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Preventive drug treatments for adults with chronic migraine: a systematic review with economic modelling

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Abstract

Preventive drug treatments for adults with chronic migraine: a systematic review with economic modelling

Hema Mistry[1,2*] Seyran Naghdi[1] Anna Brown[3] Sophie Rees[4] Jason Madan[1] Amy Grove[3] Saval Khanal[3] Callum Duncan[5] Manjit Matharu[6] Andrew Cooklin[1] Aiva Aksentyte[1] Natasha Davies[1] and Martin Underwood[1,2]

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Background: Chronic migraine is a disabling condition, affecting 2–4% of adults globally. With the introduction of expensive calcitonin gene-related peptide monoclonal antibodies, it is timely to compare the clinical effectiveness and cost-effectiveness of preventive drugs for chronic migraine.

Objective: To assess the clinical effectiveness and cost-effectiveness of medications used for chronic migraine through systematic reviews and economic modelling.

Eligibility criteria: Randomised controlled trials of drug treatments for efficacy with > 100 participants with chronic migraine per arm; for adverse events > 100 participants with episodic or chronic migraine per arm. Previous economic analyses of preventive drugs for chronic migraine.

Data sources: Eight databases.

Reviews methods: Systematic reviews, network meta-analysis and economic modelling.

Outcomes: Monthly headache days, monthly migraine days, headache-related quality of life, cost-effectiveness.

Results: We found 51 individual articles, reporting 11 randomised controlled trials, testing 6 drugs (topiramate, Botox, eptinezumab, erenumab, fremanezumab, galcanezumab), versus placebo, on 7352 adults with chronic migraine. Calcitonin gene-related peptide monoclonal antibodies, Botox and topiramate reduced headache/migraine days by 2.0–2.5, just under two, or by less than 1.5 days per month, respectively. In the network meta-analysis, eptinezumab 300 mg and fremanezumab monthly ranked in first place in both monthly headache day and monthly migraine day analyses. The calcitonin gene-related peptide monoclonal antibodies were consistently the best choices for headache/migraine days and headache-related quality of life. Topiramate was very unlikely to be the best choice for headache/migraine days and headache-related quality of life when compared to calcitonin gene-related peptide monoclonal antibodies or Botox. We found no trials of the commonly used drugs, such as propranolol or amitriptyline, to include in the analysis.

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The adverse events review included 40 randomised controlled trials with 25,891 participants; 3 additional drugs, amitriptyline, atogepant and rimegepant, were included. There were very few serious adverse events – none of which were linked to the use of these medications. Adverse events were common. Most people using some calcitonin gene-related peptide monoclonal antibodies reported injection site issues; and people using topiramate or amitriptyline had nervous system or gastrointestinal issues.

The cost-effectiveness review identified 16 studies evaluating chronic migraine medications in adults. The newer, injected drugs are more costly than the oral preventatives, but they were cost-effective.

Our economic model showed that topiramate was the least costly option and had the fewest quality-adjusted life-year gains, whereas eptinezumab 300 mg was more costly but generated the most quality-adjusted life-year gains. The cost-effectiveness acceptability frontier showed that topiramate was the most cost-effective medication if the decision maker is willing to pay up to £50,000 per quality-adjusted life-year.

Our consensus workshop brought together people with chronic migraine and headache experts. Consensus was reached on the top three recommendations for future research on medications to prevent chronic migraine: (1) calcitonin gene-related peptide monoclonal antibodies and Botox versus calcitonin gene-related peptide monoclonal antibodies, (2) candesartan versus placebo and (3) flunarizine versus placebo.

Limitations: Topiramate was the only oral drug for which we were able to include data. We did not find sufficient quality evidence to support the use of other oral drugs.

Conclusions: We did not find evidence that the calcitonin gene-related peptide monoclonal antibodies are more clinically and cost-effective when compared to topiramate or Botox. We identified directions for future research these drugs might take.

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List of supplementary material

Report Supplementary Material 1 List of excluded studies for clinical effectiveness and adverse events reviews

Report Supplementary Material 2 Supplementary Information: The GRADE approach for rating the quality of estimates of treatment effect size

Report Supplementary Material 3 List of excluded studies in cost-effectiveness review

Report Supplementary Material 4 Supplementary Information: Consensus workshop

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/AYWA5297).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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List of abbreviations

ACE	angiotensin-converting enzyme
A&E	accident and emergency
AEs	adverse events
AMG334	erenumab
AWMSG	All Wales Medicine Strategy Group
BMI	body mass index
BNF	British National Formulary
BTA	onabotulinumtoxinA/botulinum toxin type A/Botox
CADTH	Canadian Agency for Drugs and Technology in Health
CEAC	cost-effectiveness acceptability curve
CGRP	calcitonin gene-related peptide
CEAF	cost-effectiveness acceptability frontier
CHD	chronic daily headache
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CM	chronic migraine
CrI	credible interval
CTCAE	Common Terminology Criteria for Adverse Events
DIC	deviance information criterion
ED	emergency department
EoI	expression of interest
EQ-5D	EuroQol EQ-5D
EVPI	expected value of perfect information
FIMQ	Functional Impact of Migraine Questionnaire
Fremanezumab-M	fremanezumab monthly
Fremanezumab-Q	fremanezumab quarterly
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HIT-6	headache impact test-6
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IBMS	International Burden of Migraine Studies
ICER	incremental cost-effectiveness ratio
ICHD	International Classification of Headache Disorders
ICHD-2	International Classification of Headache Disorders, version 2
ICHD-3	International Classification of Headache Disorders, version 3
ICTRP	International Clinical Trials Registry Platform
IM	intramuscular
ITT	intention to treat
IV	intravenous
MAb	monoclonal antibody
MD	mean difference
MHD	monthly headache day
MIDAS	Migraine Disability Assessment
MMD	monthly migraine day
MSQ	migraine-specific quality of life
MSQ-EF	migraine-specific quality of life – emotional function
MSQ-PR	migraine-specific quality of life – preventative role
MSQ-RR	migraine-specific quality of life – restrictive role
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMC	National Migraine Centre
OL	open label
ONS	Office for National Statistics
PBO	placebo
PHQ-9	Patient Health Questionnaire 9-item

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PICO	population, intervention, comparators, outcomes
PPI	patient and public involvement
PREEMPT	Participants in The Phase III REsearch Evaluating Migraine Prophylaxis Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	personal social service
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RoB	risk of bias
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SNRIs	serotonin noradrenaline reuptake inhibitors
SOC	system organ class
SUCRA	Surface Under the Cumulative Ranking Area
TAE	treatment-related adverse event
TSAE	treatment-related serious adverse event
U	units
UME	unrelated mean effect
WHO	World Health Organization
WPAI:SHP	Work Productivity and Activity Impairment – Specific Health Problem
WTP	willingness to pay

Plain language summary

What is the problem?

Chronic migraine is a disabling condition that can destroy work and family life. Treatments include cheap tablets (e.g. amitriptyline, propranolol and topiramate), Botox and expensive new drugs (the calcitonin gene-related peptide monoclonal antibodies). It is not known which of these drugs is the best choice.

What did we want to find out?

We wanted to find out which of these drugs works best. We wanted to know if they reduced the number of headache/migraine days and improved headache-related quality of life, how many side effects people experienced, and if they provided good value for the National Health Service.

How did we do this?

We first looked for research comparing these drugs to placebo (fake) drugs, and to each other. We then worked out which provide best value for money.

What did we find out?

Calcitonin gene-related peptide monoclonal antibodies reduced headache/migraine days by 2.0–2.5 days per month; Botox reduced headache/migraine days per month by around 1.9; and topiramate reduced headache/migraine days by 1.1–1.5 days per month. Many people taking topiramate or amitriptyline have nervous system and/or stomach/bowel side effects. Some people using calcitonin gene-related peptide monoclonal antibodies reported side effects associated with injections. Some calcitonin gene-related peptide monoclonal antibodies and Botox provide worthwhile benefits on headache-related quality of life. We were not able to identify any studies of sufficient quality to assess the effectiveness of other oral drugs.

The best value drug was topiramate which gave better health outcomes at a lower cost than the placebos.

What does this mean?

After sharing the results with a panel of people with chronic migraine and headache experts, we identified a need for new studies comparing commonly used cheap oral drugs with placebo, Botox and calcitonin gene-related peptide monoclonal antibodies.

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Scientific summary

Background

Chronic migraine is a profoundly disabling condition and affects 2–4% of the world's adult population. It is defined as headaches on 15 days or more a month with features of migraine on at least 8 of those days. Since 2020, expensive calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) have become established as specific treatments for people with chronic migraine who have failed to improve with other medications. Little is known about the effectiveness of these drugs when compared with each other, or with other well-established, cheaper, oral drugs used to treat chronic migraine. Therefore, it is timely to compare the clinical effectiveness and cost-effectiveness of these medications to treat chronic migraine. We set out to address the following research question:

What is the clinical effectiveness and cost-effectiveness of prophylactic drug treatments for people with chronic migraine?

Objectives

Our overall aim is to produce evidence needed for people with chronic migraines and their doctors to make more informed decisions about prophylactic medications for chronic migraine.

Our objectives were:

- What is the comparative effectiveness of prophylactic drugs for chronic migraine?
- What are the comparative incidences of adverse events (AEs) of prophylactic drugs used for migraine?
- What is known about the cost-effectiveness of prophylactic drugs for chronic migraine?
- Which prophylactic drugs for the management of chronic migraine are the most cost-effective?
- Based on our findings, what should the research recommendations be?

Methods

Systematic reviews of trial evidence on:

1. The clinical effectiveness of prophylactic medications for chronic migraine; analyses included headache days, migraine days and headache-related quality of life: migraine- specific quality of life (MSQ); headache impact test-6 (HIT-6). Only randomised controlled trials (RCTs) with at least 100 people per arm were included. We report the comparative effectiveness using a network meta-analysis (NMA) for these different outcomes to see which drug was the most 'effective'.
2. To identify the comparative incidence of AEs of prophylactic drugs used for chronic or episodic migraine. RCTs with at least 100 people per arm were included.
3. The cost-effectiveness studies of prophylactic drugs used for treatment of chronic migraine.

We developed an economic model comparing the cost-effectiveness of prophylactic drugs for chronic migraine for the adult population from a National Health Service (NHS) and personal social services (PSS) perspective. The base-case analysis used a 2-year time horizon, with a starting age of 30 years for the patient cohort. Health states in the model were based on effectiveness data [reduction in the mean difference (MD) in monthly headache days (MHDs)] from the NMA. Costs are in 2021–2 prices and

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utilities were estimated based on EuroQol-5 Dimensions, five-level version (EQ-5D-5L) scores from the CHESS trial using the Hernandez-Alava crosswalk algorithm. Cost-effectiveness was measured in terms of an incremental cost per quality-adjusted life-year (QALY) gained [Institute for Clinical and Economic Review (ICER)]. Probabilistic sensitivity analysis (PSA) was undertaken to account for uncertainty in model parameters. Uncertainty around the cost-effectiveness of the various medications showing which is the preferred strategy is presented using a cost-effectiveness acceptability frontier (CEAF).

At the end of the project, we held a consensus workshop bringing together people with chronic migraine and clinicians and other health professionals who are experts in chronic migraine. We presented the findings from our reviews, NMA, the economic model and some potential recommendations. We then split into groups (mixed with health professionals and participants) and asked them to discuss our suggested research recommendations, identify any other recommendations, and rank these recommendations in terms of priority. We then had another breakaway session, where all participants with chronic migraine met and all health professionals met. Finally, everyone was bought back together to discuss their rankings as a wider group and to reach a consensus using anonymous polling.

Results

The clinical effectiveness review focused on prophylactic medications which might be used in the UK for the prevention of chronic migraine. We found 11 RCTs reported across 51 individual publications, involving 7352 adult participants with chronic migraine, which showed that all pharmacological treatments for all outcomes of interest were beneficial in preventing migraine when compared to placebo. There were no trials of sufficient quality of the commonly used drugs, such as amitriptyline, candesartan, flunarizine or propranolol. Overall, the CGRP MAbs reduced headache/migraine days by 2.0 to 2.5 days per month. The most effective medication in reducing MHDs was eptinezumab 300 mg which reduced MHDs by 2.46 [95% credible interval (CrI) 3.24 to −1.67] days. The most effective medication in reducing monthly migraine days (MMDs) was fremanezumab monthly which reduced MMDs by 2.76 (95% CrI −3.36 to −2.15) days. Botox (BTA) reduced MHDs by 1.87 (95% CrI −2.55 to −1.18) days per month and MMDs by 1.96 (95% CrI −2.69 to −1.24) days per month. Topiramate was the least effective, prescribable drug and only reduced headache/migraine days by less than 1.5 fewer headache/migraine days per month. The NMA results showed that eptinezumab 300 mg had the highest probability ranking to reduce MHDs and MMDs – Surface Under the Cumulative Ranking Area (SUCRA) was 0.88 and 0.77, respectively.

The CGRP MAbs provided a worthwhile improvement on the HIT-6 measure of headache-related quality of life (eptinezumab 300 mg reducing the HIT-6 by a score of 3.22 points); BTA had a worthwhile effect on the HIT-6 measure, reducing the HIT-6 score by 2.10 points; and there was no convincing benefit of topiramate on the MSQ measure. Galcanezumab 120 mg provided the best improvement in quality of life for the preventative role dimension of migraine-specific quality of life (MSQ-PR) (MD 6.97, 95% CrI 3.79 to 10.24, SUCRA 0.88), but for two other dimensions of the MSQ, erenumab 140 mg was superior to other treatments: for migraine-specific quality of life-restrictive role (MSQ-RR) – MD: 7.28, 95% CrI: 3.05 to 11.65, SUCRA 0.75, and for migraine- specific quality of life-emotional function (MSQ-EF) – MD: 8.89, 95% CrI: 3.20 to 14.55, SUCRA 0.79.

The results from the quality assessment using the revised Cochrane risk-of-bias (RoB 2) tool for RCTs found that approximately 46% of the included RCTs in this review had low RoB and 36% of the RCTs had some concerns of bias.

The incidence of AEs and serious adverse events (SAEs) review used evidence from 40 RCTs reported across 67 articles, which investigated pharmacological interventions to manage chronic or episodic migraine. These trials included 25,891 participants and 3 additional drugs were included – amitriptyline, atogepant and rimegepant. There were very few SAEs – none of which were linked to the use of these

drugs. Non-SAEs were common, and results suggested that all the pharmacological medications included in this review were found to be tolerable. There were differences in the incidence of AEs between the CGRP MAbs, with most people using fremanezumab and one in four people using galcanezumab reporting injection site issues. These issues were much less common in people using eptinezumab or erenumab. Most people using topiramate or amitriptyline had nervous system or gastrointestinal side effects; topiramate was also linked to a higher prevalence of psychiatric disorders; and AEs related to BTA were uncommon.

The cost-effectiveness review identified nine peer-reviewed journal articles and seven published reports of chronic migraine prophylactic medications in the adult population. All articles were model-based evaluations, and none were trial-based economic evaluations. We found that although these newer drugs (BTA and CGRP MAbs) were more costly than the oral preventatives, they were however deemed cost-effective. Generally, the articles were classed as high quality when appraised by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting tool.

We developed a Markov (state-transition) model to assess the cost-effectiveness of different pharmacological medications to treat or prevent chronic migraine in the adult population. Our base-case deterministic results showed when comparing each of the medications separately against placebo, topiramate dominated placebo (cheaper and more effective); and each of the other medications, when compared separately, were more expensive than placebo; however, they generated more QALYs than placebo. The best value medication when compared with placebo was BTA, with the cost per QALY around £25,000.

When comparing all medications together, the deterministic results showed that topiramate was the least costly option and had slightly more QALY gains than placebo, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains. Most medications were eliminated due to dominance. The ICER between BTA and topiramate and the ICER between eptinezumab 300 mg and BTA were not within plausible cost-effectiveness thresholds. Probabilistic results were similar to deterministic results. The CEAF showed that when comparing all medications topiramate was the most cost-effective medication if the decision maker is willing to pay up to £50,000 per QALY. None of the CGRP MAbs represented good value for money in this comparative analysis.

Extensive sensitivity analyses showed that when MHDs is used as an outcome measure, the results were generally in line with the base-case results. The main exception was when using MMDs as an outcome measure instead of MHDs, fremanezumab monthly generated more QALY gains than eptinezumab 300 mg; the ICERs between the plausible options, once any dominated options were removed, were not within plausible cost-effectiveness thresholds.

Our consensus workshop brought together 8 participants with chronic migraine and 11 health professionals with expertise in chronic migraine to set research priorities for preventive drugs for chronic migraine. Each of the small groups found that the need for trials of cheaper, oral medications, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors (SNRIs) when compared with placebo were ranked highly; and for trials comparing the medications with each other, the CGRP MAbs and BTA separately or in combination with each other were ranked highly.

The final (anonymised) rankings showed that the top three research priorities versus placebo were: (1) candesartan, (2) flunarizine and (3) melatonin; and for medications compared with each other were: (1) CGRP MAbs and BTA versus CGRP MAbs, (2) CGRP MAbs versus BTA and (3) a multi-arm trial of CGRPs MAbs receptor (erenumab) versus CGRP MAbs ligand (eptinezumab, fremanezumab and galcanezumab).

In terms of priority, a consensus was established regarding the three most recommended medication comparisons for treating chronic migraine: (1) CGRP MAbs and BTA versus CGRP MAbs, (2) candesartan compared to placebo and (3) flunarizine in comparison to placebo.

