	**Placebo**				
0.38 (0.08, 1.64)	0.59 (0.15, 2.33)	0.76 (0.3, 2.22)	0.83 (0.43, 1.69)	0.91 (0.57, 1.6)	**Onabotulinum toxin A 100-200 U**			
0.33 (0.04, 2.51)	0.52 (0.08, 3.62)	0.67 (0.12, 3.84)	0.73 (0.15, 3.48)	0.8 (0.18, 3.62)	0.87 (0.21, 3.54)	**Topiramate 200 mg/day**		
0.35 (0.07, 1.53)	0.55 (0.13, 2.17)	0.7 (0.29, 1.64)	0.77 (0.3, 1.8)	0.84 (0.41, 1.64)	0.92 (0.36, 2.04)	1.05 (0.19, 5.27)	**Fremanezumab 675/225 mg/month**	
NE	NE	NE	NE	NE	NE	NE	NE	**Topiramate 50 mg/day**

Tau: 0.24 (0.01, 0.85); DIC: 49.3; 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 D7. 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 width of the connecting lines are related to the number of trials available for each pair of treatments.

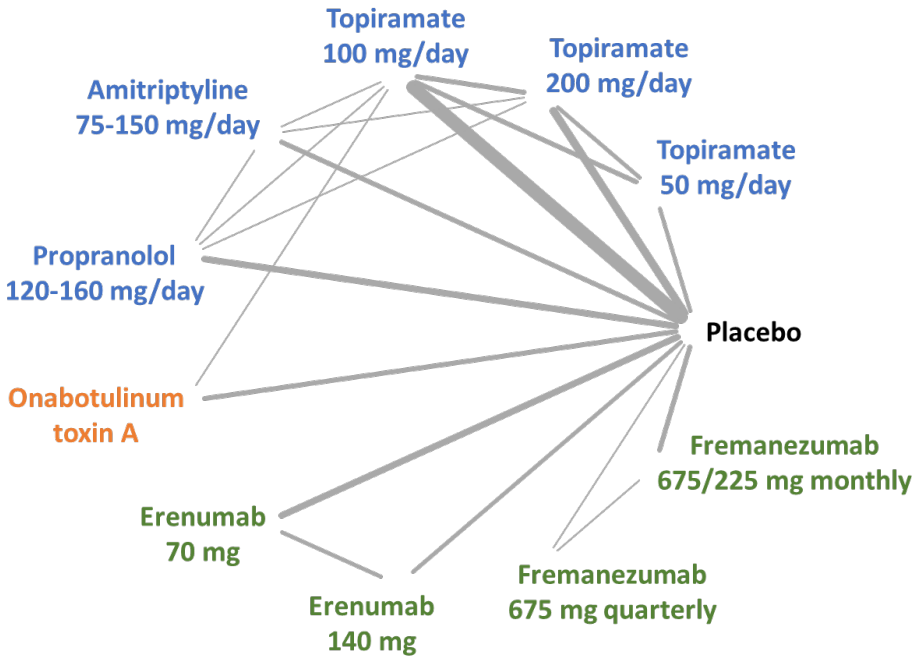
Table D25. Network Meta-Analysis Results for All-Cause Discontinuations in Episodic Migraine

Erenumab 140 mg/month									
0.84 (0.31, 2.34)	**Erenumab 70 mg/month**								
0.65 (0.23, 1.75)	0.78 (0.32, 1.75)	**Placebo**							
0.65 (0.21, 1.87)	0.77 (0.29, 1.9)	1 (0.63, 1.49)	**Topiramate 100 mg/day**						
0.66 (0.19, 1.92)	0.78 (0.26, 1.99)	1 (0.54, 1.68)	1 (0.52, 1.82)	**Propranolol 60-160 mg/day**					
0.63 (0.2, 2.16)	0.75 (0.27, 2.2)	0.96 (0.55, 1.92)	0.97 (0.55, 2.02)	0.96 (0.48, 2.41)	**Topiramate 50 mg/day**				
0.61 (0.18, 1.85)	0.72 (0.24, 1.91)	0.93 (0.49, 1.63)	0.94 (0.49, 1.72)	0.93 (0.45, 1.98)	0.97 (0.38, 2.01)	**Amitriptyline 75-150 mg/day**			
0.45 (0.08, 2.34)	0.53 (0.11, 2.49)	0.68 (0.18, 2.59)	0.68 (0.17, 2.82)	0.68 (0.17, 3.03)	0.7 (0.16, 2.93)	0.73 (0.18, 3.28)	**Galcanezumab 120 mg/month**		
0.39 (0.13, 1.15)	0.46 (0.17, 1.17)	0.59 (0.37, 0.95)	0.59 (0.36, 1.02)	0.59 (0.32, 1.21)	0.61 (0.3, 1.11)	0.63 (0.33, 1.33)	0.86 (0.21, 3.51)	**Topiramate 200 mg/day**	
0.24 (0.04, 1.3)	0.29 (0.06, 1.38)	0.37 (0.09, 1.43)	0.38 (0.09, 1.57)	0.38 (0.09, 1.68)	0.39 (0.08, 1.62)	0.4 (0.09, 1.82)	0.55 (0.08, 3.6)	0.64 (0.14, 2.63)	**Fremanezumab 225 mg/month**

Tau: 0.40 (0.15, 0.79); DIC: 99.0

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 Discontinuations from Adverse Events in Chronic or Episodic Migraine Patients



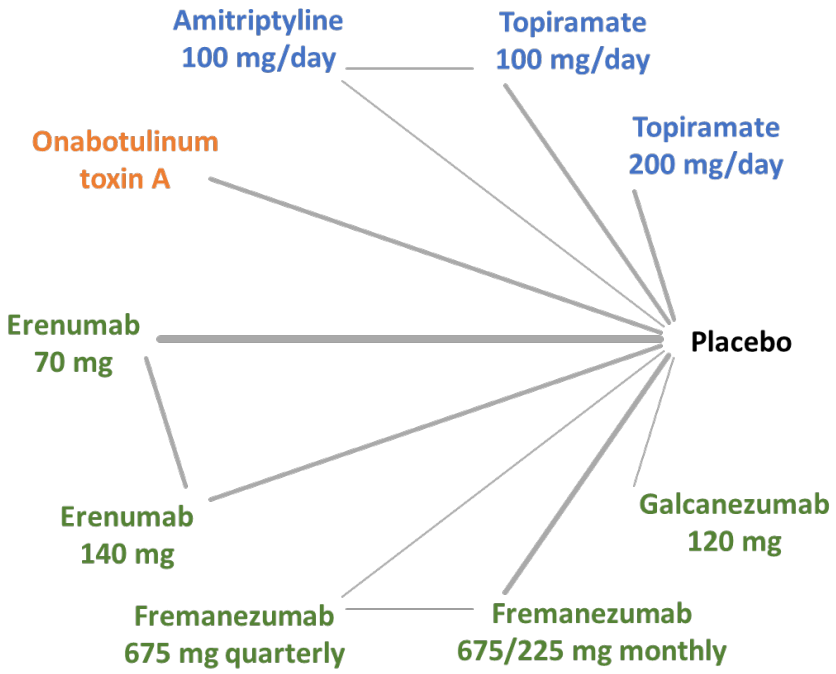
Legend: The CGRP inhibitors are depicted in green, the existing oral preventive therapies in blue, onabotulinum toxin A in orange, and placebo in black. The width of the connecting lines are related to the number of trials available for each pair of treatments.