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Discussion and conclusions

Of the treatments included in the NMA, the CGRP MAbs overall were consistently the best choices for headache days, migraine days and headache-related quality of life. BTA was less likely than CGRP MAbs to be the best choice for headache days, migraine days and headache-related quality of life. Topiramate was very unlikely to be the best choice for headache days, migraine days and headache-related quality of life when compared to CGRP MAbs or BTA. The economic model found that topiramate was the best value drug if you are prepared to pay up to £50,000 per QALY. It is likely that CGRP MAbs are likely to be cost-effective in people who have failed treatment with BTA. At the workshop, general consensus was agreed on the top three choices of medication for chronic migraine.

Topiramate was the only established oral drug for which we were able to include data. It is disappointing that we did not find a sufficient quality evidence base to support the use of drugs, such as amitriptyline, candesartan, flunarizine and propranolol that are recommended by National Institute for Health and Care Excellence (NICE) and/or Scottish Intercollegiate Guidelines Network (SIGN). Our consensus meeting identified the need for trials comparing candesartan and flunarizine with placebo as the top priorities for placebo-controlled trials. Only for topiramate can we make any observations for how this may compare with CGRP MAbs. The CGRP MAbs appear to be clinically superior, but even so topiramate, in spite of its high incidence of AEs, represents the best value for money. Within the current care pathway, it is unlikely that CGRP MAbs will be recommended ahead of topiramate without a very substantial reduction on price. What is perhaps a more critical decision point is whether BTA or CGRP MAbs might be preferred as the first choice after failure of oral medication. Our findings support continuing with the current care pathway since our CEAF found that only topiramate met an acceptable threshold. Data from our health economics review, however, do support the use of CGRP MAbs after failure of BTA for chronic migraine.

Our consensus group identified the direct comparison of BTA and CGRP MAbs as a key research question. They also identified the question of whether these drug effects might be additive. The effect sizes, in terms of mean monthly migraine/headache days for each of these drugs, are at best modest, the largest being 2.76 days for fremanezumab monthly dose. As these drugs work through different pathways, it might be that more substantial effects are possible. Adding together the effects of BTA and a CGRP MAb, assuming no negative interaction, might have a mean effect size of 4–5 days that would be transformative for many people with chronic migraine. Our consensus group identified the comparative, and additive, effects of BTA and CGRP MAbs as high priority research questions.

In conclusion, we have summarised the existing clinical and cost-effectiveness data on preventive drugs for chronic migraine and identified which directions future research on these drugs might take. We did not find convincing evidence that the CGRP MAbs are more clinically effective and cost-effective compared to topiramate or BTA.

Study registration

This study is registered as PROSPERO CRD42021265990, CRD42021265993 and CRD42021265995.

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Chapter 1 Introduction

Description of health problem

Migraine is the second most common disabling disorder in the world[1] and is the leading cause of years lived with disability in those aged 15–49.[2] In the UK, migraine affects 15% of adults. Women are three times more likely as men to have migraine.[3] It is also more common in young adults (late teens to 50s) with work and family commitments.[4] As such, migraine has a huge economic and social impact, costing the UK over £1.5 billion per year due to absence from work or school,[4] and has substantial impacts in professional and social settings.[5] Our patient-partners describe it as a condition that *'redefines, and can destroy, work and family life'*.

Migraine is categorised into episodic and chronic migraine. Episodic migraine is diagnosed in people with migraine who have less than 15 headache days a month.[6] The definition of chronic migraine has changed over time. The Third International Classification of Headache Disorders (ICHD-3) defines chronic migraine as headaches on 15 days or more a month, for more than 3 months with features of migraine on at least 8 of those days.[6] The main focus of this report is on chronic migraine.

In 2011 the World Health Organization (WHO) called for action to address the 'worldwide neglect' of headache disorders.[7] Yet migraine remains a leading cause of global disease burden.[2,8,9] Around 2–4% of the world's population meet an epidemiological definition of chronic headache.[10,11] In a 2022 trial of supportive self-management for those living with chronic headache, 99% (727/736) of those assessed for inclusion had migraine.[12] This group has the potential to benefit from effective prophylactic drugs to prevent migraine attacks. A 2017 meta-ethnography of the lived experience of people with chronic headache (four studies) identified that chronic migraine had a profound effect on people's lives, similar to other pain conditions. Key themes identified in the findings of the meta-ethnography included the loss of control over one's life, strained relationships and social exclusion due to chronic headache.[13] The burden on family, and the care burden for those living with a person with migraine, increases with headache frequency.[14]

An evidence synthesis and an economic model on prophylactic treatments for chronic migraine is, therefore, needed to address this evidence gap and to generate recommendations.

Current treatments and existing evidence

The current state of the evidence for migraine prevention is poor, making it difficult for patients and clinicians to make decisions about which medications to consider. Various pharmacological treatments are available for the prevention of migraine. Oral medications are taken regularly (usually daily), regardless of whether a patient has a migraine at that point in time, with the aim of trying to reduce the frequency and severity of migraine attacks. For oral medications, the current evidence base for chronic migraine comes almost exclusively from data extrapolated from trials on episodic migraine. Evidence regarding the cost-effectiveness of different pharmacological treatments is also lacking.

Prophylactic medications used to treat chronic migraine include topiramate, propranolol, tricyclic antidepressants, candesartan and valproate. Topiramate and propranolol are recommended by NICE and SIGN. The evidence contained in these guidelines is of mixed quality.[15,16] Weaker evidence supports the use of amitriptyline [recommended by National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN)], and for candesartan and valproate (recommended by SIGN, but not by NICE). The NICE recommendation for amitriptyline is based on evidence comparing amitriptyline with topiramate, but not with placebo. There remains uncertainty about the effectiveness

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of amitriptyline as a prophylactic treatment.[17] Other prophylactic medications to treat chronic migraine in the UK include botulinum toxin type A (BTA), serotonin noradrenaline reuptake inhibitors (SNRIs) antidepressants, angiotensin-converting enzyme (ACE) inhibitors, other angiotensin receptor blockers, other beta-blockers, calcium channel blockers and pizotifen.

The most recent evidence on this topic was produced by Jackson *et al.* in 2015.[18] They pooled evidence from numerous randomised controlled trials (RCTs) on oral prophylactic medications for both chronic migraine and episodic migraine to explore potential differences for continuous and dichotomous outcomes. Their systematic review identified 13 trials of oral medications (*n* = 903, range 7–306, mean 69) which included people with chronic migraine.[19–31] Jackson *et al.*[18] concluded that '*these comparisons have been somewhat haphazard, and many important potential comparisons have not been made*'. The authors of a 2023 overview of systematic reviews on the use of antidepressants for pain excluded this review because of concerns about trial selection and data analysis.[32] This 2015 review needs to be updated using methods which are able to synthesise the overall evidence for a broad range of prophylactic medications for use in people with chronic migraine, for example, using a network meta-analysis (NMA).[18] NMA extends beyond the traditional pairwise meta-analysis comparison to multiple interventions and provides a more precise estimate of a treatment effect size by combining both direct (RCT of A vs. B, or B vs. C) and indirect (A vs. C compared indirectly via the common comparator B) evidence. A NMA also allows estimation of treatment rankings which can assist policymakers, clinicians and patients to select the best treatment options.[33]

There has been an increase in the availability of the calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs), usually given as monthly injections, such as erenumab, fremanezumab and galcanezumab.[34–37] These treatment options are more expensive than oral prophylactic medications. NICE recommend BTA or a CGRP MAb after patients have failed three oral medications.[38–42]

A 2020 study by Forbes *et al.* [43] compared CGRP MAbs with placebo in the seven chronic migraine RCTs (*n* = 5292) and found that the additional pooled reduction in monthly migraine days (MMDs) from CGRP treatment was 2.24 days [95% confidence interval (CI) 1.82 to 2.65]. They further estimated that 68% of the apparent reduction in headache days in the intervention groups was due to contextual effects. In other words, participants in the control group would expect an average reduction in monthly headache days (MHDs) of four and half days, with the intervention group gaining an additional reduction of two and a quarter days, which is six and three-quarter days in total. Based on these data it is difficult to judge clinically if the treatment has been effective for this trial population as a whole and it is unclear how the effect sizes for CGRP MAbs compare with the effect size of more established oral medications or BTA injections.

Overall, the evidence of oral pharmacological treatments for adults with chronic migraine is of poor quality and extrapolated almost exclusively from trials on episodic migraine. As mentioned above, in the 2020 review on CGRP MAbs only 7 of the 21 included trials were on chronic migraine.[43] We cannot assume that medications shown to reduce the number of headache days in people with episodic migraine will have a positive effect on the long-term disability caused by chronic migraine. Therefore, this report aims to provide an up-to-date overview of the relative benefits, harms and costs of prophylactic medications to treat chronic migraine. Without this review, the only evidence available to decision-makers and guideline producers will be for expensive CGRP MAbs, which have a modest additional effect size compared to placebo.[44,45] For example, the use of erenumab 70 and 140 mg only reduced the number of MMDs by 2.46 and 2.45, respectively, compared with placebo.[45]

Economic implications and current costs

As migraine is a leading cause of global disease burden,[1] the costs associated with migraine for healthcare services and to patients and their families are significant. A 2019 review on the costs of migraine found that the direct and indirect healthcare costs of chronic migraine are 3–4 times as high

as episodic migraine.[46] For example, in the USA, the total cost for episodic migraine was $2649/year and the total cost for chronic migraine was $8243/year;[47] and, in Europe the direct costs for episodic migraine was €746/year and for chronic migraine this was €2427/year.[48] This cost may be partly due to the nature of the disease itself, as people with chronic and episodic migraine combined miss, on average, 10.2 work-equivalent days per year (absent on 4.4 days and reduced productivity on 11.4 days) due to headache-related disability.[46] Higher work-related difficulties are associated with chronic migraine versus episodic migraine (lost work days: 3–4 days vs. 1 day, respectively).[49] The burden on family, and the care burden for those living with a person with migraine, increases with headache frequency.[14]

There are increasing pressures on the NHS to provide the newer, and more expensive, treatments when oral prophylactic medications have failed.[34–37,50] The British National Formulary (BNF) price per patient (excluding administration costs) as of December 2022 for a typical 3-month course of the CGRP MAbs – erenumab, fremanezumab and galcanezumab – are £1160, £1350 and £1800 respectively,[51] whereas a BTA injection vial for a 12-week cycle costs £276.40 and the oral medications amitriptyline, candesartan, propranolol and topiramate cost on average per patient, £2.44–3.72, £4.28–6.28, £11.74–11.76 and £3.42–11.64 for 3-month treatment, respectively.[51] It is important for both patients and healthcare professionals to know the comparative effectiveness and cost-effectiveness of these older oral medications and the newer injectable treatments.

Decision problem

The commissioning brief provided the topic context:

> *SIGN guidance states that the global prevalence of migraine is approximately one in seven. The Global Burden of Disease study found migraine to be third in terms of the most common cause of worldwide disability in the under 50s. They estimate that migraines cost the UK around £3 billion per year in terms of healthcare, loss of productivity and disability.[9] Chronic migraine is defined (by NICE/SIGN) as headaches that occur 15 or more days per month, of which 8 or more are migraines (with or without aura) for more than 3 months.*

This report presents the first evidence to compare the clinical and cost-effectiveness of prophylactic medications to treat chronic migraine for adult patients. The findings of this report will help to inform decisions made by policy-makers, clinicians and patients on the most appropriate course of drug treatment(s) for adult patients who suffer from chronic migraine.

Our aim was:

- To review and compare the clinical and cost-effectiveness of drug treatments for adults with chronic migraine.

To fulfil the study aim, five research questions were identified which align to each of the report chapters:

- What is the clinical effectiveness of prophylactic drugs for chronic migraine? (see *Chapter 2*)
- What are the comparative incidences of adverse events (AEs) of prophylactic drugs used for migraine? (see *Chapter 3*)
- What is known about the cost-effectiveness of prophylactic drugs for chronic migraine? (see *Chapter 4*)
- Which prophylactic drugs for the management of chronic migraine are the most cost-effective? (see *Chapter 5*)
- Based on our findings, what should the research recommendations be? (see *Chapter 6*)

Study population, intervention, comparators, outcomes (PICOs) and inclusion and exclusion criteria for the sub-questions are presented in each subsequent chapter.

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Chapter 2 Clinical effectiveness review and network meta-analysis

Research question 1: What is the clinical effectiveness of prophylactic drugs for chronic migraine?

Introduction

This chapter presents a systematic review of published RCTs of pharmacological drug treatments for adult patients with chronic migraine. Findings from this systematic review will inform an overall synthesis of the effect of prophylactic medications for chronic migraine using a NMA.

Methods

The clinical effectiveness review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews[52] and the Cochrane Handbook for Systematic Reviews of Interventions.[53] The protocol for the clinical effectiveness review has been registered in the PROSPERO (international prospective register of systematic reviews) database a priori. The registration number is CRD42021265990.

Search strategy

The search strategy for the clinical effectiveness review (see *Chapter 2*) and the AEs review (see *Chapter 3*) was constructed by an information specialist (AB), in consultation with the project team. The search strategy was initially constructed in MEDLINE, using both free text keywords and thesaurus (MeSH) terms for migraine/headache and the prophylactic drug interventions of interest, with the addition of a search filter for RCTs. No date or language limits were applied. The MEDLINE strategy was checked by another information specialist (not involved in the project) for any omissions or errors in spelling, search syntax, structure and use of MeSH, before being translated for the other bibliographic databases. Full search strategies can be found in *Appendix 1*, *Table 22*.

The following databases and clinical trials registers were searched between 8 and 15 September 2021:

- MEDLINE All, 1946 to 7 September 2021 (via Ovid);
- EMBASE Classic + EMBASE, 1947 to 7 September 2021 (via Ovid);
- Cochrane Central Register of Controlled Trials (CENTRAL), Issue 9 of 12, September 2021 (via Cochrane Library);
- Science Citation Index Expanded, 1970 to present (via Web of Science);
- Global Index Medicus (all regional indexes, via WHO website);
- ClinicalTrials.gov;
- International Clinical Trials Registry Platform (ICTRP) (via WHO).

Records retrieved by the database and the trials register searches were exported into EndNote X9, to enable identification and systematic removal of duplicates.[54]

An additional pragmatic search in MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews was performed to identify recent systematic reviews of prophylactic migraine treatments. The reference lists of the outputs of this search, and those also of the NICE, SIGN and American Headache Society guidelines, were checked for relevant literature. Authors of key studies were contacted and asked for details of any articles (e.g. reports, papers published or unpublished) that may not have been captured in

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our search. We performed forward and backward citation tracking from all included papers using Web of Science Core Collection (and Google Scholar where papers were not available in Web of Science).

Following consultation with the study team clinical experts, we conducted a further round of searches for three medicines not previously included in the search strategies: riboflavin, magnesium and CoQ-10. Our clinical experts suggested that these medicines are currently used within the UK. This supplemental search followed the same process as initial searches and was conducted in February 2022. Searches for all the prophylactic drug interventions of interest were updated in November 2022 to identify any additional publications that had become available. Searches to check for any retractions, errata or similar, relating to included studies, were also undertaken at this time. Full details of all searches are provided in *Appendix 1*.

Assessing relevance and inclusion of studies

The first round of screening was based on title and abstract and was conducted by two reviewers (AB, SN). The second phase of screening was performed according to PICO criteria (see *Box 1* for inclusion criteria and *Box 2* for exclusion criteria). At this stage, the abstracts of the retrieved studies were reviewed independently by two out of four reviewers (MU, SN, AA, ND). The full texts of the remaining studies were retrieved, and the same combination of the reviewers conducted an additional round of full-text screening according to the pre-specified inclusion/exclusion criteria. For both the clinical effectiveness review (see *Chapter 2*) and AEs review (see *Chapter 3*), the screening process was the same.

BOX 1 Eligibility criteria – inclusion criteria

Inclusion criteria

Study design

- RCTs in any setting.
- RCTs with more than 100 participants per arm. (We excluded studies with fewer than 100 participants per arm, in each pairwise comparison, to avoid risk of low-quality studies contributing disproportionally to our overall conclusions.)

Population

- Adults (≥ 18 years old) with chronic migraine.

Intervention

- Available or anticipated to be available pharmacological medications in the UK: CGRP MAbs, BTA, antidepressants, ACE inhibitors and angiotensin receptor blockers, beta-blockers, calcium channel blockers, pizotifen, flunarizine and anti-convulsants (topiramate, valproate/divalproex, gabapentin).

Comparator

- Placebo, or
- Usual care, or
- Other prophylactic drugs.

Primary outcome(s) of interest

- Headache days.
- Migraine days.

Secondary outcome(s) of interest

- Headache-related quality of life.
- Migraine-specified quality of life.
- Headache intensity and duration.
- Health service activity.
- Days lost from usual activities.
- Any other reported outcomes.

BOX 2 Eligibility – exclusion criteria

Exclusion criteria

Study design

- Non-randomised trials, quasi-randomised trials, observational studies (e.g. case reports and case series), subgroup analysis and other designs.
- RCTs with fewer than 100 per arm.

Population

- Children and young people aged < 18 years.
- Participants with menstrual migraine, acute migraine, abdominal migraine, vestibular migraine or any other conditions-related migraine.
- Trials that examined participants with other primary headaches including tension-type headaches, cluster headaches and secondary headaches.

Intervention and comparator

- Studies comparing cognitive–behavioural therapy, psychological interventions, exercise, dietary and relaxation.
- Studies which were dose–response trials.
- Studies comparing different preparations of the same drug in the absence of placebo.
- Laboratory studies without clinical outcomes.
- Chinese traditional medicines, that is, herbal medicine/drugs and other herbal remedies which are not prescribed in the UK.
- Drugs which are not prescribed by NHS or recommended by NICE or Scottish Medicines Consortium (SMC).