Table D26. Network Meta-Analysis Results for Discontinuations from Adverse Events in Chronic or Episodic Migraine

Placebo										
1.05 (0.22, 4.99)	Fremanezumab 675 mg/3 months									
0.74 (0.33, 1.76)	0.7 (0.12, 4.29)	Propranolol 120 mg/day								
0.74 (0.27, 1.96)	0.7 (0.11, 4.4)	0.99 (0.26, 3.51)	Erenumab 70 mg/month							
0.72 (0.2, 2.5)	0.69 (0.09, 4.99)	0.98 (0.21, 4.21)	0.99 (0.28, 3.45)	Erenumab 140 mg/month						
0.62 (0.3, 1.43)	0.6 (0.11, 3.58)	0.85 (0.29, 2.5)	0.85 (0.25, 3.17)	0.86 (0.21, 4.03)	Topiramate 50 mg/day					
0.48 (0.2, 1.14)	0.45 (0.08, 2.75)	0.64 (0.19, 2.07)	0.65 (0.17, 2.48)	0.66 (0.15, 3.1)	0.7 (0.23, 2.33)	Onabotulinum toxin A 100-200 U				
0.46 (0.13, 1.36)	0.44 (0.09, 1.89)	0.63 (0.13, 2.38)	0.63 (0.13, 2.7)	0.64 (0.11, 3.28)	0.74 (0.16, 2.71)	0.98 (0.21, 3.87)	Fremanezumab 225 mg/month			
0.4 (0.24, 0.61)	0.38 (0.07, 1.87)	0.54 (0.21, 1.21)	0.54 (0.18, 1.6)	0.54 (0.14, 2.06)	0.63 (0.27, 1.29)	0.83 (0.32, 2.09)	0.85 (0.26, 3.15)	Topiramate 100 mg/day		
0.38 (0.18, 0.77)	0.36 (0.06, 1.98)	0.51 (0.18, 1.35)	0.51 (0.15, 1.75)	0.52 (0.12, 2.23)	0.61 (0.21, 1.58)	0.8 (0.25, 2.37)	0.81 (0.22, 3.4)	0.96 (0.45, 2.04)	Amitriptyline 75-150 mg/day	
0.27 (0.15, 0.5)	0.26 (0.05, 1.39)	0.37 (0.14, 0.89)	0.37 (0.12, 1.2)	0.38 (0.1, 1.55)	0.44 (0.19, 0.95)	0.58 (0.21, 1.61)	0.59 (0.18, 2.38)	0.69 (0.39, 1.32)	0.72 (0.32, 1.73)	Topiramate 200 mg/day

Tau: 0.50 (0.17, 0.94); DIC: 128.0 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 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 width of the connecting lines are related to the number of trials available for each pair of treatments.

Table D27. Network Meta-Analysis Results for Serious Adverse Events in Chronic or Episodic Migraine

Erenumab 140 mg/month									
1.11 (0.17, 8.24)	**Fremanezumab 675 mg/3 months**								
0.62 (0.21, 1.67)	0.56 (0.09, 2.73)	**Placebo**							
0.59 (0.13, 2.65)	0.52 (0.07, 3.71)	0.94 (0.32, 2.93)	**Topiramate 100 mg/day**						
0.56 (0.18, 1.52)	0.5 (0.07, 2.94)	0.9 (0.4, 2)	0.95 (0.23, 3.7)	**Erenumab 70 mg/month**					
0.52 (0.05, 5.23)	0.47 (0.03, 6.27)	0.84 (0.1, 6.66)	0.89 (0.08, 9.52)	0.93 (0.09, 8.71)	**Topiramate 200 mg/day**				
0.52 (0.1, 2.34)	0.46 (0.08, 2.14)	0.84 (0.23, 2.69)	0.88 (0.16, 4.28)	0.93 (0.21, 3.8)	0.98 (0.09, 11.28)	**Fremanezumab 675/225 mg/month**			
0.29 (0.07, 1.04)	0.26 (0.04, 1.54)	0.47 (0.2, 1.05)	0.49 (0.12, 1.93)	0.52 (0.16, 1.63)	0.55 (0.06, 5.58)	0.55 (0.14, 2.62)	**Onabotulinum toxin A 155U**		
0.2 (0.05, 0.81)	0.18 (0.02, 1.17)	0.32 (0.12, 0.86)	0.34 (0.11, 1.07)	0.36 (0.1, 1.29)	0.39 (0.04, 4.15)	0.39 (0.09, 1.98)	0.7 (0.2, 2.55)	**Amitriptyline 100 mg/day**	
NE	NE	NE	NE	NE	NE	NE	NE	NE	**Galcanezumab 120 mg/month**

Tau: 0.23 (0.01, 1.00); DIC: 58.8; 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.

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 D28. 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
Erenumab 70 mg monthly	-2.35 (-5.08, 0.37)	-2.65 (-5.21, -0.09)	-2.41 (-4.65, -0.15)	-2.58 (-12.81, 4.99)	-2.4 (-5.16, 0.38)
Erenumab 140 mg monthly	-2.43 (-5.13, 0.28)	-2.89 (-5.45, -0.32)	-2.4 (-4.66, -0.16)	-2.57 (-12.8, 4.99)	-2.4 (-5.17, 0.39)
Fremanezumab 675 mg quarterly	-2.13 (-4.64, 0.38)	-1.48 (-3.85, 0.91)	-1.29 (-3.4, 0.8)	-1.47 (-11.65, 6.05)	-1.29 (-3.88, 1.3)
Fremanezumab 675/225 mg monthly	-2.06 (-4.02, -0.09)	-1.84 (-3.69, 0.09)	-1.65 (-3.35, 0.02)	-1.82 (-12, 5.54)	-1.66 (-3.71, 0.38)
Onabotulinum toxin A 155U quarterly	-2.11 (-3.99, -0.22)	-1.8 (-3.57, -0.02)	-1.4 (-2.94, 0.15)	-1.71 (-13.45, 14.81)	-1.95 (-3.89, 0)
Topiramate 100 mg/day				-2.29 (-4.94, -0.14)	-2.22 (-4.7, -0.24)
Tau	0.82 (0.06, 2.48)	0.65 (0.03, 2.56)	0.55 (0.02, 2.16)	0.69 (0.03, 3.01)	0.68 (0.03, 3.02)
B				-0.32 (-24.3, 16.51)	
DIC	21.5	20.7	20.1	28.0	28.2

Tau: standard deviation of treatment effect estimates; B: coefficient on the analysis adjusting for timepoint; DIC: deviance information criteria

Table D29. Analysis by Timepoint and with Covariate Adjustment for Monthly Migraine days in Episodic Migraine

	4 Weeks	8 Weeks	12 Weeks	24 to 26 Weeks	Covariate Adjustment	No Covariate Adjustment
Erenumab 70 mg monthly	-1.17 (-2.11, -0.18)	-1.15 (-2.34, 0.06)	-1.16 (-2.1, -0.2)	-1.59 (-2.84, -0.34)	-1.37 (-2.07, -0.66)	-1.29 (-1.92, -0.65)
Erenumab 140 mg monthly	-1.7 (-3.17, -0.19)	-1.52 (-3.41, 0.36)	-1.74 (-3.2, -0.26)	-2.09 (-3.34, -0.84)	-1.88 (-2.88, -0.88)	-1.94 (-2.89, -0.98)
Fremanezumab 675 mg quarterly			-1.38 (-3.05, 0.1)		-1.63 (-3, -0.32)	-1.38 (-2.52, -0.28)
Fremanezumab 225 mg monthly	-2.12 (-4.19, -0.08)	-2.49 (-4.9, -0.09)	-1.86 (-3.31, -0.74)		-2.12 (-3.38, -0.97)	-1.87 (-2.88, -0.96)
Galcanezumab 120 mg monthly	-0.76 (-2.47, 0.96)	-0.59 (-2.74, 1.57)	-0.9 (-2.49, 0.68)		-1.16 (-2.4, 0.11)	-0.9 (-1.9, 0.11)
Topiramate 50 mg/day				-0.18 (-1.16, 0.76)	0.09 (-1.08, 1.2)	-0.18 (-1.05, 0.66)
Topiramate 100 mg/day				-1.19 (-1.88, -0.54)	-0.92 (-1.9, 0.01)	-1.19 (-1.78, -0.63)
Topiramate 200 mg/day				-1.06 (-1.86, -0.34)	-0.78 (-1.83, 0.17)	-1.05 (-1.74, -0.43)
Amitriptyline 25 mg/day	-1.11 (-2.86, 0.67)	-1.2 (-3.35, 0.95)	-1.1 (-2.83, 0.65)		-1.36 (-2.84, 0.14)	-1.11 (-2.38, 0.19)
Amitriptyline 100 mg/day				-1.08 (-2.83, 0.62)	-0.83 (-2.61, 0.91)	-1.09 (-2.65, 0.46)
Propranolol 160 mg/day				-1.24 (-2.4, -0.14)	-0.97 (-2.24, 0.24)	-1.24 (-2.22, -0.29)
Tau	0.37 (0.02, 1.83)	0.54 (0.03, 2.19)	0.34 (0.01, 1.99)	0.4 (0.03, 1.2)	0.34 (0.02, 0.94)	0.33 (0.02, 0.88)
B					-0.54 (-2.02, 0.95)	
DIC	24.5	25.4	30.1	35.3	59.8	59.3