Outcome(s) of interest

- Non-human outcomes.
- Outcomes with insufficient information.

We excluded studies with fewer than 100 participants per arm to ensure that we included better-quality studies and to avoid loss of precision on our NMA by including heterogenous studies.[55,56] Studies with fewer than 200 participants will not have been adequately powered to show a standardised mean difference of less than 0.5. Smaller studies are also typically older and do not use an adequate definition of chronic migraine and are of poor quality.

Data extraction for systematic review and network meta-analysis

Data for included studies were extracted by one reviewer (SN) and 20% were randomly checked for accuracy by another reviewer (SK). Data extraction forms were developed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) to capture the following information: ClinicalTrials.gov identifier (National Clinical Trial number), study name, study characteristics, patient demographics including baseline characteristics, intervention and comparator details, outcome(s) of interest with relevant data and measure of variability, time point of outcome measurements, duration of treatments, AEs and serious adverse events (SAEs).

Means and standard deviations (SDs) for continuous outcomes were extracted. If SDs were not provided, we calculated them from standard errors, CIs or other measures.[57] We also contacted authors by e-mail to ask for the original data in the event of any missing data.

Assessment of risk of bias for included trials

The Cochrane risk-of-bias (RoB 2) tool for randomised trials[58] was applied for assessing the risk of bias of all trials independently by two members (SN, SK). The tool was used to determine whether there was high, some, or low risk of bias in the following domains: (1) arising from the randomisation process, (2) due to deviations from the intended interventions (effect of assignment to intervention), (3) missing outcome data, (4) measurement of the outcome and (5) selection of the reported result. In this approach, the rating low risk of bias 'is judged to be at "low risk of bias" for all domains', and the trial 'is judged to raise "some concerns" in at least one domain for this result, but not to be at "high risk of bias" for other

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domains, whereas the trial 'is judged to be at "high risk of bias" in at least one domain' or the trial 'is judged to have "some concerns" for multiple domains in a way that substantially lowers the confidence in the result'.[58]

Assessment of certainty in evidence for included trials

We assessed the degree of certainty of evidence, all comparisons for each outcome, by using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework independently by two members (SN, SK).[59] Any discrepancies in any of the screening steps were referred to the third reviewer (MU). In GRADE, RCTs were considered as a high quality of evidence (where authors have a lot of confidence that the true effect is similar to the estimated effect) to very low-quality evidence (where authors believe that the true effect is probably markedly different from the estimated effect). There are five domains for rating down GRADE including: study limitations (risk of bias), imprecision, inconsistency, indirectness and publication bias. There are three domains for rating up GRADE including: large magnitude of effect, dose–response gradient, and all plausible confounding.

Outcomes of interest

1. **Monthly headache days:** As reported in the original papers.
2. **Monthly migraine days:** As reported in the original papers.
3. **Migraine-specific quality of life (MSQ):** The MSQ version 2.1 is a 14-item questionnaire that measures a patient's quality of life over the last 4 weeks across three domains: migraine-specific quality of life-restrictive role function (MSQ-RR), seven items that assess the functional impact of migraine through limitations on a patient's daily work and social activities; migraine-specific quality of life-preventive role function (MSQ-PR), four items that measure the impact of migraine through prevention of daily work and social activities; and migraine-specific quality of life-emotional function (MSQ-EF), three items that evaluate the emotional impact on migraine. The score ranges from 0 to 100, with a higher score indicating better quality of life.[60]
4. **The headache impact test-6 (HIT-6):** The HIT-6 consists of six items: pain, social functioning, role functioning, vitality, cognitive functioning and psychological distress. There are five responses to each of the six items: 'never', 'rarely', 'sometimes', 'very often' or 'always'. These responses are summed together to produce a total score for the HIT-6. A lower score (49 or less) is categorised as having little or no impact and a higher score (60–78) is categorised as having a severe impact.[61]
5. **EuroQol-5 Dimensions, five-level version (EQ-5D-5L):** The EQ-5D-5L descriptive system is a preference-based health-related quality of life (HRQoL) measure with five dimensions that include mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each dimension assessed at five levels: from no to extreme problems.[62]
6. **Migraine Disability Assessment (MIDAS):** The instrument was developed to assess headache-related disability for migraine patients over a 3-month recall period.[63] The questionnaire contains five questions regarding the number of days of missed work/school, reduced productivity at work/school, missed household work, reduced productivity in household work, and missed family and/or social activities. The MIDAS score is calculated by summing the five items. Higher scores depict increased disability due to headache. The total MIDAS score can be categorised according to disability: 0–5, minimal or infrequent disability; 6–10, mild or infrequent disability; 11–20, moderate disability; and 21+, severe disability.[63]
7. **Work Productivity and Activity Impairment – Specific Health Problem (WPAI:SHP).** The WPAI:SHP questionnaire measures the effect of different health conditions on work productivity, generating scores for absenteeism, presenteeism, absenteeism plus presenteeism, and activity impairment outside work.[64] WPAI:SHP is a version of Work Productivity and Activity Impairment that can be modified for use with a specific disease, such as migraine.[64]
8. **Patient Health Questionnaire 9-item (PHQ-9):** The PHQ-9 is a self-administered instrument for screening, diagnosing, monitoring and measuring the severity of depression over the last 2 weeks. Each question is scored from '0' (not at all) to '3' (nearly every day). The total score for PHQ-9 is obtained by summing the score for each question.[65]

9. **Functional Impact of Migraine Questionnaire (FIMQ):** The FIMQ is a 20-item questionnaire that measures patient-relevant impacts of migraine in the past 7 days across three domains: activity impairment (14 items), emotional functioning (3 items) and cognitive functioning (3 items). Individual items are then transformed to a 0–100 scale, with higher scores indicating a greater level of migraine impact.[66]

Selection of data and synthesising data for the network meta-analysis

Network meta-analysis is a methodology that simultaneously combines three or more interventions in a single analysis using data from several studies. Results for each pairwise comparison combine both the direct evidence in primary studies and the indirect evidence, which has not been made directly within the studies to form a network.[67] In other words, a NMA provides an estimation of treatment effect size for each pair of interventions, regardless of whether they have been compared directly in a RCT or not.[67] In addition to facilitating comparisons between interventions, NMA provides a ranking of the interventions based on their effectiveness. This can help decision-makers choose the most suitable and effective treatments.[68]

The stepwise feasibility framework was used to ensure that the underlying assumptions are systematically explored, and also to ensure that pooling and comparing the treatment effects for a particular research question are transparent.[69] It comprises of four steps to illustrate the heterogeneity and differences within or between direct treatment comparisons in terms of treatment and outcome characteristics, the study and patient characteristics, baseline risk and observed treatment effects.[69]

We conducted a NMA for those outcomes which were provided data for more than three interventions to obtain the treatment effect size for the clinical effectiveness review.

Two different NMA models were conducted:

- Fixed-effects model – this model assumes that all studies included in a NMA are estimating a single true underlying effect. However, if there is significant variation in the effect sizes, known as statistical heterogeneity, then the fixed-effects model may not be appropriate.
- Random-effects model – this model assumes that the estimated treatment effects observed across studies can differ due to both actual differences in the treatment effect in each study, as well as differences in sampling.[70]

We chose between the different NMA models by using the posterior mean deviance as an indicator of model fit and the deviance information criterion (DIC). DIC is a metric used to assess the goodness of fit of a statistical model while also taking into account its complexity. It penalises models for their complexity and therefore favours simpler models over more complex ones.[71] DIC differences of three or more are considered meaningful between models.[72] When both model results were similar, we chose the results from the most parsimonious model.

Network plots were created for each analysed outcome. The node sizes of the network plots are proportional to the number of participants randomised to each of the interventions, whereas the thickness of the edges (lines) is proportional to the number of participants contributing to that comparison.[73] Stata SE17 was used to generate the forest plots for each intervention's comparison with placebo as the reference treatment.[74] The comparisons of all interventions were interpreted using leagues tables showing all pairwise comparisons with associated 95% credible intervals (CrIs).

In our review, all outcomes are presented in continuous format (change from baseline). The calculated point estimates were mean differences (MDs) with their associated 95% CrIs. We considered follow-up periods of 12 and 16 weeks as a measurement time point for all outcomes, because most of the interventions in the included trials had reported outcomes at week 12 or 16. The only exception to this was the data for BTA as most of their outcomes were reported at week 24. Hence, data for BTA are

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evaluated in a longer time frame of 6 months. Where outcome data were presented for multiple time points, we took the data closest to 3 months follow-up as the main time point.

We excluded studies that had insufficient information about the mean change from baseline (SD) for each outcome per arm [e.g. in the absence of the mean change from baseline, we calculated it by subtracting the post-treatment value from the baseline. However, we were not able to produce the related SDs for those mean change because calculating the SDs requires some more data (e.g. 95% CI, or at least *p*-value according to the Cochrane Library guidance)]. We used a fixed-effects approach to the meta-analyses.[75] Statistical heterogeneity was quantified using the between-study SD and Tau^2 or I^2-statistic. The between-study SD gives a direct measure of variance in the treatment effect across studies,[76,77] while the I^2-statistic is used to quantify the percentage of variation in effect estimates across studies that is due to heterogeneity rather than chance. In other words, it measures the proportion of variance across studies that can be attributed to differences in population characteristics.[78,79]

The statistical analyses were conducted within a Bayesian framework using multinma package[80] in R software version 4.1.3.[81] We estimated the posterior densities using Markov Chain Monte Carlo (MCMC) simulations; there were four Markov chains with 4000 iterations for each chain. All baseline and intervention effect parameters were given flat (uninformative) normal (0, 1000) priors and the between-study SD flat uniform distributions with an appropriately large range given the scale of measurement. The generalised linear model settings for continuous was a normal link.[71] We assessed the convergence of the Markov chains by using the potential scale reduction factor and examining the history and autocorrelation plots for each estimated parameter.[82]

Intervention ranking

To rank the interventions, we calculated the probability of each intervention being the best, second best, and so on. In addition, we used the Surface Under the Cumulative Ranking Area (SUCRA) values (ranging from 0 to 1) to summarise the probabilities of treatment ranking. A higher SUCRA value indicates a greater likelihood of a therapy being ranked at the top.[83] The validity of the NMA depends on the main assumption that there is no effect modification of the pairwise intervention effects or similarity of the prevalence of effect modifiers in the different studies. This key assumption has been considered for exchangeability, transitivity, similarity and consistency.[84,85]

To determine the overall consistency of each network, we compared the posterior mean residual deviance, the DIC, and the between-study SD for both the NMA model (consistency model) and the unrelated mean effects (UMEs) model (inconsistency model).[82] Local consistency can be obtained through the node splitting approach for agreement between the direct and indirect evidence[86] within specific comparisons, which it was not possible to assess. Nevertheless, this is not necessarily a limitation because multi-arm trials are designed to allow multiple comparisons within a single trial controlling for confounding and so inconsistency is not always possible within those trials. All analyses were performed by SN and checked for accuracy by JM.

Sensitivity analysis

Based on discussions with our clinical experts, we conducted sensitivity analyses for the mean change in MHDs, and the mean change in MMDs, by excluding the lower doses of eptinezumab (10 and 30 mg), since these doses are currently not available in the UK.

Results

Included studies

Study selection

The PRISMA flow diagram in *Figure 1* summarises the results of our searches for the clinical effectiveness review. The electronic searches yielded 18,528 records after the removal of duplicates.

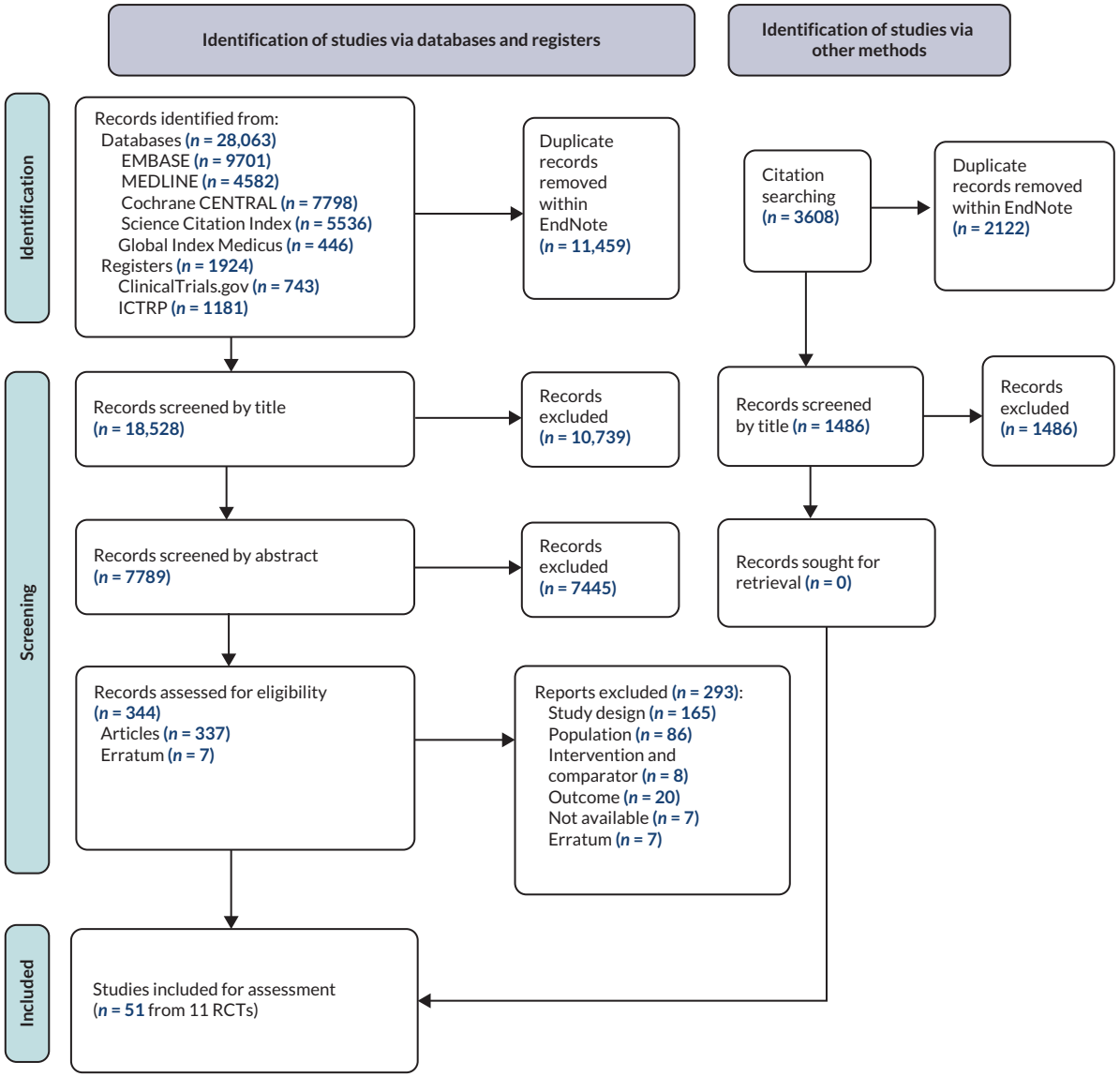

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram summarising the flow of studies for the clinical effectiveness review.

Of these, 18,184 citations were excluded at the title and abstract sifting phase. Three hundred and forty-four records were obtained for screening. We found that many articles provided a poor definition of migraine in the abstract. Of these, 293 studies were excluded based on full-text screening. A list of excluded papers and their reasons for excluding them are presented in *Report Supplementary Material 1*. Seven full-text articles were not available to be sifted, despite an extensive search by the University of Warwick Library Document Supply service. Thus, these seven papers were excluded. We identified 51 articles which described data from 11 trials for the clinical effectiveness review and/or NMA. Although these linked articles were cited, we used the main trial paper for the main citation, as the other linked papers only reported some subgroup analyses, were either repetitive or combined the data.