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 50% Responders in Episodic Migraine

	4 Weeks	8 Weeks	12 Weeks	Covariate Adjustment	No Covariate Adjustment
Erenumab 70 mg monthly	2.22 (1.21, 4.02)	1.76 (1.06, 2.87)	1.83 (1.25, 2.72)	1.93 (1.38, 2.71)	1.89 (1.35, 2.66)
Erenumab 140 mg monthly	2.73 (1.08, 6.94)	2.34 (1.08, 5.03)	2.5 (1.4, 4.51)	2.07 (1.27, 3.42)	2.17 (1.31, 3.59)
Fremanezumab 675 mg quarterly			2.07 (1.15, 3.77)	2.34 (1.32, 3.98)	2.07 (1.24, 3.46)
Fremanezumab 225 mg monthly	3.36 (1.12, 10.41)	2.31 (0.91, 5.89)	2.36 (1.46, 3.87)	2.68 (1.63, 4.24)	2.35 (1.55, 3.63)
Galcanezumab 120 mg monthly			1.95 (0.84, 4.73)	2.22 (0.96, 5.19)	1.97 (0.88, 4.5)
Topiramate 50 mg/day				1.38 (0.85, 2.33)	1.56 (1.02, 2.46)
Topiramate 100 mg/day				2.34 (1.62, 3.55)	2.64 (1.97, 3.67)
Topiramate 200 mg/day				2.04 (1.41, 3.08)	2.28 (1.66, 3.2)
Amitriptyline 25 mg/day			2.54 (0.97, 6.85)	2.86 (1.09, 7.61)	2.54 (1.02, 6.49)
Amitriptyline 100 mg/day				1.57 (0.79, 3.31)	1.76 (0.9, 3.6)
Propranolol 120-160 mg/day			1.65 (0.67, 4.11)	2.47 (1.54, 3.98)	2.64 (1.63, 4.2)
Tau	0.25 (0.01, 1.05)	0.22 (0.01, 0.83)	0.14 (0.01, 0.71)	0.14 (0.01, 0.47)	0.16 (0.01, 0.46)
B				0.26 (-0.28, 0.73)	
DIC	16.7	15.6	32.9	72.9	72.7

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

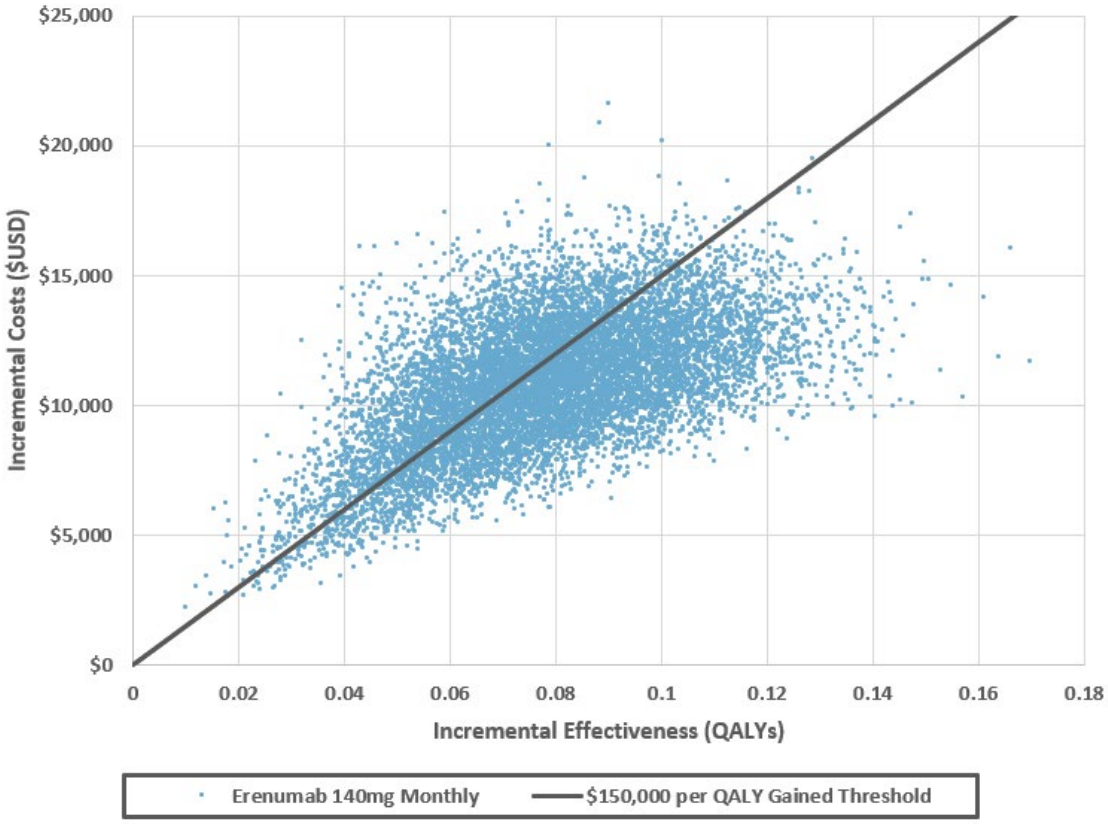
Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of 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.[174]