Study characteristics

The study-level baseline participant characteristics of the included RCTs are summarised in *Table 1* and *Appendix 2*, *Table 23*. The participants randomised in all trials satisfied the diagnostic criteria of chronic migraine in accordance with the ICHD.[87] Trials were conducted across the world with six multi-country trials including the UK, USA, Canada, Australia, New Zealand, Japan, Korea and other European countries. The number of participants with chronic migraine randomised across the 11 trials evaluating the prophylactic effects of pharmaceutical treatment ranged from 282[88] to 1130[37] (total of 7352). The mean age of trial participants ranged from 35.7[89] to 46.8[90] years; the mean body mass

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TABLE 1 Baseline characteristics of the 11 RCTs presented in 51 included studies

Author, year (primary study) (trial name)	Author, year (secondary publications)	Country	Definition criteria	Treatment duration (week)	Treatment				Number of participants (ITT)	Female (%)	Mean Age	Mean BMI	Mean MMD	Mean MHD	Mean MSQ-RR	Mean MSQ-PR	Mean MSQ-EF
					Name	Dose	Route of administration	Frequency									
Aurora, 2010[92] (PREEMPT1)	Dodick, 2019;[96] 2010;[97] Silberstein, 2020;[98] Aurora, 2014;[99] Lipton, 2016[100]	56 sites in North America	ICHD-3	24DB	Placebo	–	–	–	338	85.8	42.1	27.3	19.1	19.8	38.8[a]	56.1[a]	43.3[a]
					OnabotulinumtoxinA	155U + 40U	IM at 39 sites	Every 12 week	341	89.1	41.2	26.7	19.1	20	39[a]	56.7[a]	43.3[a]
Detke, 2018[95] (REGAIN)	Ruff, 2019;[101] Ford, 2021;[102] Förderreuther, 2018;[103] Ailani, 2020;[104] Ament, 2021[105]	116 centres in Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, UK and USA	ICHD-3	12DB	Placebo	–	–	–	558	87	41.6	26.5	19.6	21.5	38.4	55	44.2
					Galcanezumab	120 mg	SC	Monthly	278	85	39.7	26.4	19.4	21.2	39.3	55.5	45.3
						240 mg	SC	Monthly	277	82	41.1	26.7	19.2	21.4	38.9	57.1	45.7
Diener, 2010[93] (PREEMPT2)	Dodick, 2019,[96] 2010;[97] Silberstein, 2020;[98] Aurora, 2014;[99] Lipton, 2016[100]	56 sites in North America	ICHD-3	24DB	Placebo	–	–	–	358	84.6	40.9	27.1	18.7	19.7	38.8[a]	56.1[a]	43.3[a]
					OnabotulinumtoxinA	155U + 40U	IM at 39 sites	Every 12 week	347	86.2	41	26.7	19.2	19.9	39[a]	56.7[a]	43.3[a]
Dodick, 2019[89]	–	92 clinics/ sites in USA, Australia, New Zealand and Republic of Georgia	ICHD-3	12DB	Placebo	–	–	–	121	90	37.2	27.6	16.4	21.1	–	–	–
					Eptinezumab	300 mg	IV	Single dose	121	81	37.2	27.3	16.5	21.1	–	–	–
						100 mg	IV	Single dose	122	85	36.7	27.9	16.9	21.7	–	–	–
						30 mg	IV	Single dose	122	91	35.7	27.1	16.2	21	–	–	–
						10 mg	IV	Single dose	130	87	36.4	27.4	16.4	21	–	–	–
Ferrari, 2019[90] (FOCUS)	Spierings, 2021[106]	104 sites in Europe and the USA	ICHD-3	12DB	Placebo	–	–	–	279	84	46.8	25.3	–	–	–	–	–
					Fremanezumab	675 mg	SC	Single dose	276	83	45.8	25.1	–	–	–	–	–
						675 + 225 + 225 mg	SC	Monthly	283	84	45.9	25.3	–	–	–	–	–

TABLE 1 Baseline characteristics of the 11 RCTs presented in 51 included studies (*continued*)

Author, year (primary study) (trial name)	Author, year (secondary publications)	Country	Definition criteria	Treatment duration (week)	Treatment				Number of participants (ITT)	Female (%)	Mean Age	Mean BMI	Mean MMD	Mean MHD	Mean MSQ-RR	Mean MSQ-PR	Mean MSQ-EF
					Name	Dose	Route of administration	Frequency									
Lipton, 2020[94] (PROMISE2)	Diener, 2021;[107] Silberstein, 2020[108]	128 sites in 13 countries across the USA and Europe	ICHD-3	24DB	Placebo	–	–	–	366	88.8	39.6	27	16.2	20.6	–	–	–
					Eptinezumab	300 mg	IV	Single dose	350	89.7	41	26.2	16.1	20.6	–	–	–
						100 mg	IV	Single dose	356	86.2	41	26.4	16.1	20.4	–	–	–
Rothrock, 2019[88] (FORWARD)	Blumenfeld, 2020[109]	USA	ICHD-3	24OL	OnabotulinumtoxinA	155U	IM at 31 sites	Every 12 week	140	84	40.2	28.9	–	22.1	–	–	–
					Topiramate	100 mg	Oral	Twice daily	142	86	39.4	28.8	–	21.9	–	–	–
Sakai, 2021[91]	–	67 institutions in Japan and Korea	ICHD-3	12DB	Placebo	–	–	–	191	85.3	42.1	22.8	15.4	21.2	–	–	–
					Fremanezumab	675 mg	SC	Single dose	191	86.4	43.5	22.4	15.2	21.1	–	–	–
						675 + 225 + 225 mg	SC	Monthly	189	86.2	42.7	23.4	16.4	21.6	–	–	–
Silberstein, 2007[28]	Silberstein, 2009;[110] Dodick, 2007[111]	46 clinics/sites in USA	ICHD-2	16DB	Placebo	–	–	–	153	86.9	38.6	28	15.1	20.8	42.4	62.4	40.6
					Topiramate	100 mg	Oral	Twice daily	153	83.7	37.8	29.1	15.2	20.4	43.7	63.5	43.7
Silberstein, 2017[37] (HALO)	Winner, 2019;[112] Lipton, 2020;[113] Silberstein, 2020;[114] Blumenfeld, 2021[115]	132 sites in 9 countries across the USA and Europe	ICHD-3	12DB	Placebo	–	–	–	375	88	41.4	26.5	20.3	16.4	–	–	–
					Fremanezumab	675 mg	SC	Single dose	376	88	42	26.6	20.4	16.2	–	–	–
						675 + 225 + 225 mg	SC	Monthly	379	87	40.6	26.5	20.3	16	–	–	–
Tepper, 2017[45]	Brandes, 2020;[116] Ashina, 2018;[117] Tapper, 2019;[118] Lipton, 2019[119]	69 headache and clinical research centres in Canada, USA and Europe	ICHD-3	12DB	Placebo	–	–	–	286	79	42.1	26.3	18.2	21.1	42.8	60.3	53
					Erenumab	70 mg	SC	Monthly	191	87	41.4	26	17.9	20.5	44.7	61.9	53.6
						140 mg	SC	Monthly	190	84	42.9	26	17.8	20.7	45.6	62.9	56.7

BMI, body mass index; DB, double blind; IM, intramuscular; ITT, intention to treat; IV, intravenous; OL, open label; PREEMPT, Participants in The Phase III Research Evaluating Migraine Prophylaxis Therapy; SC, subcutaneous.
a The baseline values were not reported separately for PREEMPT1 and PREEMPT2.

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index (BMI) ranged from 22.4(25) to 29.1(24); and the percentage of female participants ranged from 79%[45] to 91%.[89]

Delivery setting for all included trials were in headache and clinical research centres; the number of sites ranged from 32 to 132. Ten trials were double-blinded trials,[28,37,45,88,90–95] while one trial was open label.[88] The duration of drug treatment ranged from 12 to 36 weeks for the double-blind trials and was 48 weeks for the open label trial. The included RCTs evaluated 10 different dosing regimens of CGRP MAbs (including eptinezumab 10, 30, 100 and 300 mg, erenumab 70 and 140 mg, fremanezumab 225 and 675 mg, and Galcanezumab 120 and 240 mg), BTA 155 Units (U) and topiramate 100 mg. Seven trials measured their primary outcome at week 12 (25, 26, 29–32) and the measurement time point for one trial was week 16.[28]

Narrative synthesis of results by primary outcome(s) of interest

We present the summary of evidence from 11 included RCTs for each outcome of interest narratively.

1. **Monthly headache days:** Eight trials reported the change in MHDs from baseline.[37,88,89,92–95,110] Two double-blind RCTs evaluating BTA versus placebo in 1384 chronic migraine participants for 24 weeks, followed by a 32-week open label phase in the USA.[92,93] Reduction in headache days from baseline (mean change; 95% CI) in BTA groups in both trials were [9 (−9.69 to −8.31) and 7.8 (−8.5 to −7.1)] while for placebo groups were [6.7 (−7.39 to −6) and 6.4 (−7.11 to −5.69)].[92,93] The efficacy and safety of BTA 155U every 12 weeks for 3 cycles was assessed in comparison with topiramate 'immediate release' 50–100 mg/day in 282 chronic migraine participants for 36 weeks in the open label trial.[88] After week 12, participants initially randomised to topiramate could cross over to BTA group. BTA was significantly superior to topiramate in reduction of headache days at week 32 [8.3 (−9.77 to −6.83) and 2.1 (−3.02 to −1.18), respectively].[88]
   A double-blind trial evaluated the efficacy and safety of topiramate 100 mg (twice daily) with 306 chronic migraine participants in 46 clinics in the USA for 16 weeks.[28,110] Topiramate produced a statistically significant reduction in headache days compared with placebo treatment [least square mean change from baseline (95% CI); 5.8 (−6.69 to −4.91) and 4.7 (−5.59 to −3.81), respectively].[28,110]
   Two double-blind trials comparing the efficacy and safety of different doses of eptinezumab against placebo in the chronic migraine population.[89,94,108] One of the trials was conducted in 128 sites across the USA and Europe with 1072 participants and outcomes were measured at weeks 12 and 24. The reduction in headache days (mean change from baseline and 95% CI) for eptinezumab 100 and 300 mg were 8.2 (−8.8 to −7.6) and 8.8 (−9.44 to −8.16), respectively versus placebo 6.4 (−7.01 to −5.79) at week 12. The reduction in headache days for 100 and 300 mg of eptinezumab at week 24 was 9.6 (−10.27 to −8.91) and 10.6 (−11.3 to −9.88), respectively compared with placebo 8.1 (−8.07 to −7.4).[94,108] Another trial was performed at 92 sites across the USA, Australia, New Zealand and the Republic of Georgia with 558 participants. Treatment duration was measured at 12 weeks.[89] The results for reduction in headache days [mean change from baseline (95% CI)] for 100, 300, 30 and 10 mg of eptinezumab were 8.9 (−10.12 to −7.67), 9.6 (−10.87 to −8.33), 9.2 (−10.35 to −8.05) and 7.5 (−8.72 to −6.28), respectively in comparison with placebo 6.9 (−8.06 to −5.74).[89]
   The efficacy and safety of fremanezumab was assessed in 1121 chronic migraine subjects for 12 weeks in 132 sites in 9 countries across the USA and Europe.[37] In this double-blind RCT, participants received fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8) or matching placebo.[37] Headache days' reduction from baseline was measured at 4 weeks after first dose and at 12 weeks. Fremanezumab resulted in a lower frequency of headaches than placebo in this trial. Fremanezumab quarterly reduced mean headache days per month by 4.3 (95% CI −4.89 to −3.71) and fremanezumab monthly decreased mean headache days per month by 4.6 (95% CI −5.18 to −4.01), while the reduction in MHDs for the placebo group was 2.5 (95% CI −3.09 to −1.91).[37]
   A double-blind RCT compared the efficacy and safety of two doses of galcanezumab in a sample of 1085 chronic migraine for a period of 12 weeks (3 injections) in 116 headache and clinical research centres across 13 countries.[95] Both doses of galcanezumab were superior to placebo in reducing the

number of MHDs. The mean change in headache days from baseline for 120 and 240 mg of Galcanezumab were −4.8 (95% CI −5.58 to −4.01) and −4.6 (95% CI −5.38 to −3.8) compared with placebo −3 (95% CI −4.1 to −1.9).[95]
In summary, eight trials showed that all included medications – the CGRP MAbs (fremanezumab, eptinezumab and galcanezumab), BTA and topiramate were superior to reduction in headache days in comparison with placebo. The headache days' reduction ranged from 2.5 days for placebo[37] to 10.6 days for eptinezumab 300 mg.[108]

2. **Monthly migraine days:** Eleven studies from ten trials investigated MMDs.[28,37,45,89–95,108] Two double-blind RCTs evaluating BTA versus placebo in 1384 chronic migraine participants for 24 weeks followed by a 32-week open label phase in the USA.[92,93] Reduction in migraine days from baseline mean change (95% CI) in BTA groups in both trials were 8.7 (−9.4 to −8) and 7.6 (−8.29 to −6.91), while for placebo groups were 6.3 (−7 to −5.6) and 6.1 (−6.82 to −5.38).[92,93]

   - Three trials evaluated the efficacy of fremanezumab. One of them was performed in 1121 chronic migraine subjects for 12 weeks in 132 sites in 9 countries across the USA and Europe.[37] In this double-blind RCT, participants received fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8) or matching placebo.[37] MMDs reduction from baseline was measured at 12 weeks. Fremanezumab resulted in a lower frequency of migraine days than placebo in this 12-week trial. Fremanezumab quarterly reduced mean migraine days per month by 4.9 (95% CI −5.68 to −4.12) and fremanezumab monthly decreased mean migraine days per month by 5 (95% CI −5.78 to −4.22), while the reduction in MMDs for the placebo group was 3.2 (95% CI −3.98 to −2.4).[37] The other double-blind RCT which compared the efficacy of fremanezumab was conducted in 104 sites (including hospitals, medical centres, research institutes and group practice clinics) across European countries and the USA.[90] The trial population included both episodic and chronic migraine patients who had documented failure to 2 to 4 classes of migraine preventive medications in the past 10 years, although the results for reduction in MMDs was provided separately for the 837 chronic migraine participants. Fremanezumab quarterly (month 1: 675 mg; months 2 and 3: placebo), fremanezumab monthly (month 1: 675 mg; months 2 and 3: 225 mg) and matched monthly placebo for 12 weeks were administered.[90] Reductions from baseline in mean MMDs over 12 weeks were greater versus placebo; 3.9 (95% CI −4.56 to −3.23) for quarterly, −4.5 (95% CI −5.16 to −3.83) for monthly and 0.7 (−1.35 to −0.04) for placebo.[90] The double-blind trial for evaluating the efficacy and safety of fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8), fremanezumab quarterly (675 mg at baseline and placebo at weeks 4 and 8) or matching placebo in Japan and Korea was conducted in 571 chronic migraine participants.[91] The change in migraine days from baseline (95% CI) for monthly and quarterly administration were −4.9 (−5.56 to −4.23), −4.1 (−5.07 to −3.12) respectively compared with placebo −2.8 (−3.78 to −1.82).[91]
   - A double-blind RCT comparing the efficacy and safety of two doses (120 and 240 mg) of galcanezumab in a sample of 1085 chronic migraine participants for a period of 12 weeks (3 injections) in 116 headache and clinical research centres across 13 countries.[95] The mean change in migraine days from baseline for 120 and 240 mg of galcanezumab were superior [−4.8 (95% CI −5.58 to −4.01) and −4.6 (95% CI −5.38 to −3.8)] compared with placebo [−2.7 (95% CI −3.48 to −1.91)].[95]
   - A double-blind trial compared different doses of erenumab efficacy and safety in 69 headache and clinical research centres in North America and Europe. 667 chronic migraine patients were randomly assigned to be administered monthly 70 mg, 140 mg of erenumab or matched placebo for 12 weeks.[45] The results demonstrated that erenumab 70 and 140 mg reduced the number of MMDs compared with placebo: the mean change from baseline (95% CI) −6.64 (−7.05 to −6.23), −6.63 (−7.04 to −6.22) and −4.18 (−4.51 to −3.85), respectively.[45]
   - A double-blind trial evaluated the efficacy and safety of topiramate 100 mg (twice daily) for 306 chronic migraine participants in 46 clinics in the USA for 16 weeks.[28] Topiramate treatment

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resulted in a mean (95% CI) reduction from baseline of 5.6 (−6.56 to −4.63) migraine days per month compared with 4.1 (−5.07 to −3.13) for the placebo group.[28]

- Two double-blind trials comparing the efficacy and safety of different doses of eptinezumab against placebo in the chronic migraine population.[89,94] One trial was conducted in 128 sites across the USA and Europe with 1072 participants and outcomes were measured at week 12. Treatment with eptinezumab 100 mg [7.7, 95% CI (−8.41 to −6.99)] and 300 mg [8.2, 95% CI (−9.13 to −7.26)] was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo [5.6, 95% CI (−6.42 to −4.78)]. The MD (95% CI) from placebo for 100 and 300 mg during 24 weeks were −1.98 (−2.94 to −1.01) and −2.65 (−3.62 to −1.68), respectively.[94] The other trial was performed across 92 sites in the USA, Australia, New Zealand and the Republic of Georgia with 558 participants. Treatment duration and time point measurement was 12 weeks.[89] Participants were assigned in eptinezumab 100, 300, 30, 10 mg or placebo, administered as a single IV infusion. The results for reduction in migraine days [mean change from baseline (95% CI)] for 100, 300, 30 and 10 mg of eptinezumab were 7.7 (−8.94 to −6.46), 8.2 (−9.48 to −6.91), 7.9 (−9.06 to −6.74) and 6.7 (−7.9 to −5.5) respectively in comparison with placebo 5.6 (−6.78 to −4.41).[89]
- In summary, 10 trials investigated different doses of CGRP MAbs drugs (including fremanezumab, erenumab, eptinezumab and galcanezumab), BTA and topiramate. These trials illustrated data from different time points in comparison with placebo. The results demonstrated superiority of pharmacological medications versus placebo in the reduction of migraine days from baseline. Migraine days were reduced ranging from 0.7 days for placebo[90] to 8.7 days for BTA.[93]