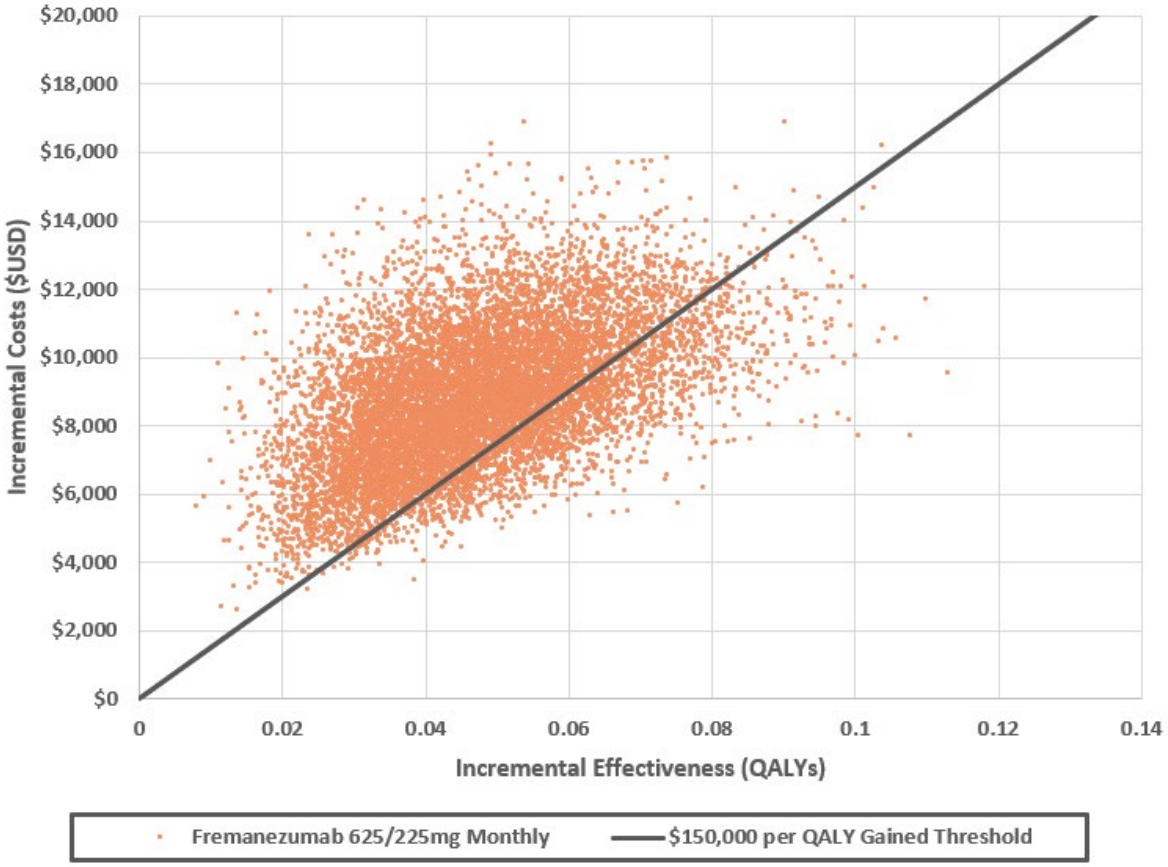
Probabilistic Sensitivity Analyses

Figure E1. Scatterplot of Costs and Effects Comparing Erenumab 140 mg Monthly to No Treatment in Patients with Chronic Migraine for Whom Prior Preventive Therapies Failed*



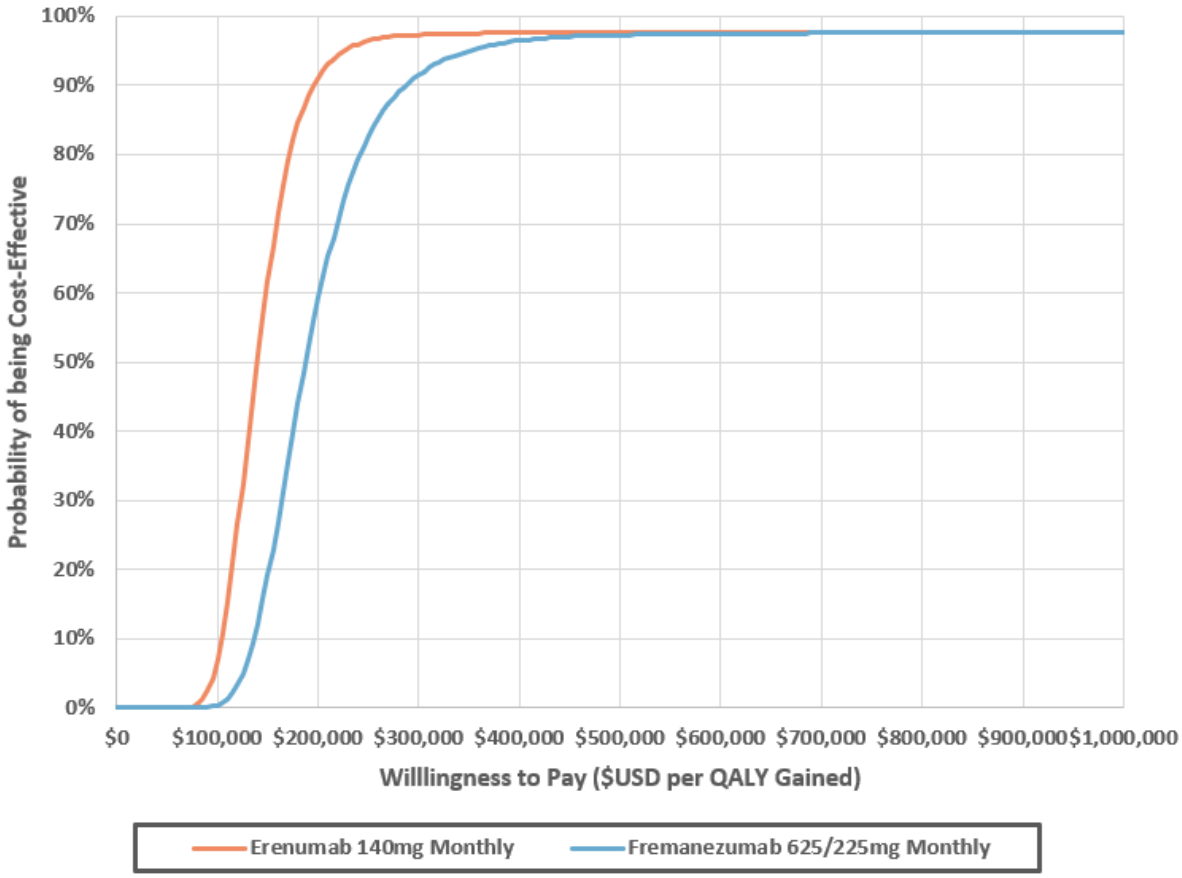
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E2. Scatterplot of Costs and Effects Comparing Fremanezumab 625/225mg Monthly to No Treatment in Patients with Chronic Migraine for whom Prior Preventive Therapies Failed*



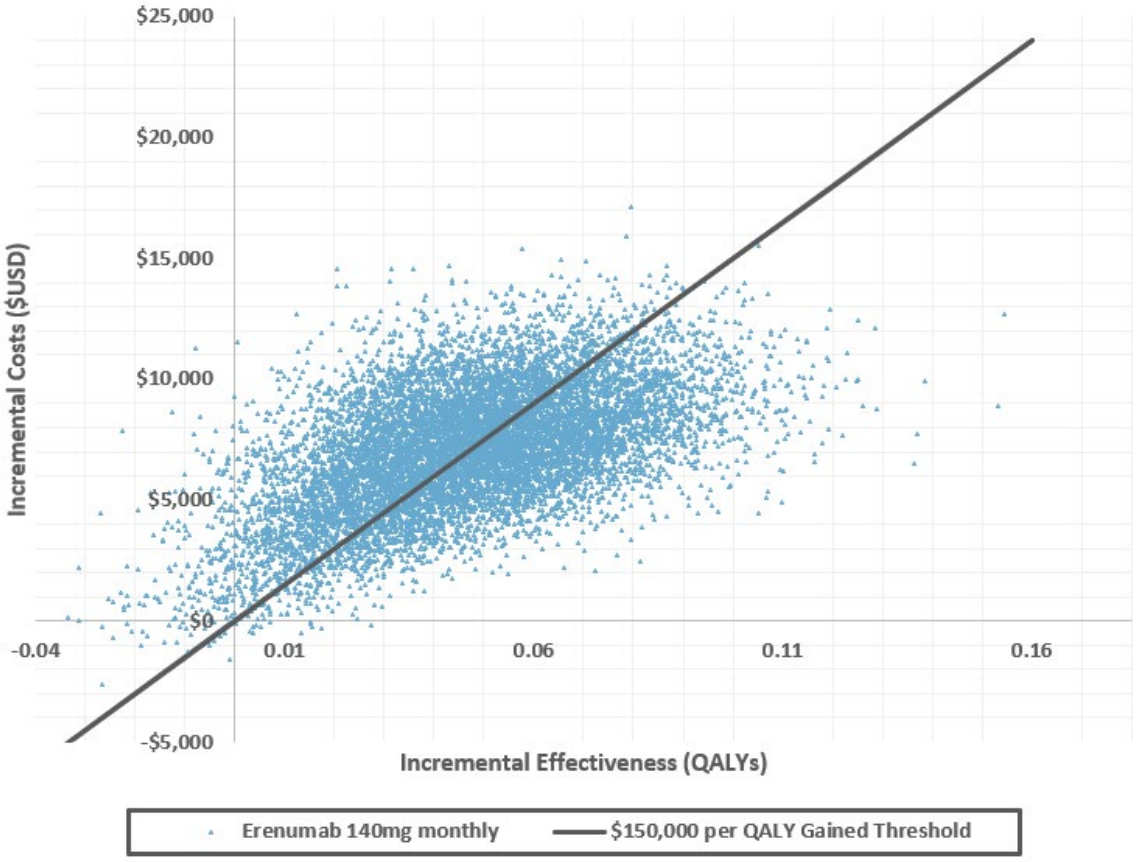
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E3. Cost-Effectiveness Acceptability Curves Comparing CGRP Inhibitors to No Treatment in Chronic Migraine*