Narrative synthesis of results by secondary outcomes of interest

3. **Migraine-specific quality of life:** Ten studies from five trials used the MSQ questionnaire at multiple time points.[45,92,93,95,97,102,110,111,113,119] A double-blind trial compared the efficacy and safety of two doses of galcanezumab in a sample of 1085 chronic migraine patients for a period of 12 weeks (3 injections) in 116 headache and clinical research centres across 13 countries.[102] At week 12, the least-squares mean change (95% CI) in total MSQ for galcanezumab-treated patients were 20.51 (20.33 to 20.69) (120 mg) and 20.49 (20.31 to 20.67) (240 mg), both statistically significantly greater than the placebo-treated patients 14.55 (14.44 to 14.66).[102] Improvement in all domains of MSQ for both doses were significantly greater than placebo; restrictive role function [120 mg: 21.8 (19.48 to 24.12), 240 mg: 23.1 (20.62 to 25.58) than placebo 16.8 (14.65 to 18.95)], preventative role function [120 mg: 18 (15.69 to 20.32), 240 mg: 16.1 (13.77 to 18.43) than placebo 11 (8.56 to 13.14)], and emotional function [120 mg: 21 (18.3 to 23.7), 240 mg: 20.7 (17.99 to 23.41) than placebo 14.1 (11.62 to 16.58)].[102]
   A double-blind trial evaluated efficacy and safety of topiramate 100 mg (twice daily) with 306 chronic migraine participants in 46 clinics in the USA for 16 weeks.[111] The MSQ analysis demonstrated significant improvements at week 4 in all three domains, and at weeks 8 and 16 in both restrictive role function and emotional function domains. The preventative role function closely approached, but did not reach statistical significance at week 8.[111] The mean improvement from baseline (95% CI) for topiramate-treated subjects was 23.7 (20.04 to 27.36), 16.1 (12.69 to 19.51) and 26.3 (21.9 to 30.71) for MSQ-RR, MSQ-PR and MSQ-EF, respectively. The mean improvement from baseline (95% CI) for placebo-treated subjects was 18.8 (15.22 to 22.38), 12.6 (9.27 to 15.93) and 21.0 (16.22 to 25.78) for MSQ-RR, MSQ-PR and MSQ-EF, respectively. The differences between treatment groups were statistically significant for MSQ-RR and MSQ-EF but were not statistically significant for MSQ-PR at week 16.[110]
   Fremanezumab efficacy and safety was assessed in 1121 chronic migraine subjects for 12 weeks in 132 sites in 9 countries across the USA and Europe. In this double-blind trial, participants received fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8) or matching placebo.[113] Fremanezumab quarterly and monthly was associated with significant improvements over placebo in mean change from baseline in MSQ in all 3 domains to week 12.[113] Least square mean change in MSQ-RR

(95% CI) from baseline for quarterly and monthly group was 20.3 (18.33 to 22.27) and 21 (18.77 to 23.23), respectively versus 14.7 (12.55 to 16.85) for placebo. Improvement in MSQ-PR for quarterly, monthly and placebo group was 15.9 (14.16 to 17.64), 15.5 (13.79 to 17.21) and 11.6 (9.86 to 13.34), respectively; and improvement in MSQ-EF was 20.9 (18.75 to 23.05), 20.3 (18.53 to 22.07) and 17 (15.08 to 18.92) for quarterly and monthly administration of fremanezumab and placebo.[113]
A double-blind trial evaluating BTA versus placebo in 1384 chronic migraine participants for 24 weeks followed by a 32-week open label phase in the USA[92,93,97] found that the improvement in MSQ-RR [mean change from baseline (95% CI)] at week 12 for BTA was 16.2 (13.55 to 18.85) against placebo 9.9 (7.26 to 12.54). For MSQ-PR, the mean change from baseline (95% CI) favoured BTA [13 (10.89 to 15.11)] rather than placebo [13 (12.41 to 13.59)]. MSQ-EF improvement was superior in the BTA group, 18.3 (15.23 to 21.37) rather than placebo 11 (7.95 to 14.05).[97]
A double-blind trial conducted in 69 headache and clinical research centres in North America and Europe randomly assigned 677 chronic migraine patients to be administered monthly 70 or 140 mg of erenumab or matched placebo for 12 weeks.[45,119] Participants in the lower dose (70 mg) of erenumab experienced less improvement in MSQ-RR function [mean change from baseline (95% CI)] than the higher dose (140 mg) participants, 17.7 (14.77 to 20.63) versus 19.1 (16.15 to 22.53), while the mean change from baseline for the placebo group was 11.8 (9.25 to 14.35). The results showed participants in the 70 mg, 140 mg and placebo group had improvement in MSQ-PR function, 13 (10.51 to 15.49), 13.8 (11.31 to 16.29) and 8.9 (6.87 to 10.93), respectively. Improvement in the MSQ-EF for the 70 mg, 140 mg and placebo group was 18.2 (13.15 to 23.24), 18.8 (14.73 to 22.87) and 9.9 (5.98 to 13.82), respectively.[119]
In summary, five trials reported MSQ data for three dimensions separately, including MSQ-RR, MSQ-PR and MSQ-EF. Galcanezumab, erenumab, fremanezumab, topiramate and BTA were investigated in this diverse time window in the included trials. All these drugs were associated with a better improvement in quality of life compared with placebo.

4. **The HIT-6:** Eleven studies from six trials evaluated headache disability through HIT-6.[37,88,89,91–94,97,100,109,119] Two trials were associated with efficacy and safety of fremanezumab. The first trial which was double blind was conducted in 1121 chronic migraine subjects for 12 weeks in 132 sites in 9 countries across the USA and Europe. The participants received fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8) or matching placebo.[37] The degree of headache-related disability decreased between baseline and the 4-week period after the last dose, with significantly greater reductions [mean change from baseline (95% CI)] in HIT-6 scores with quarterly [6.4 (−7.38 to −5.42)] and monthly [6.8 (−7.58 to −6.02)] rather than with placebo [4.5 (−5.48 to −3.52)].[37] The second trial found a greater reduction with quarterly or monthly administration of Fremanezumab compared with placebo at 4 weeks after the final (third) trial medication administration [4.1 (−4.89 to −3.31), 4.1 (−4.90 to −3.3) and 2.4 (−3.21 to −1.59), respectively].[91] This double-blind trial assessed 571 participants with chronic migraine who received subcutaneous fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8), fremanezumab quarterly (675 mg at baseline and placebo at weeks 4 and 8) or matching placebo in Japan and Korea.[91]

   - Two double-blind trials evaluated BTA versus placebo in 1384 chronic migraine participants for 24 weeks followed by a 32-week open label phase in the USA.[92,93,97] The pooled results showed a statistically significant and clinically meaningful difference for BTA versus placebo at all time points starting at the first post-treatment study visit (week 4) and including week 24 for the mean change from baseline in total HIT-6 score.[97] Mean change from baseline (95% CI) at week 12 for BTA was −4.7 (−5.58 to −3.82) compared with placebo −2.6 (−3.48 to −1.72).[97] Efficacy and safety of BTA 155U every 12 weeks for 3 cycles was assessed in comparison with topiramate 'immediate release' 50–100 mg/day in 282 chronic migraine participants for 36 weeks in the open label trial.[88,109] After week 12, participants initially randomised to topiramate could cross over to BTA group. At week 30, BTA resulted in a mean (95% CI) reduction in HIT-6 scores from baseline of 5.6 (−6.95 to −4.25)

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compared with 1.3 (−2.01 to −0.59) for topiramate, with a significant between-group difference favouring BTA.[88,109]

- Two double-blind trials compared the efficacy and safety of different doses of eptinezumab against placebo in the chronic migraine population.[89,94] The first trial was conducted in 128 sites across the USA and Europe with 1072 participants, and outcomes were measured at weeks 12 and 24.[94] Patients in the eptinezumab 300 mg group demonstrated a statistically significant improvement on the HIT-6 at week 12, with an estimated MD from placebo.[94] Reduction [mean change from baseline (95% CI)] in HIT-6 for 100 and 300 mg was 6.2 (−6.92 to −5.48) and 7.3 (−8.34 to −6.26) versus placebo 4.5 (−5.27 to −3.73).[94] The second trial was performed at 92 sites across the USA, Australia, New Zealand and the Republic of Georgia with 558 participants. Participants were assigned to eptinezumab 100, 300, 30, 10 mg or placebo, administered as a single IV infusion.[89] The greatest effect of eptinezumab, as measured by the HIT-6, was observed at week 12, with changes in baseline scores of −10.0 (−11.54 to −8.46), −6.9 (−8.24 to −5.56), −6.5 (−7.83 to −5.16) and −6.5 (−7.91 to −5.09) for the 300, 100, 30 and 10 mg groups, respectively, compared with −5.8 for the placebo group.[89]
- A double-blind trial comparing different doses of erenumab in 69 headache and clinical research centres in North America and Europe had 677 chronic migraine patients who were randomly assigned monthly 70 or 140 mg of erenumab or matched placebo for 12 weeks.[45,119] The change from baseline (95% CI) in HIT-6 score was greater in the erenumab groups than in placebo as early as month 1 and this improvement was sustained throughout the trial [70 and 140 mg 5.6 (−6.80 to −4.40) and placebo 3.1 (−4.04 to −2.17)].[119]
- In brief, six trials aimed to explore the change of disability measured by HIT-6. All pharmacological medications (BTA, fremanezumab, erenumab and eptinezumab) were more effective in the reducing the disabilities score compared with placebo. Reduction in HIT-6 score ranged from 1.3 for placebo[88] to 17.4 for BTA.[109]

5. **EuroQol-5 Dimensions, five-level version (EQ-5D-5L):** A double-blind, placebo RCT assessed the effect of treatment with fremanezumab on HRQoL in 1130 participants with chronic migraine.[113] Fremanezumab quarterly (675 mg at baseline, placebo at weeks 4 and 8) or monthly (225 mg at baseline, weeks 4 and 8) led to statistically significant improvements in the EQ-5D-5L visual analogue scale score, compared with placebo. Differences were reported as least-mean squares changes which were 4.6 and 4.8 for fremanezumab quarterly and monthly respectively, compared with 2.2 for placebo.

6. **Migraine disability assessment:** Three trials reported the MIDAS at different time points.[102,110,119] The first trial reported the MIDAS total score in a study which aimed to assess topiramate for 306 participants.[110] The MIDAS score [mean (95% CI)] decreased from baseline, indicating that improvement was greater in the topiramate group [31.4 (22.87 to 39.92)] compared with the placebo group [21.0 (12.73 to 29.27)]. The second trial evaluated the effect of erenumab in 667 participants with chronic migraine.[119] Reductions from baseline to month 3 in MIDAS total score was greater in the erenumab group compared to the placebo group, indicating better improvement. Respective differences from baseline [least-squares mean (CI)] were −11.9 (−19.3 to −4.4) and −12.2 (−19.7 to −4.8) for erenumab 70 and 140 mg. The final trial assessed galcanezumab in 1117 chronic migraine participants.[102] At week 12, the difference in the least-squares mean (CI) from baseline in the MIDAS total score for galcanezumab indicated a decrease in disability that was significantly greater for the 120 mg dose only [8.74 (−16.4 to −1.1)] and similar for the 240 mg dose [5.49 (−13.1 to 2.1)] compared with placebo.
   In summary, the three trials found that there was improvement in MIDAS score for erenumab, galcanezumab and topiramate in comparison with placebo.

7. **Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI:SHP):** An open label trial compared BTA with topiramate 100 mg for ≤ 36 weeks in people with chronic migraine.[109] Overall, 85.7% participants in the BTA group completed the study, while only 19.7% of

the participants randomised to topiramate completed their initial treatment. 56.3% of those participants who discontinued topiramate, from week 12 switched to BTA. Work productivity assessed by the WPAI:SHP scores reported at week 36 revealed significant improvements with BTA versus topiramate in work productivity loss [MD: 0.67 (−1.25 to −0.09)] and activity impairment [MD: 1.53 (−2.07 to −1.0)] domains. In summary, this trial found that there was an improvement in work productivity measured by WPAI:SHP which favoured BTA compared to topiramate.

8. **Patient Health Questionnaire 9-item (PHQ-9)**: The same trial that used the WPAI:SHP questionnaire[109] also compared BTA with topiramate and reported outcomes for depression at week 36. Improvements in depression were observed via larger changes in PHQ-9 scores with BTA than topiramate [MD: 1.86 (−2.63 to −1.10)]. In summary, BTA led to a better reduction on depression in comparison with topiramate.

9. **Functional Impact of Migraine Questionnaire (FIMQ):** The open-label trial comparing BTA with topiramate reported FIMQ at week 30.[109] The FIMQ total score showed a greater reduction from baseline with BTA versus topiramate [MD: 11.38 (−16.01 to −6.75)] and also a greater reduction in the following domains: activity impairment [MD: 0.75 (−15.38 to −6.13)]; emotional functioning [MD: 10.81 (−15.76 to −5.86)]; and cognitive functioning [MD: 14.49 (−19.90 to −9.07)]. In brief, BTA had a favourable profile in reduction of activity and functional impairment.

Feasibility of a network meta-analysis

From the eight studies which reported MHDs, seven trials were eligible for inclusion in the NMA. Following guidance from our clinical experts, they recommended that 12 weeks can be used as the measurement time point for the NMA. They also agreed that the 16 weeks measurement time point for topiramate was comparable and can be pooled with the 12 weeks time point. The project team also decided to pool the BTA data which was measured at the 24 weeks time point. However, we excluded the open label trial evaluating BTA efficacy and safety versus topiramate[88] for the NMA as the data were reported at 32 weeks. We planned to perform a sensitivity analysis to reflect the effect of the study design (open-label vs. double-blind), but it was not possible because there was insufficient information for MHDs at week 12. The other studies included in the NMA were comparable in terms of participants characteristics, treatment dosing and schedules, baseline risk and observed treatment effects.

For MMDs, 10 studies were eligible for the NMA. Five studies evaluated the change in MSQ score from baseline and were eligible in another separate NMA. Only the 12 weeks time point was included for this NMA and any other time points were excluded. From the seven trials which reported HIT-6 score, six studies were eligible to be included in NMA. We used the same reasoning for excluding the open label trial as we did for MHDs. In summary, we conducted an NMA for those outcomes which were reported in at least three trials.

Network meta-analysis results

We performed a NMA on two primary outcomes: mean change in MHD from baseline, and the mean change in MMDs from baseline.

We also performed NMA on two QoL outcomes: the mean change in MSQ score from baseline for three dimensions – (1) MSQ-RR function; (2) MSQ-PR function; and (3) MSQ-EF and the mean change in HIT-6 score from baseline.

We fitted both fixed and random-effects NMA models based on the model fit indices; we selected the fixed-effects NMA model for all outcomes (see *Appendix 3*, *Tables 24*, *28*, *32*, *36*, *40* and *44*). We found no indirect evidence in the results, as all trials included in the analysis were placebo-controlled, where no two active treatments were directly compared (*Figures 2–19*); thus the direct evidence and NMA estimates are the same for each outcome.

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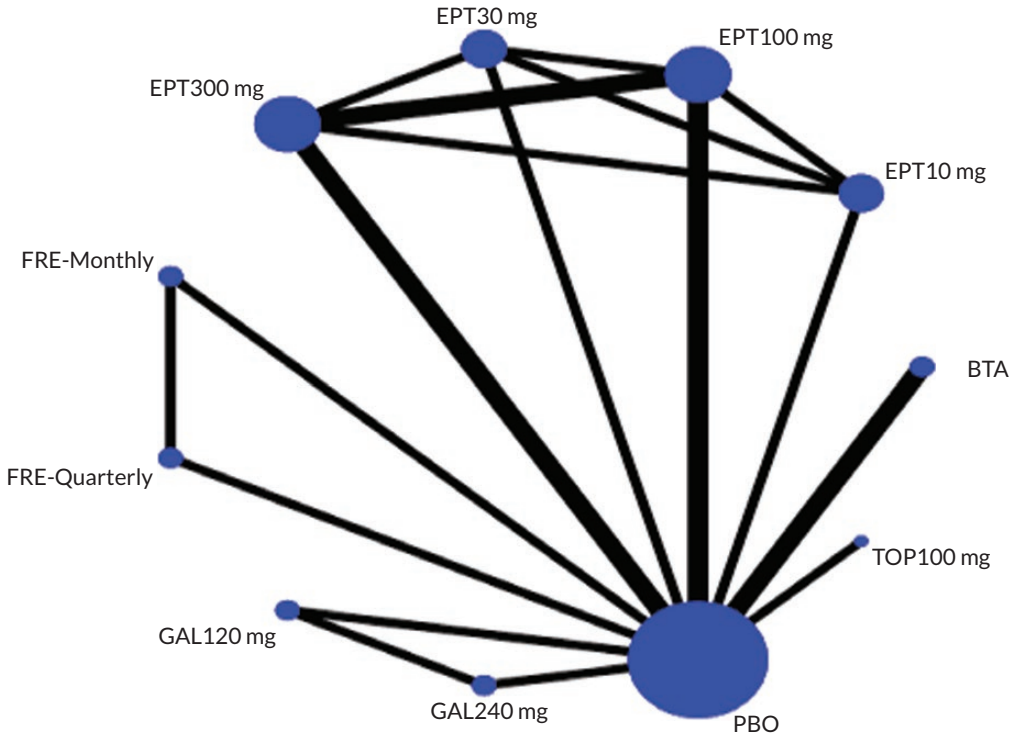

FIGURE 2 Summary of the change in MHD from baseline – network plot. Nodes and edges are weighted according to the number of participants and studies evaluating each treatment and direct comparison, respectively. EPT10 mg, eptinezumab 10 mg IV infusion; EPT30 mg, eptinezumab 30 mg IV infusion; EPT100 mg, eptinezumab 100 mg IV infusion; EPT300 mg, eptinezumab 300 mg IV infusion; FRE-Quarterly, fremanezumab 675 mg (quarterly) SC single dose; FRE-Monthly, fremanezumab 675 + 225 + 225 mg SC; GAL120 mg, galcanezumab 120 mg SC; GAL240 mg, galcanezumab 240 mg SC; TOP100 mg, topiramate 100 mg oral; BTA, onabotulinumtoxinA 155 + 40U SC; IV, intravenous; PBO, placebo; SC, subcutaneous.

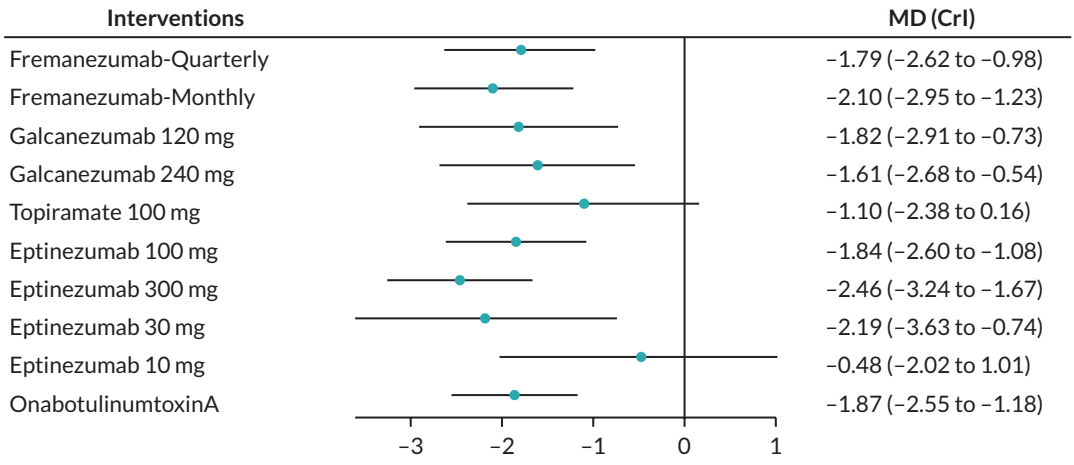

FIGURE 3 Summary of the change in MHD from baseline – forest plot. The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention.

Mean change in monthly headache days

For the primary outcome, mean change in MHD from baseline, this was reported in 8 RCTs with a total of 5838 participants. The NMA included two trials comparing BTA with Topiramate (27, 28) at week 24, two trials evaluating eptinezumab versus placebo (29, 41, 58) at weeks 12 and 24, a trial evaluating topiramate versus placebo (34) at week 16, a trial comparing fremanezumab with placebo[37] at weeks 4 and 12, a trial evaluating galcanezumab versus placebo (30) at week 12, and a trial comparing BTA with Topiramate (33) at week 32 (*Table 2*).

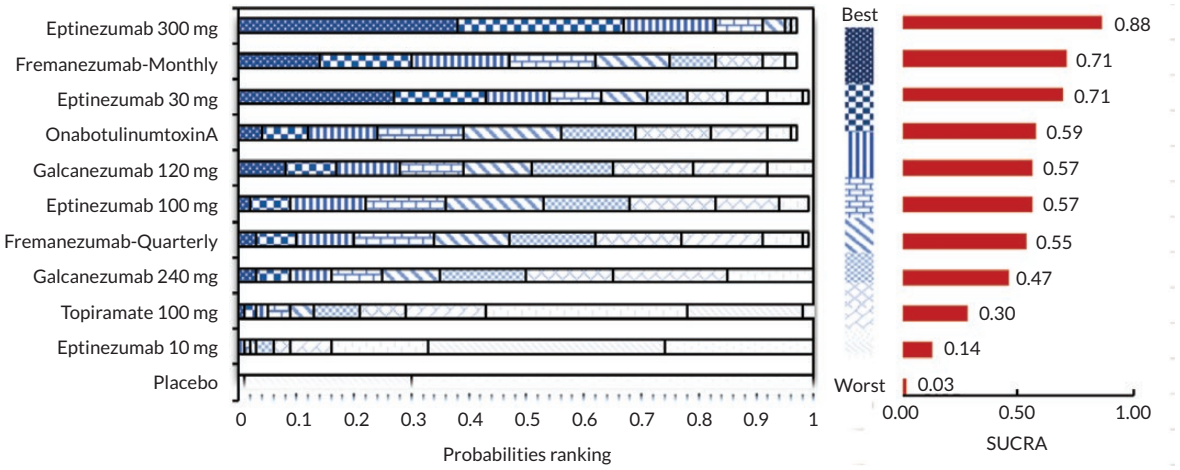

FIGURE 4 Summary of the change in MHD from baseline – rankings and SUCRA. Ranking probabilities graph (hatching blue bars) of each treatment and red bars are the SUCRA values for each treatment. The probabilities ranking ranged from 0 to 1. Due to rounding in R software these do not equate to one. SUCRA, surface under the cumulative ranking curve.

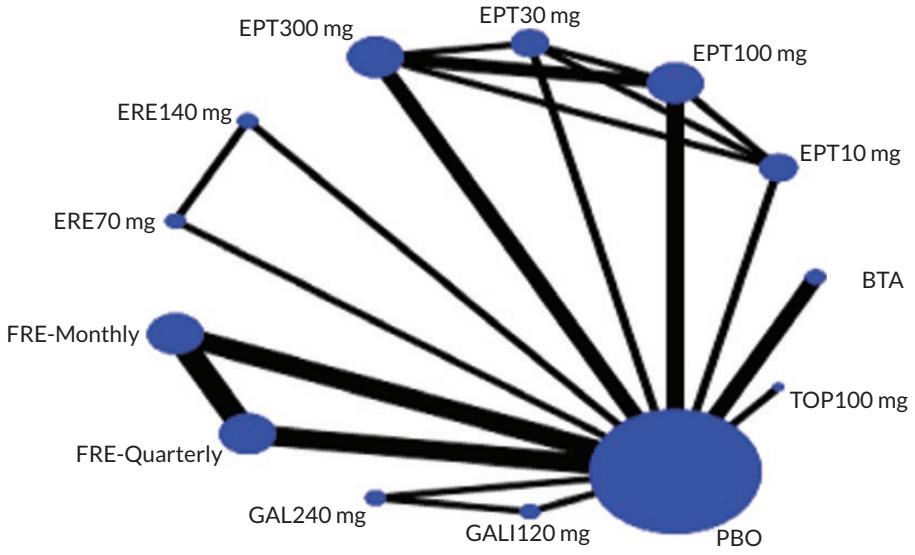

FIGURE 5 Summary of the change in MMD from baseline – network plot. Nodes and edges are weighted according to the number of participants and studies evaluating each treatment and direct comparison, respectively. EPT10 mg, eptinezumab 10 mg IV infusion; EPT30 mg, eptinezumab 30 mg IV infusion; EPT100 mg, eptinezumab 100 mg IV infusion; EPT300 mg, eptinezumab 300 mg IV infusion; ERE70 mg, erenumab 70 mg SC; ERE140 mg, erenumab 140 mg SC; FRE-Quarterly, fremanezumab 675 mg (quarterly) SC single dose; FRE-Monthly, fremanezumab 675 + 225 + 225 mg SC; GAL120 mg, galcanezumab 120 mg SC; GAL240 mg, galcanezumab 240 mg SC; TOP100 mg, topiramate 100 mg oral; BTA, onabotulinumtoxinA 155 + 40U SC; IV, intravenous; PBO, placebo; SC, subcutaneous.

We considered follow-up periods of 12 and 16 weeks as a measurement point for the NMA. We pooled the BTA data at week 24, as the primary time point for evaluating BTA is usually 6 months. Hence, we have included 10 different doses of drugs from 7 trials for the NMA and compared this with placebo as a reference treatment.

The network plot is presented in *Figure 2*, where thicker edges represent comparisons with a larger number of randomised trials. Similarly, interventions with a larger number of randomised participants have larger circles. All interventions were compared with placebo. *Figure 3* displays the result for the fixed-effects NMA model in comparison with placebo. According to the forest plot, all treatments significantly reduced the mean MHDs compared to placebo. The most effective intervention is eptinezumab 300 mg (MD: −2.46, 95% CrI: −3.24 to −1.67) as this reduced MHD by 2.46, followed by eptinezumab 30 mg (MD: −2.19, 95% CrI: −3.63 to −0.74), fremanezumab monthly (MD: −2.10, 95% CrI: −2.95 to −1.23),

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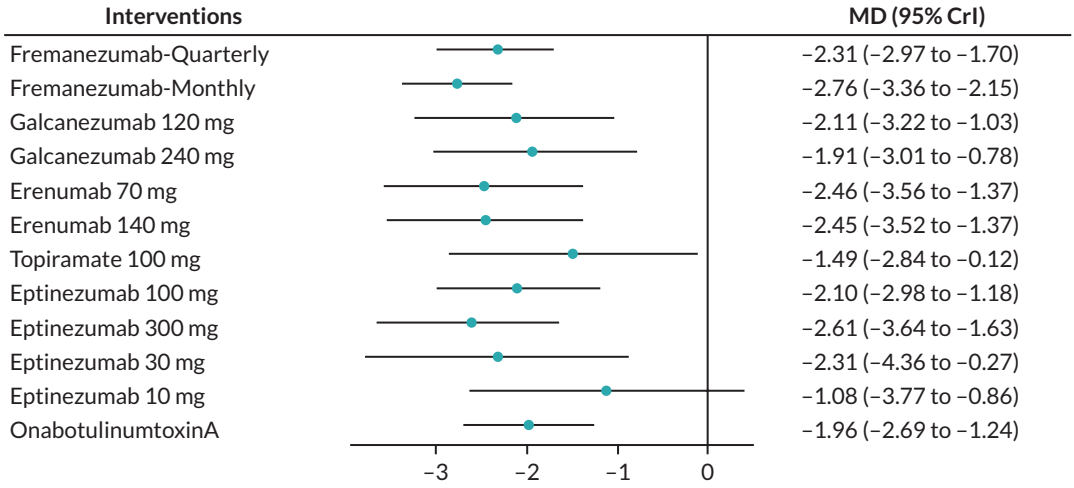

FIGURE 6 Summary of the change in MMD from baseline – forest plot. The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention.

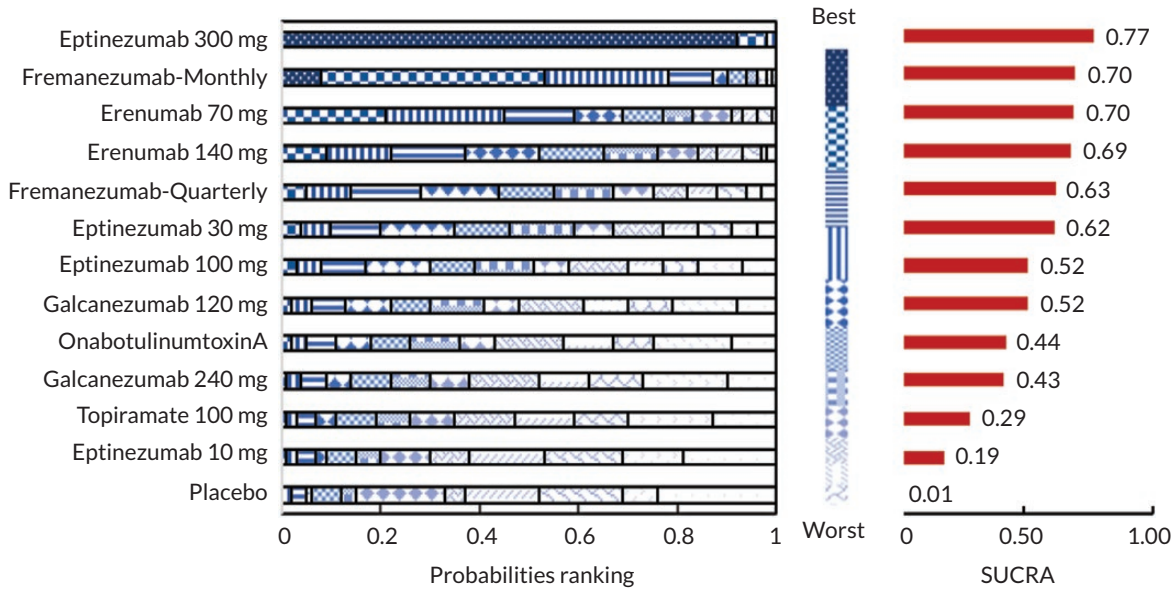

FIGURE 7 Summary of the change in MMD from baseline – rankings and SUCRA. Ranking probabilities graph (hatching blue bars) of each treatment and red bars are the SUCRA values for each treatment. The probabilities ranking ranged from 0 to 1. Due to rounding in R software these do not equate to one. SUCRA, surface under the cumulative ranking curve.

onabotulinumtoxinA (MD −1.87, 95% CrI −2.55 to −1.18), eptinezumab 100 mg (MD: −1.84, 95% CrI: −2.60 to −1.08), galcanezumab 120 mg (MD: −1.82, 95% CrI: −2.91 to −0.73), fremanezumab-quarterly (MD: −1.79, 95% CrI: −2.62 to −0.98), galcanezumab 240 mg (MD: −1.61, 95% CrI: −2.68 to −0.54) and topiramate 100 mg (MD: −1.10, 95% CrI: −2.38 to 1.01). The least effective treatment was eptinezumab 10 mg (MD: −0.48, 95% CrI: −2.02 to 1.01). We presented the league tables for all comparisons in *Table 2*.

The 11 node analysis in *Figure 4* showed that eptinezumab 300 mg (SUCRA 0.88) had the highest probability ranking to reduce MHD, followed by fremanezumab monthly and eptinezumab 30 mg (SUCRA 0.71), onabotulinumtoxinA (SUCRA 0.59), eptinezumab 100 mg and galcanezumab 120 mg (SUCRA 0.57), fremanezumab-quarterly (SUCRA 0.55), galcanezumab 240 mg (SUCRA 0.47), topiramate 100 mg (SUCRA 0.30), eptinezumab 10 mg (SUCRA 0.14), and the lowest probability ranking is placebo (SUCRA 0.03). Treatment probabilities ranking and cumulative ranking curves were obtained and tabulated in *Appendix 3*, *Figures 28* and *29* and *Tables 25* and *26*.

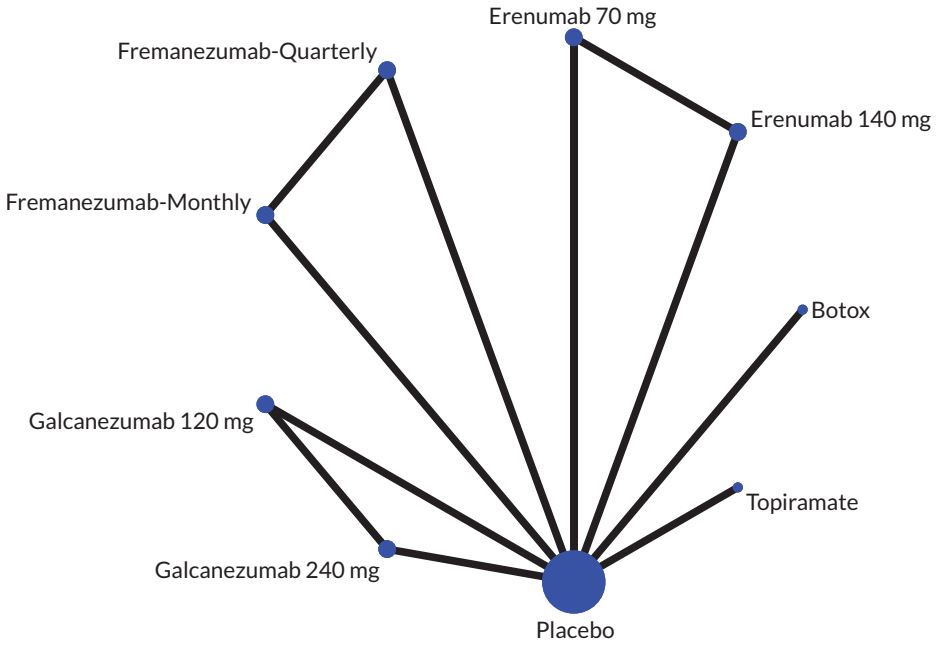

FIGURE 8 Summary of the change in MSQ-RR from baseline – network plot. Nodes and edges are weighted according to the number of participants and studies evaluating each treatment and direct comparison, respectively.

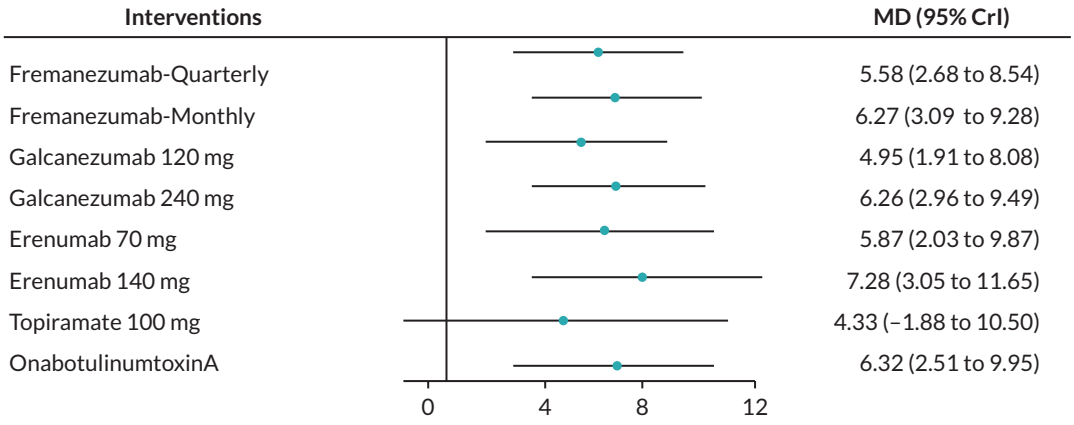

FIGURE 9 Summary of the change in MSQ-RR from baseline – forest plot. The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention.

The global approach to test for overall consistency shows no evidence of inconsistency in the data points. It is presented in *Appendix 3*, *Figure 30*. Also, the result of comparing the fit of NMA and Unrelated Mean Effects (UME) inconsistency models illustrated a good fit which is tabulated in *Appendix 3*, *Table 27*.

Mean change in monthly migraine days

For the second primary outcome, the mean change in MMD from baseline, this was reported in 10 RCTs with a total of 7821 participants trials comparing BTA with topiramate (27, 28) at week 24, two trials evaluating eptinezumab versus placebo (29, 41, 58) at weeks 12 and 24, a trial evaluating topiramate versus placebo (34) at week 16, three trials comparing fremanezumab with placebo at weeks 4 and 12,[37,90,91] a trial investigating erenumab against placebo, and a trial evaluating galcanezumab versus placebo (30) at week 12 (*Table 3*).