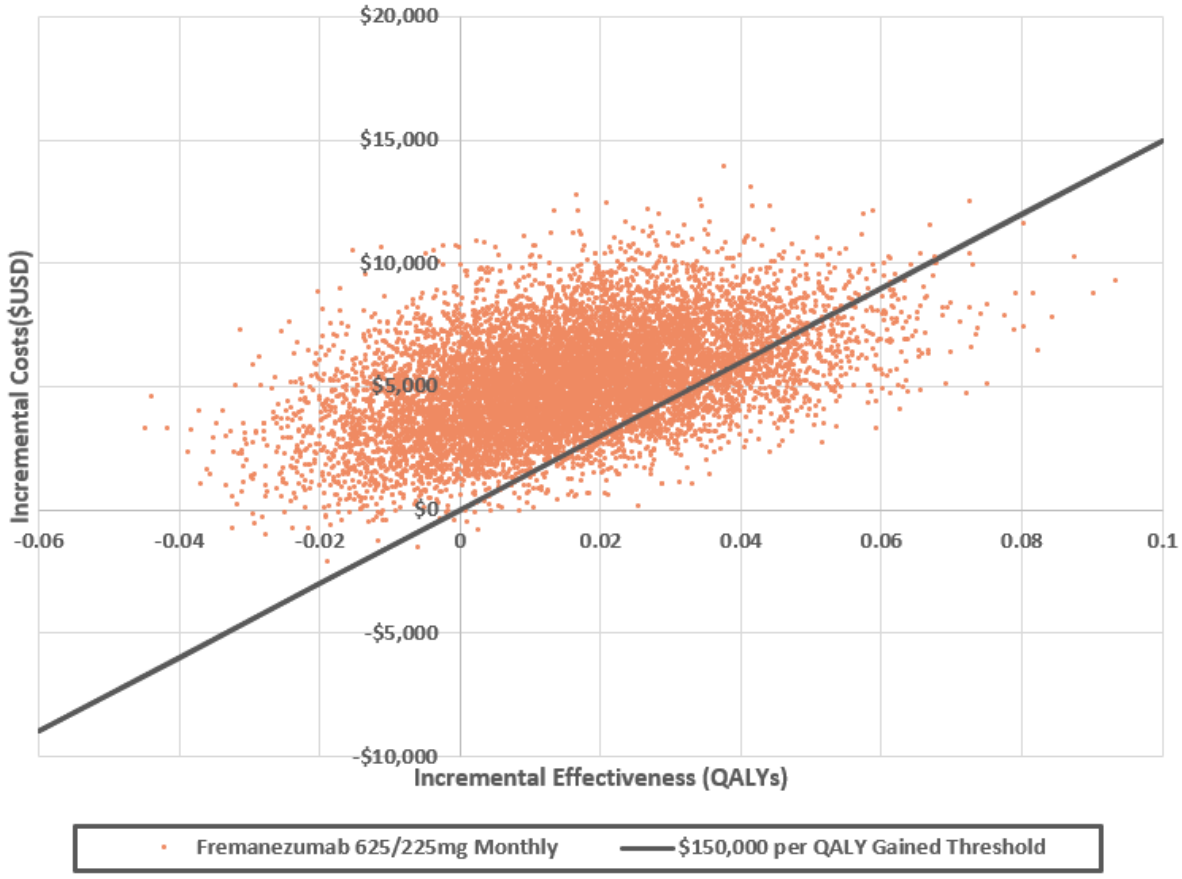
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E4. Scatterplot of Costs and Effects Comparing Erenumab 140mg Monthly to Onabotulinum Toxin A in Patients with Chronic Migraine for whom Prior Preventive Therapies Failed*



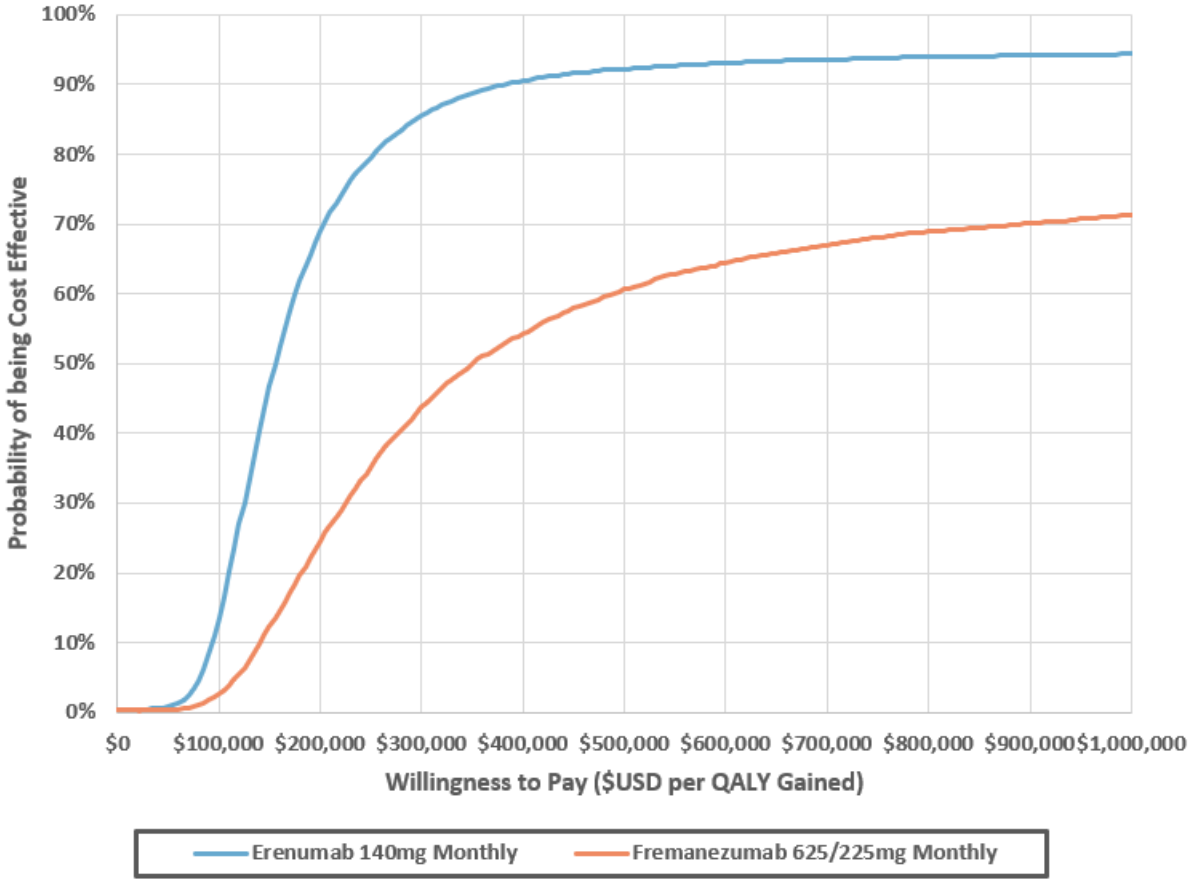
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E5. 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*