We considered follow-up periods of 12 and 16 weeks as a measurement point for NMA. We pooled the BTA data at week 24, as the primary time point for evaluating the BTA is usually 6 months. Hence, we

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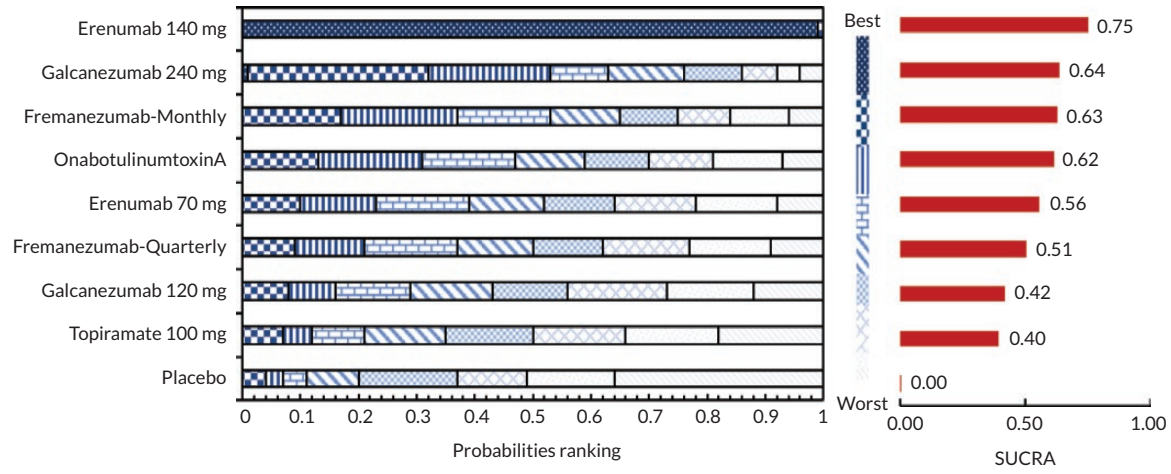

FIGURE 10 Summary of the change in MSQ-RR from baseline – rankings and SUCRA. Ranking probabilities graph (hatching blue bars) of each treatment and red bars are the SUCRA values for each treatment. The probabilities ranking ranged from 0 to 1. Due to rounding in R software these do not equate to one. MSQ-RR, migraine-specific quality of life – restrictive role; SUCRA, surface under the cumulative ranking curve.

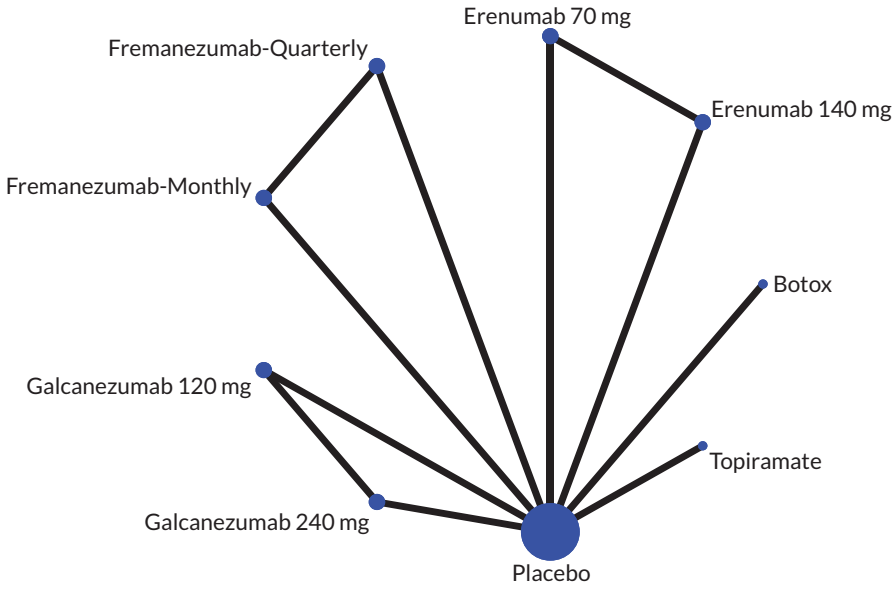

FIGURE 11 Summary of the change in MSQ-PR from baseline – network plot. Network plot shows that the nodes and edges are weighted according to the number of participants and studies evaluating each treatment and direct comparison, respectively.

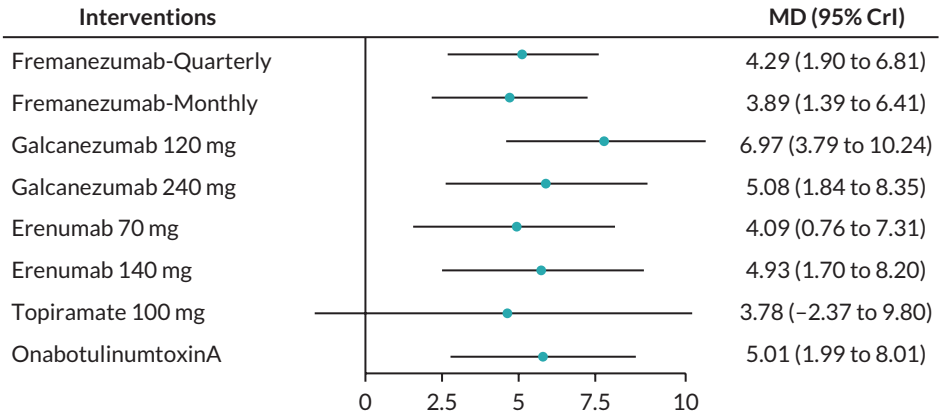

FIGURE 12 Summary of the change in MSQ-PR from baseline – forest plot. The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention.

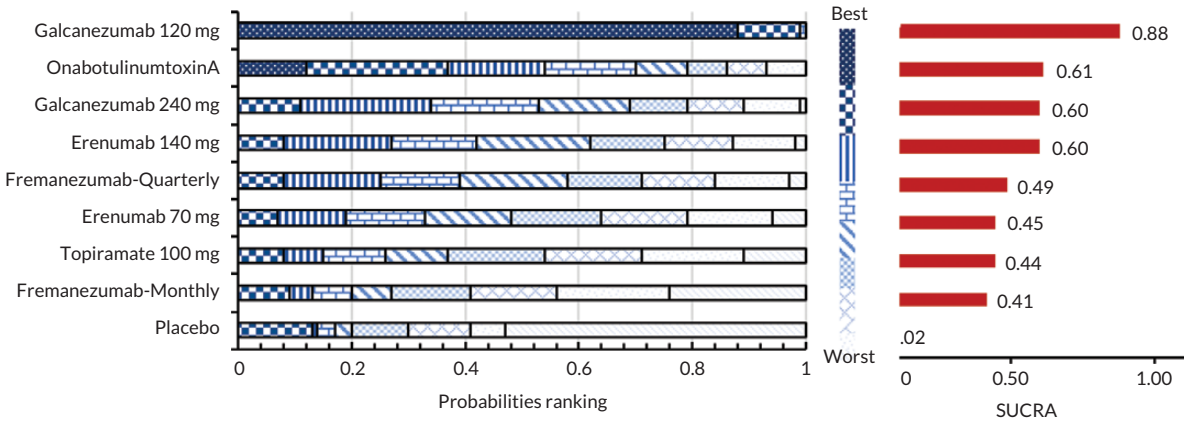

FIGURE 13 Summary of the change in MSQ-PR from baseline – rankings and SUCRA. Ranking probabilities graph (hatching blue bars) of each treatment and red bars are the SUCRA values for each treatment. The probabilities ranking ranged from 0 to 1. Due to rounding in R software these do not equate to one. MSQ-PR, migraine-specific quality of life – preventative role; SUCRA, surface under the cumulative ranking curve.

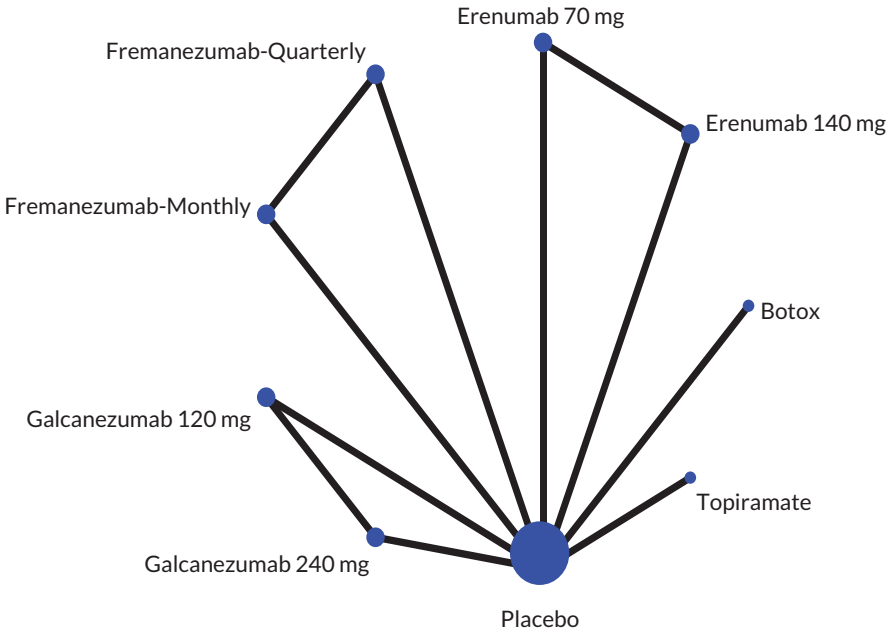

FIGURE 14 Summary of the change in MSQ-EF from baseline – network plot. Nodes and edges are weighted according to the number of participants and studies evaluating each treatment and direct comparison, respectively.

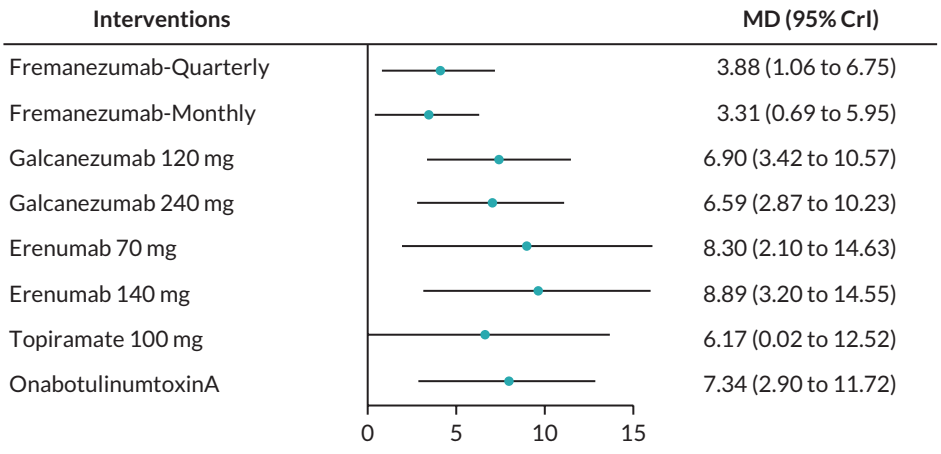

FIGURE 15 Summary of the change in MSQ-EF from baseline – forest plot. The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention.

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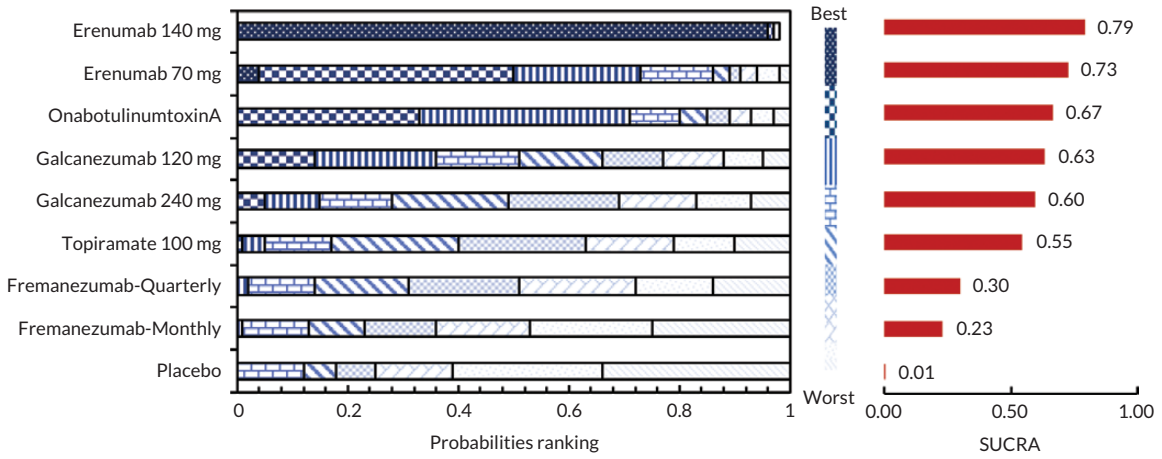

FIGURE 16 Summary of the change in MSQ-EF from baseline – rankings and SUCRA. Ranking probabilities graph (hatching blue bars) of each treatment and red bars are the SUCRA values for each treatment. The probabilities ranking ranged from 0 to 1. Due to rounding in R software these do not equate to one. MSQ-EF, migraine-specific quality of life – emotional function; SUCRA, surface under the cumulative ranking curve.

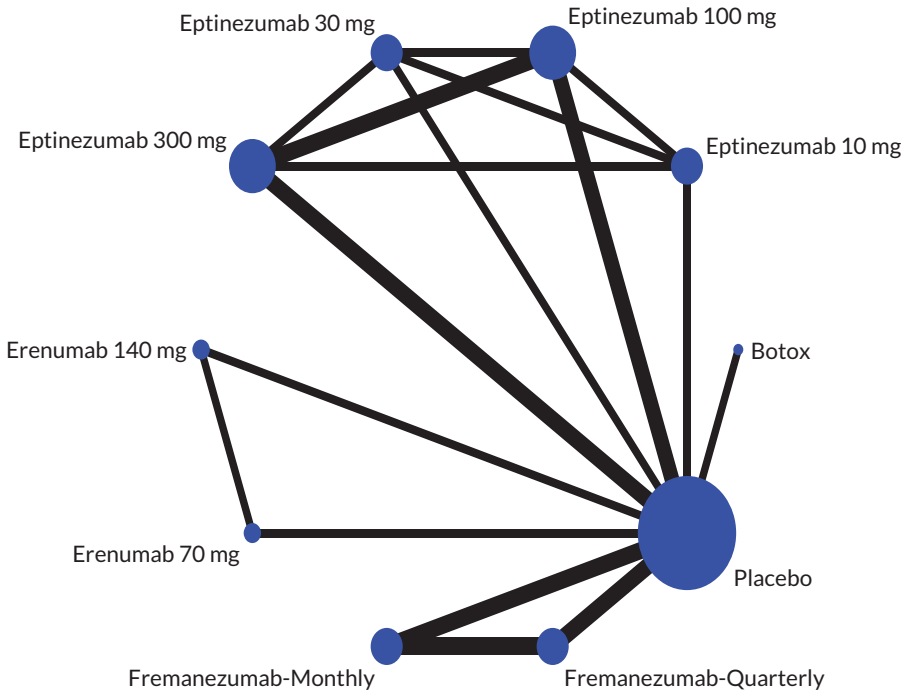

FIGURE 17 Summary of the change in HIT-6 from baseline – network plot. Nodes and edges are weighted according to the number of participants and studies evaluating each treatment and direct comparison, respectively.

included 12 different doses of drugs from 10 trials for the NMA and compared this with placebo as a reference treatment.

The network plot is presented in *Figure 5*. *Figure 6* depicts the result for the fixed-effects NMA model in comparison with placebo. According to the forest plot, all treatments significantly reduced the mean MMDs compared to placebo.

The most effective drug is fremanezumab monthly (MD: −2.76, 95% CrI: −3.36 to −2.15) followed by eptinezumab 300 mg (MD: −2.61, 95% CrI: −3.64 to −1.63), erenumab 70 mg (MD: −2.46, 95% CrI: −3.56 to −1.37), erenumab 140 mg (MD: −2.45, 95% CrI: −3.52 to −1.37), fremanezumab-quarterly

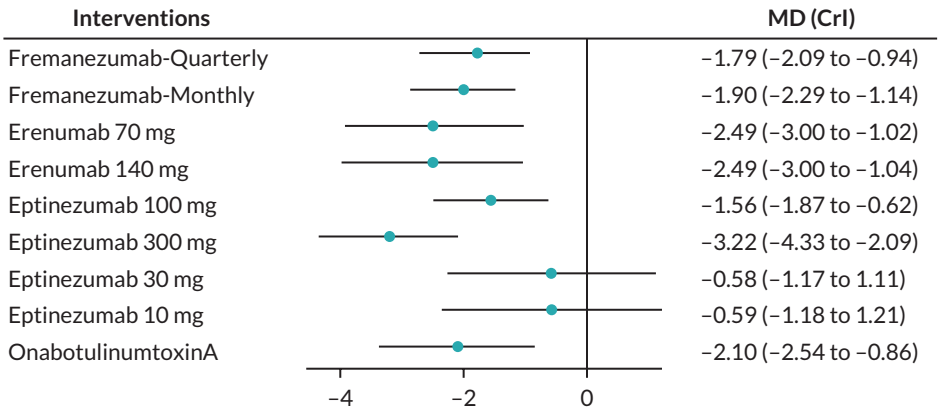

FIGURE 18 Summary of the change in HIT-6 from baseline – forest plot. The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention.