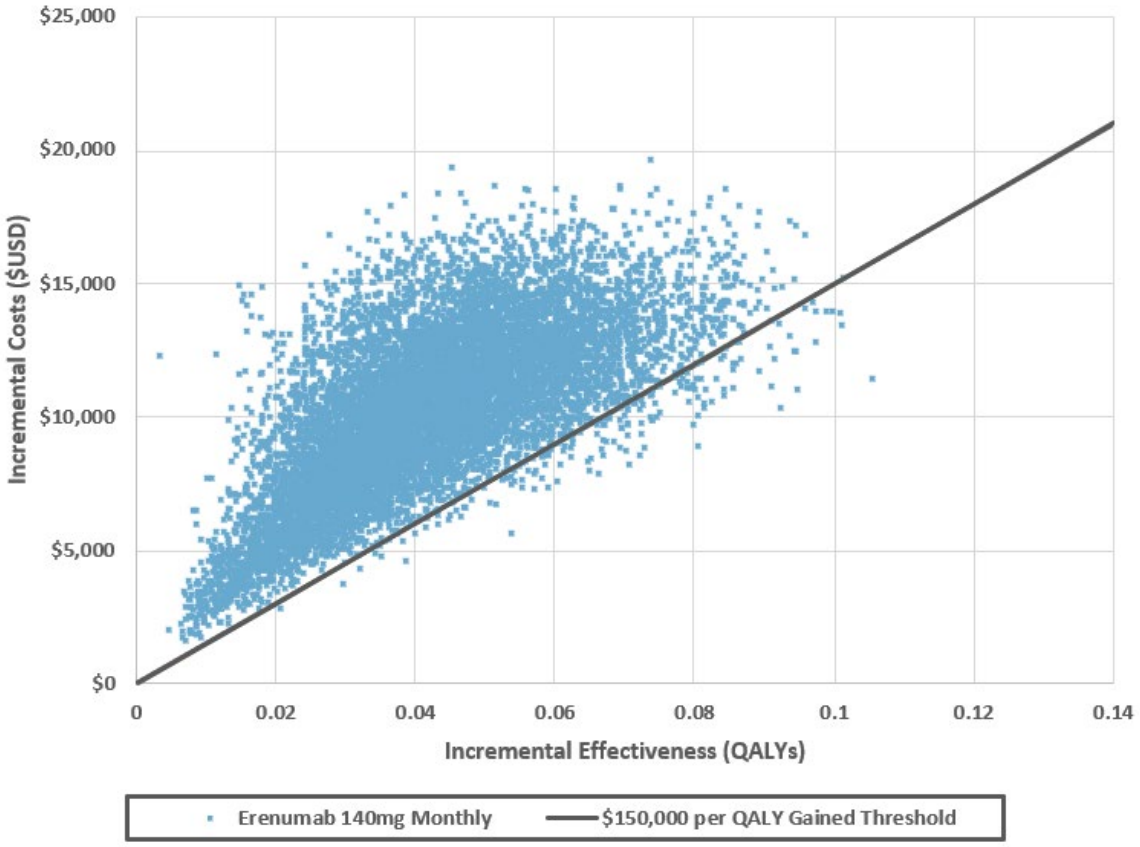
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E6. Cost-Effectiveness Acceptability Curves Comparing CGRP Inhibitors to Onabotulinum Toxin A in Chronic Migraine*



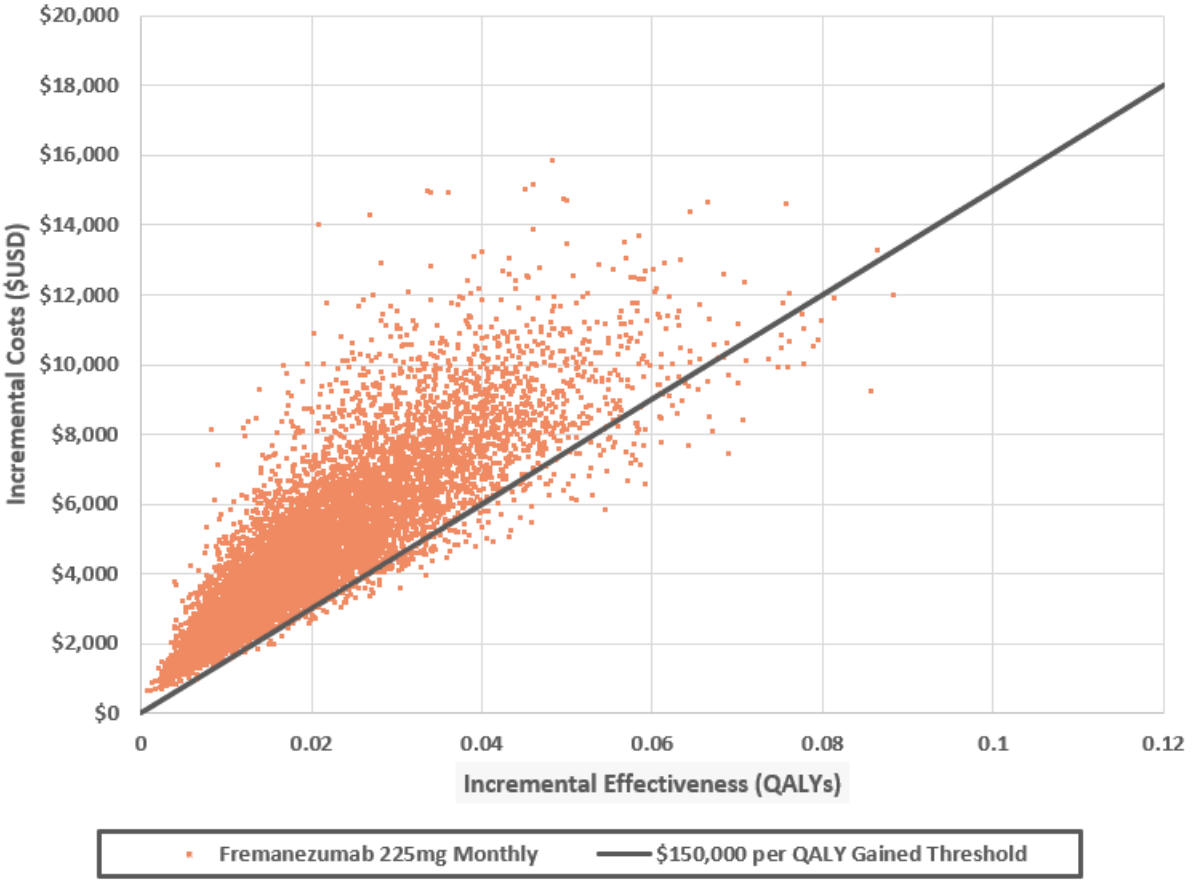
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E7. Scatterplot of Costs and Effects Comparing Erenumab 140mg Monthly to No Treatment in Patients with Episodic Migraine for whom Prior Preventive Therapies Failed*



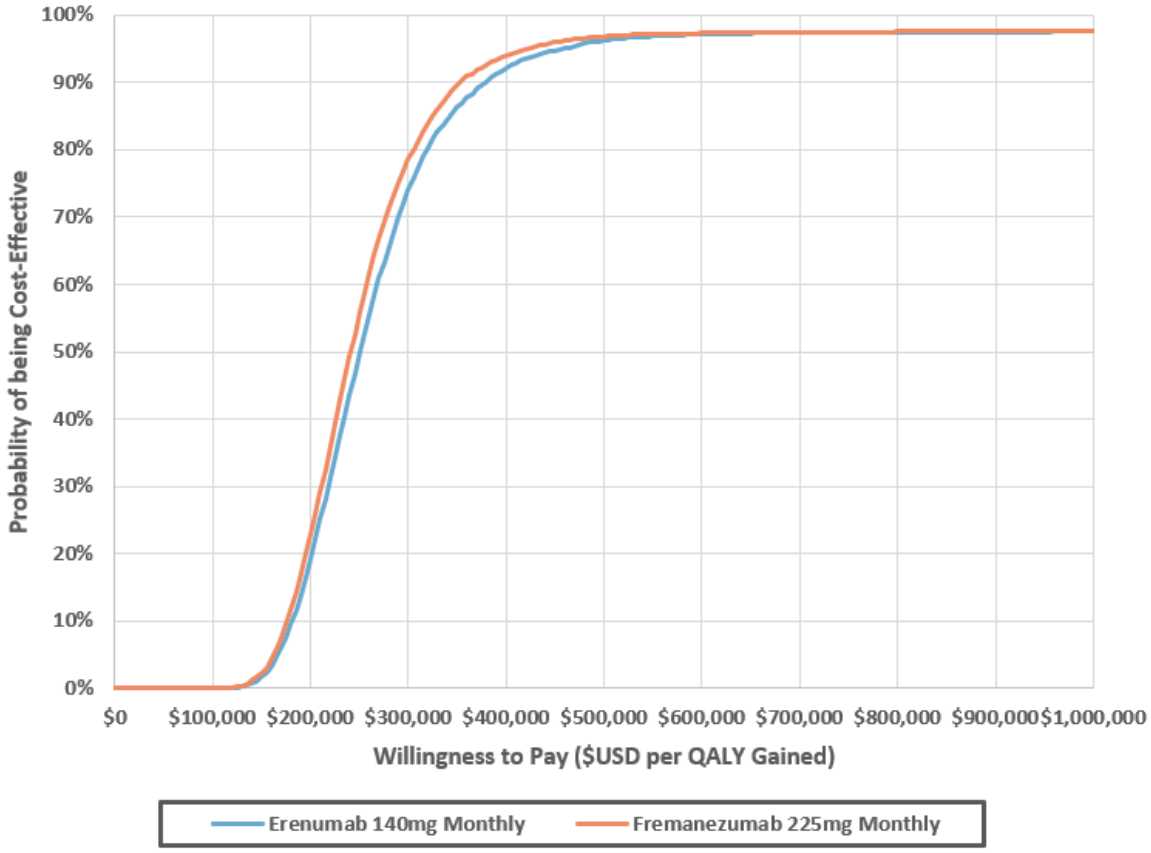
* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E8. Scatterplot of Costs and Effects Comparing Fremanezumab 225mg Monthly to No Treatment in Patients with Episodic Migraine for whom Prior Preventive Therapies Failed*



* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E9. Cost-Effectiveness Acceptability Curves Comparing CGRP Inhibitors to No Treatment in Episodic Migraine*



* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Scenario Analyses

CGRP Inhibitors Versus Preventive Treatments

Inputs used in the scenario analyses comparing CGRP inhibitors to preventive treatments are shown in Tables E1 – 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[9]
Propranolol	26.8	11.1	Ford et al. 2017[9]
Topiramate	56.9	55.6	Ford et al. 2017[9]
Onabotulinum toxin A	--	23.3	Ford et al. 2017[9]

*The distributions 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[9]
Propranolol	13.9	10.6	Ford et al. 2017[9]
Topiramate	29.6	53.1	Ford et al. 2017[9]
Onabotulinum toxin A	--	22.2	Ford et al. 2017[9]
No Treatment	48.1	4.4	Ford et al. 2017[9]

* The distributions were re-weighted for the preventive treatments included in the review

Table E4. Treatment Effects for CGRP Inhibitors and Active Preventive Treatments in Episodic Migraine

Treatment	Mean Reduction in Migraine Days (95% CI)
Erenumab 140 mg monthly	-1.94 (-2.76, -1.12)
Fremanezumab 225 mg monthly	-2.79 (-4.44, -1.16)
Galcanezumab 120 mg monthly	-1.90 (-3.10, -0.69)
Topiramate 100 mg daily	-1.18 (-1.70, -0.69)
Amitriptyline 100 mg daily	-1.15 (-2.02, -0.29)
Propranolol 160 mg daily	-1.03 (-1.91, -0.17)

CI: confidence interval

Table E5. Treatment Effects for CGRP Inhibitors and Active Preventive Treatments in Chronic Migraine

Treatment	Mean Reduction in Migraine Days (95% CI)
Erenumab 140 mg monthly	-2.40 (-5.16, 0.38)
Fremanezumab 675/225 mg monthly	-1.66 (-3.72, 0.38)
Topiramate 100 mg daily	-2.23 (-4.70, -0.23)
Amitriptyline 100 mg daily	-1.15 (-2.02, -0.29)
Propranolol 160 mg daily	-1.03 (-1.91, -0.17)
Onabotulinum toxin A	-1.96 (-3.88, -0.01)

CI: confidence interval

Table E6. Reduction in Days per Month of Acute Treatments for Active 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	-0.96 (-1.48, -0.46)	-1.29 (-3.52,0.63)
Amitriptyline 100 mg daily	-1.16 (-2.32, 0)	-1.16 (-3.12, 0)
Propranolol 160 mg daily	-0.93 (-1.75, -0.12)	-0.93 (-2.35, -0.16)
Onabotulinum toxin A	--	-1.10 (-1.74, -0.61)

CI: confidence interval

Table E7. Monthly Discontinuation Rates for CGRP Inhibitors and Active Treatments

Treatment	Episodic Migraine: Discontinuation Rate (95% CI)	Chronic Migraine: Discontinuation Rate (95% CI)
Erenumab 140 mg monthly	0.038 (0.007,0.174)	0.026 (0.006, 0.094)
Fremanezumab 225 mg monthly	0.191 (0.048,0.833)	0.052 (0.022, 0.121)
Active Treatments (weighted*)	0.084 (0.026,0.274)	0.060 (0.030,0.121)

CI: confidence interval

* Weighted mean of the mix of active treatments

Table E8. Proportion of Patients Experiencing an Adverse Event Each Cycle for the Active Preventive Treatments

Treatment	Episodic Migraine: Adverse Event Rate	Source	Chronic 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

Table E9. Preventive Drug Cost Inputs 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

WAC: wholesale acquisition cost

Table E10. 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	$12,806	$17,867	54.92	1.349
Fremanezumab 625/225 mg monthly	$10,271	$15,755	42.03	1.331
Preventive Treatment	$2096	$8416	45.16	1.335

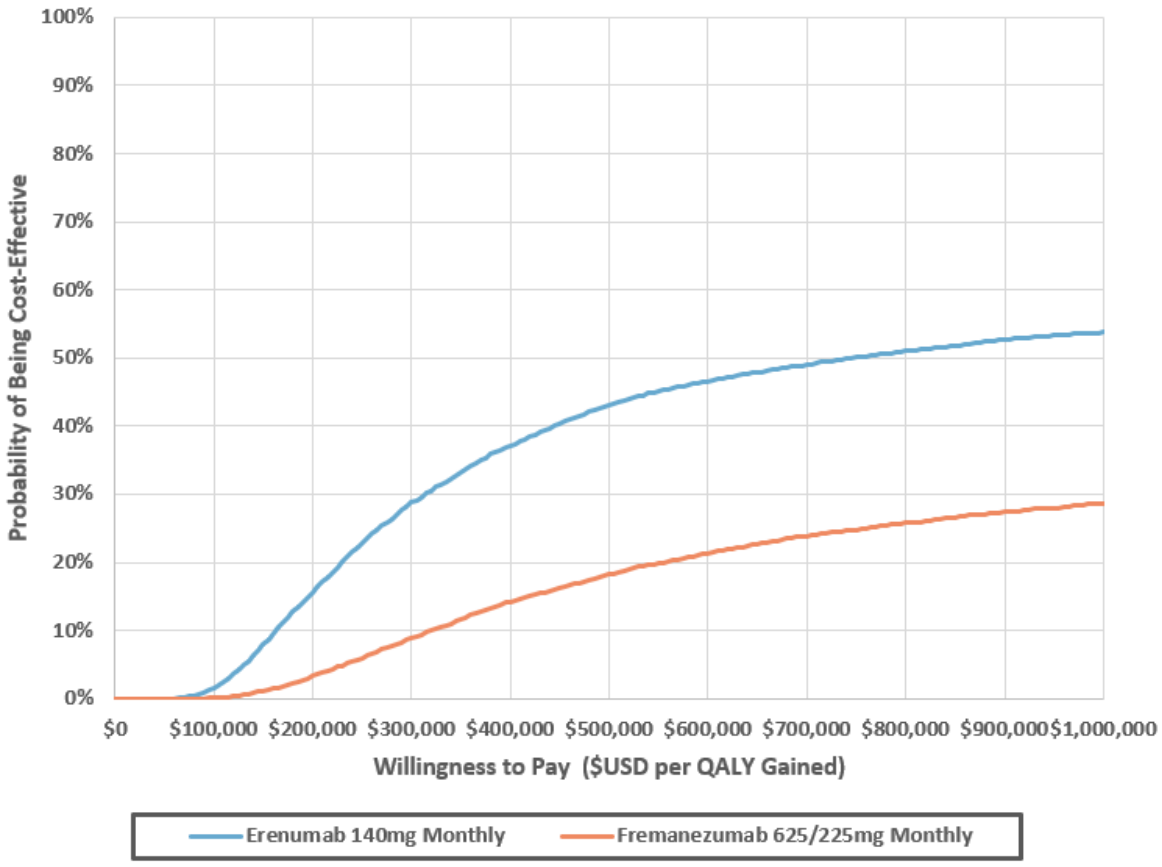
QALYs: quality-adjusted life years

Table E11. 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	$10,935	$12,552	34.13	1.645
Fremanezumab 225 mg monthly	$3694	$5546	23.00	1.632
Preventive Treatment	$645	$2697	19.79	1.627

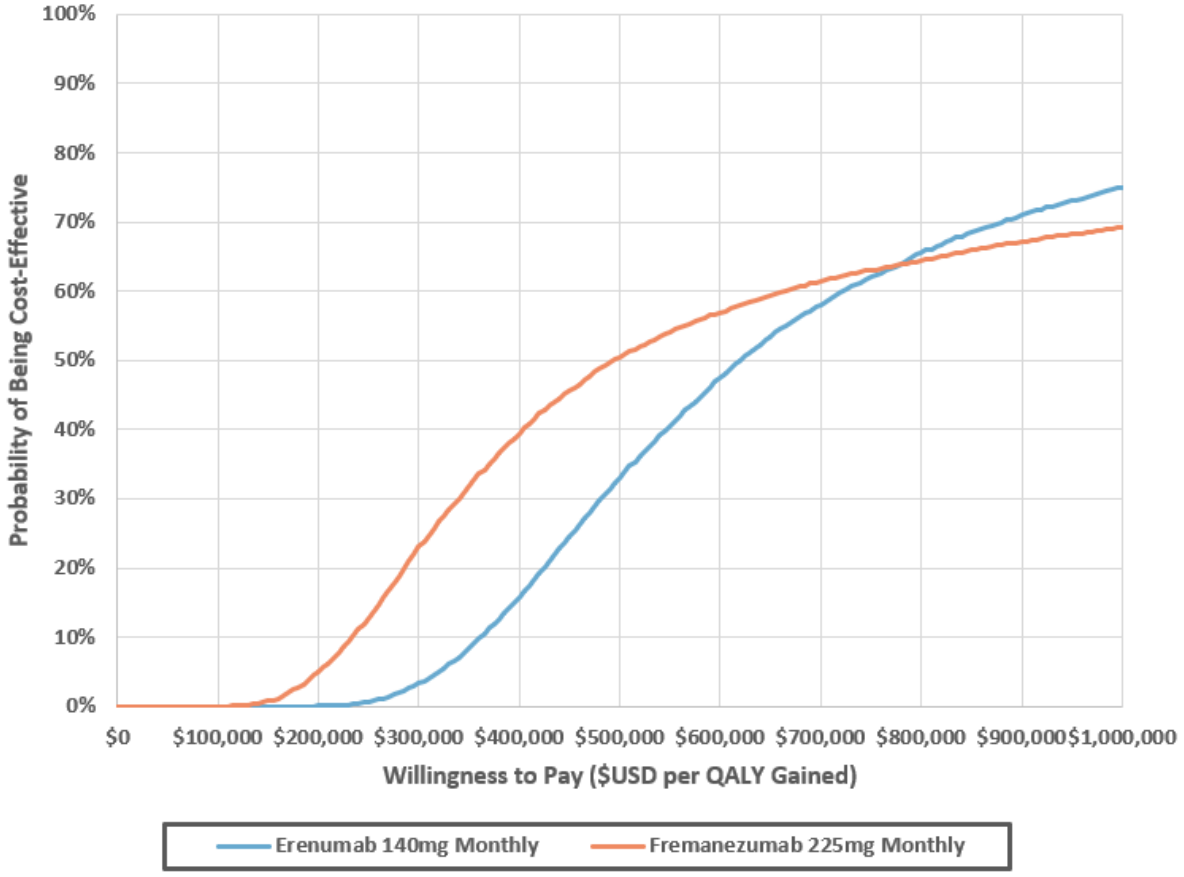
QALYs: quality-adjusted life years

Figure E10. Cost-Effectiveness Acceptability Curves for Scenario Analysis Comparing CGRP Inhibitors to Other Preventive Treatment in Chronic Migraine*



* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Figure E11. Cost-Effectiveness Acceptability Curves for Scenario Analysis Comparing CGRP Inhibitors to Other Preventive Treatment in Episodic Migraine*



* All results presented in this figure for the CGRP inhibitors are based on placeholder costs

Table E12. 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[156]; Buse et al., 2012[157]

Table E13. 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[156]

Table E14. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Erenumab in Chronic Migraine Patients Who Previously Failed Current Preventive Therapy

	Average Annual Per Patient Budget Impact			
	Placeholder WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$9,606	$10,292	$8,040	$5,789
No Active Preventive Treatment	$3,508			
Difference	$6,098	$6,784	$4,533	$2,282

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

Table E15. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Erenumab in Episodic Migraine Patients Who Previously Failed Current Preventive Therapy

	Average Annual Per Patient Budget Impact			
	Placeholder WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$7,090	$4,980	$3,744	$2,508
No Active Preventive Treatment	$1,244			
Difference	$5,846	$3,736	$2,500	$1,246

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

Table E16. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Fremanezumab in Chronic Migraine Patients Who Previously Failed Current Preventive Therapy

	Average Annual Per Patient Budget Impact			
	Placeholder WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$8,535	$7,623	$6,260	$4,898
No Active Preventive Treatment	$3,508			
Difference	$5,028	$4,115	$2,753	$1,391

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

Table E17. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Fremanezumab in Episodic Migraine Patients Who Previously Failed Current Preventive Therapy

	Average Annual Per Patient Budget Impact			
	Placeholder WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Erenumab	$3,830	$2,978	$2,408	$1,839
No Active Preventive Treatment	$1,244			
Difference	$2,586	$1,734	$1,164	$594

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