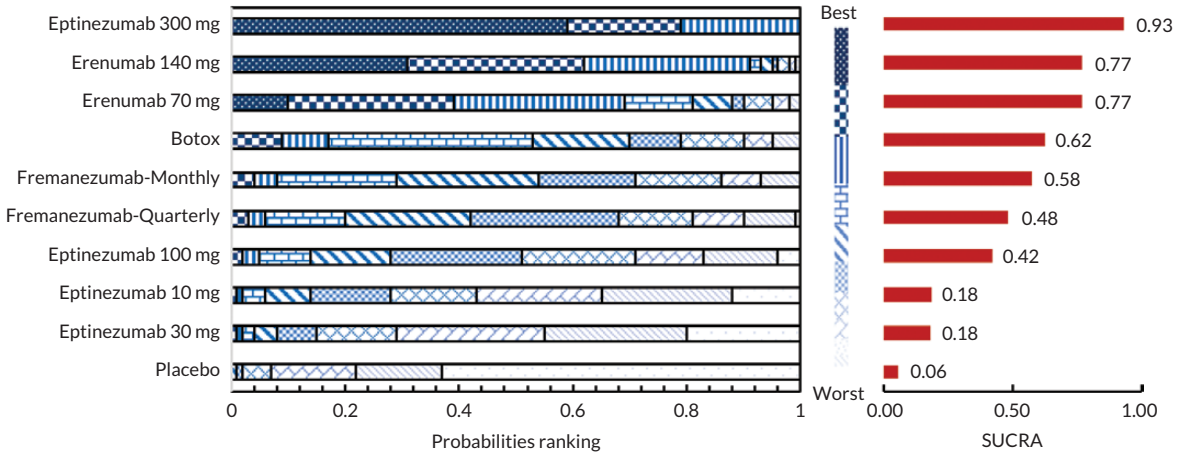

FIGURE 19 Summary of the change in HIT-6 from baseline – rankings and SUCRA. Ranking probabilities graph (hatching blue bars) of each treatment and red bars are the SUCRA values for each treatment. The probabilities ranking ranged from 0 to 1. Due to rounding in R software these do not equate to one. HIT-6, Headache Impact Test; SUCRA, surface under the cumulative ranking curve.

(MD: −2.31, CrI: −2.97 to −1.7), eptinezumab 30 mg (MD: −2.31, CrI: −4.36 to −0.27), galcanezumab 120 mg (MD: −2.11, 95% CrI: −3.22 to −1.3), eptinzumab 100 mg (MD: −2.10, 95% CrI: −2.98 to −1.18), BTA (MD: −1.96, 95% CrI: −2.69 to −1.24), galcanezumab 240 mg (MD: −1.91, 95% CrI: −3.01 to −0.78), topiramate 100 mg (MD: −1.49, 95% CrI: −2.84 to 0.72). The evidence shows the least effective treatment was eptinezumab 10 mg (MD: −1.08, 95% CrI: −3.77 to −0.86). We presented the league tables for all comparisons in *Table 3*.

The 13 node analysis in *Figure 7* showed that eptinezumab 300 mg (SUCRA 0.77) had the highest probability ranking to reduce MMD, followed by fremanezumab monthly and erenumab 70 mg (SUCRA 0.70), erenumab 140 mg (SUCRA 0.69), fremanezumab-quarterly (SUCRA 0.63), eptinezumab 30 mg (SUCRA 0.62), eptinezumab 100 mg and galcanezumab 120 mg (SUCRA 0.52), onabotuliumtoxin A (SUCRA 0.44), galcanezumab 240 mg (SUCRA 0.43), topiramate 100 mg (0.29), eptinezumab 10 mg (SUCRA 0.19) and lowest probability ranking is placebo (SUCRA 0.01). Treatment probabilities ranking and cumulative ranking curves were estimated and tabulated in *Appendix 3*, *Figures 31* and *32* and *Tables 29* and *30*.

According to the data points presented in *Appendix 3*, *Figure 33*, there is no indication of inconsistency, as determined by the global method for testing overall consistency. Also, the result of comparing the fit of NMA and UME inconsistency models illustrated a good fit which is tabulated in *Appendix 3*, *Table 31*.

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TABLE 2 Head-to-head comparisons of treatments for mean change in MHD from baseline (MDs, 95% CrI)

Eptinezumab 300 mg									
−0.36 (−1.52 to 0.81)	Fremanezumab-M								
0.28 (−1.18 to 0.79)	−0.09 (−1.74 to 1.54)	Eptinezumab 30 mg							
0.60 (−0.47 to 1.67)	0.23 (−0.84 to 1.34)	0.32 (−1.25 to 1.95)	BTA						
−0.64 (−2.02 to 0.74)	0.28 (−1.16 to 1.67)	−0.37 (−2.22 to 1.48)	−0.05 (−1.33 to 1.23)	Galcanezumab 120 mg					
−0.62 (−1.42 to 0.17)	0.26 (−0.92 to 1.39)	−0.35 (−1.81 1.05)	−0.02 (−1.05 to 1.02)	−0.02 (−1.35 to 1.31)	Eptinezumab 100 mg				
−0.67 (−1.85 to 0.49)	−0.30 (−1.16 to 0.55)	−0.39 (−2.04 to 1.23)	−0.07 (−1.16 to 0.98)	−0.02 (−1.44 to 1.33)	−0.05 (−1.18 to 1.10)	Fremanezumab-Q			
−0.86 (−2.25 to 0.49)	0.49 (−0.86 to 1.89)	−0.58 (−2.37 to 1.20)	−0.26 (−1.54 to 1.04)	0.21 (0.85 to 1.29)	−0.23 (−1.56 to 1.08)	0.19 (−1.20 to 1.56)	Galcanezumab 240 mg		
−1.36 (−2.89 to 0.14)	0.99 (−0.52 to 2.50)	−1.08 (−3.08 to 0.79)	−0.76 (−2.21 to 0.70)	0.71 (−0.99 to 2.37)	−0.74 (−2.21 to 0.75)	−0.69 (−0.78 to 2.19)	0.50 (−1.18 to 2.15)	Topiramate 100 mg	
1.98 (0.52 to 3.52)	1.62 (−0.13 to 3.34)	1.70 (0.85 to 3.32)	−1.38 (0.85 to 0.29)	1.34 (−0.50. 3.27)	1.36 (−0.13 to 2.87)	1.31 (−0.47 to 3.03)	1.13 (−0.70 to 3.00)	0.62 (−1.36 to 2.69)	Eptinezumab 10 mg
−2.46 (−3.24 to −1.67)	**−2.10 (−2.95 to −1.23)**	**−2.19 (−3.63 to −0.74)**	**−1.87 (−2.55 to −1.18)**	**−1.82 (−2.91 to −0.73)**	**−1.84 (−2.60 to −1.08)**	**−1.79 (−2.62 to −0.98)**	**−1.61 (−2.68 to −0.54)**	−1.10 (−2.38 to 0.16)	−0.48 (−2.02 to 1.01)	Placebo

Fremanezumab-M, fremanezumab monthly; fremanezumab-Q, fremanezumab quarterly.

Note
Mean differences lower than 0 favour the column-defining treatment; CrIs not including 0 are highlighted in bold.

TABLE 3 Head-to-head comparisons of treatments for mean change in MMD from baseline (MDs, 95% CrI)

Eptinezumab 300 mg											
0.15 (−1.04 to 1.31)	Fremanezumab-M										
−0.15 (−1.62 to 1.33)	0.30 (−0.96 to 1.57)	Erenumab 70 mg									
−0.16 (−1.65 to 1.28)	0.31 (−0.94 to 1.57)	0.01 (−1.10 to 1.11)	Erenumab 140 mg								
−0.30 (−1.48 to 0.88)	−0.45 (−1.06 to 0.17)	−0.15 (−1.42 to 1.16)	−0.13 (−1.41 to 1.13)	Fremanezumab-Q							
0.30 (−1.20 to 1.78)	0.45 (−1.13 to 2.05)	0.15 (−1.70 to 1.94)	0.13 (−1.65 to 1.94)	0.00 (−1.60 to 1.66)	Eptinezumab 30 mg						
−0.51 (−1.51 to 0.48)	0.66 (−0.43 to 1.77)	0.36 (−1.09 to 1.78)	0.35 (−1.06 to 1.75)	0.21 (−0.89 to 1.37)	−0.21 (−1.64 to 1.24)	Eptinezumab 100 mg					
−0.50 (−1.93 to 0.97)	0.65 (−0.61 to 1.88)	−0.35 (−1.89 to 1.21)	−0.34 (−1.87 to 1.24)	0.20 (−1.09 to 1.46)	−0.21 (−2.01 to 1.57)	0.01 (−1.43 to 1.43)	Galcanezumab 120 mg				
0.65 (−0.53 to 1.89)	0.80 (−0.15,1.75)	0.50 (−0.79 to 1.81)	0.49 (−0.80 to 1.76)	0.35 (−0.62 to 1.32)	0.36 (−1.24 to 1.99)	0.14 (−1.01 to 1.33)	0.15 (−1.16 to 1.47)	BTA			
−0.70 (−2.20 to 0.76)	0.85 (−0.40 to 2.12)	−0.55 (−2.15 to 0.96)	−0.54 (−2.10 to 0.98)	0.40 (−0.85 to 1.70)	−0.40 (−2.24 to 1.42)	−0.19 (−1.62 to 1.20)	0.20 (−0.89 to 1.29)	−0.05 (−1.36 to 1.26)	Galcanezumab 240 mg		
−1.12 (−2.85 to 0.56)	1.27 (−0.20 to 2.78)	0.97 (−0.78 to 2.71)	0.96 (−0.81 to 2.71)	0.82 (−0.68 to 2.37)	−0.83 (−2.83 to 1.23)	−0.61 (−2.27 to 1.04)	0.62 (−1.13 to 2.38)	−0.47 (−2.01 to 1.07)	0.42 (−1.32 to 2.19)	Topiramate 100 mg	
1.49 (−0.04 to 3.01)	1.64 (0.08 to 3.30)	1.34 (−0.52 to 3.23)	1.33 (−0.53 to 3.16)	1.19 (−0.37 to 2.90)	1.19 (−0.47 to 2.88)	0.98 (−0.49 to 2.46)	0.99 (−0.85 to 2.85)	−0.84 (−2.44 to 0.83)	0.79 (−1.03 to 2.73)	−0.37 (−1.65 to 2.39)	Eptinezumab 10 mg
−2.61 (−3.64 to −1.63)	**−2.76 (−3.36 to −2.15)**	**−2.46 (−3.56 to −1.37)**	**−2.45 (−3.52 to −1.37)**	**−2.31 (−2.97 to −1.7)**	**−2.31 (−4.36 to −0.27)**	**−2.10 (−2.98 to −1.18)**	**−2.11 (−3.22 to −1.03)**	**−1.96 (−2.69 to −1.24)**	**−1.91 (−3.01 to −0.78)**	**−1.49 (−2.84 to −0.12)**	**−1.08 (−3.77 to −0.86)**	Placebo

Fremanezumab-M, fremanezumab monthly; fremanezumab-Q, fremanezumab quarterly.

Note
Mean differences lower than 0 favour the column-defining treatment; CrIs not including 0 are highlighted in bold.

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Mean change in migraine-specific quality of life

Five trials provided improvement in MSQ scores at week 12 with a total 4626 participants, including a trial comparing galcanezumab against placebo,[95] a trial evaluating topiramate versus placebo,[111] a trial investigating fremanezumab versus placebo,[113] a trial comparing erenumab against placebo,[119] and a trial evaluating BTA versus placebo at week 12.[100] The network plots obtained for three dimensions are shown in *Figures 8*, *11* and *14* (which is the same). However, the other results are presented for each dimension separately.

Mean change in migraine-specific quality of life – restrictive role

Forest plots in *Figures 9* and *10* show that all treatments were more effective than placebo. Our analysis demonstrated that erenumab 140 mg (MD: 7.28, 95% CrI: 3.05 to 11.65, SUCRA 0.75) was superior to other drugs in improvement of MSQ-RR and had the highest probability of being ranked best. This was followed by galcanezumab 240 mg (MD: 6.26, 95% CrI: 2.96. to 9.49, SUCRA 0.64) which was the next best ranked treatment, fremanezumab monthly (MD: 6.27, 95% CrI: 3.09 to 9.28, SUCRA 0.63), BTA (MD: 6.32, 95% CrI: 2.51 to 9.95, SUCRA 0.62), erenumab 70 mg (MD: 5.87, 95% CrI: 2.03 to 9.87, SUCRA 0.56), fremanezumab-quarterly (MD: 5.58, 95% CrI: 2.68 to 8.54, SUCRA 0.51), galcanezumab 120 mg (MD: 4.95, 95% CrI: 1.91 to 8.08, SUCRA 0.42), and then topiramate 100 mg (MD: 4.33, 95% CrI: −1.88 to 10.5, SUCRA 0.40). All head-to-head comparisons are shown in *Table 4*.

The ranking probabilities and cumulative ranking probabilities for each treatment are tabulated in *Appendix 3*, *Tables 33* and *34*. Also, plots can be found in *Appendix 3*, *Figures 34* and *35*. The result of comparing the fit of NMA (consistency) model and UMEs inconsistency model is presented in *Appendix 3*, *Table 35*. As presented in *Appendix 3*, *Figure 36* there was no evidence of inconsistency among the data points.

Mean change in migraine-specific quality of life – preventative role

Figures 12 and *13* illustrate that all treatments were more effective than placebo. The NMA results indicate that galcanezumab 120 mg (MD: 6.97, 95% CrI: 3.79 to 10.24, SUCRA 0.88) is more effective in comparison with placebo and had a larger SUCRA, followed by BTA (MD: 5.01, 95% CrI: 1.99 to 8.01, SUCRA 0.61), galcanezumab 240 mg (MD: 5.08, 95% CrI: 1.84 to 8.35, SUCRA 0.60), erenumab 140 mg (MD: 4.93, 95% CrI: 1.70 to 8.20, SUCRA 0.60), fremanezumab-quarterly (MD: 4.29, 95% CrI: 1.90 to 6.81, SUCRA 0.49), erenumab 70 mg (MD: 4.09, 95% CrI: 0.76 to 7.31, SUCRA 0.45), topiramate 100 mg (MD: 3.78, 95% CrI −2.37 to 9.80, SUCRA 0.44), and finally fremanezumab monthly (MD: 3.89 95% CrI: 1.39 to 6.41, SUCRA 0.41). *Table 5* presents all head-to-head comparisons of treatment. The ranking probabilities and cumulative ranking probabilities for each treatment are tabulated in *Appendix 3*, *Tables 37* and *38*. The corresponding plots can be found in *Appendix 3*, *Figures 37* and *38*. The result of comparing the fit of NMA model and UME model are presented in *Appendix 3*, *Table 39*. Based on the available data points, there was no indication of inconsistency (see *Appendix 3*, *Figure 39*).

Mean change in migraine-specific quality of life – emotional function

The study results confirmed that all treatments are more effective than placebo. The results of mean change in MSQ-EF for each drug in comparison with placebo have been presented as forest plot and ranked by SUCRA in *Figures 15* and *16*. Erenumab 140 mg (MD: 8.89, 95% CrI: 3.20 to 14.55, SUCRA 0.79) was the most effective in improving of MSQ-EF and was superior to others in terms of ranking, followed by erenumab 70 mg (MD: 8.30, 95% CrI: 2.10 to 14.63, SUCRA 0.73), BTA (MD: 7.34 95% CrI: 2.90 to 11.72, SUCRA 0.67), galcanezumab 120 mg (MD: 6.90, 95% CrI: 3.42 to 10.57, SUCRA 0.63), galcanezumab 240 mg (MD: 6.59, 95% CrI: 2.87 to 10.23, SUCRA 0.60), topiramate 100 mg (MD: 6.17, 95% CrI: 0.02 to 12.52, SUCRA 0.55), and fremanezumab-quarterly (MD: 3.88, 95% CrI: 1.06 to 6.75, SUCRA 0.30), while the least effective treatment was fremanezumab monthly (MD: 3.31, 95% CrI: 0.69 to 5.95, SUCRA 0.23). *Table 6* presents all head-to-head comparisons of treatment. The ranking probabilities and cumulative ranking probabilities for each treatment are tabulated in *Appendix 3*, *Tables 41* and *42*. Also, the ranking graphs are available in *Appendix 3*, *Figures 40* and *41*. The result of

TABLE 4 Head-to-head comparisons of treatments for mean change in MSQ-RR from baseline

Erenumab 140 mg							
1.02 (−4.32 to 6.49)	Galcanezumab 240 mg						
1.02 (−4.15 to 6.29)	0.01 (−4.58 to 4.60)	Fremanezumab-M					
−0.96 (−6.59 to 4.94)	0.06 (−4.79 to 4.89)	0.06(−4.78 to 4.75)	BTA				
1.41 (−3.01 to 5.86)	−0.39 (−5.47 to 4.59)	−0.39 (−5.42 to 4.53)	0.45 (−5.09 to 5.81)	Erenumab 70 mg			
1.71 (−3.49 to 6.85)	0.68 (−3.68 to 5.07)	0.69 (−2.38 to 3.66)	0.75 (−4.04 to 5.37)	0.30 (−4.68 to 5.26)	Fremanezumab-Q		
2.33 (−2.82 to 7.76)	1.31 (−2.02 to 4.76)	−1.31 (−5.72 to 3.21)	1.37 (−3.53 to 6.16)	0.92 (−4.06 to 5.88)	−0.62 (−4.95 to 3.81)	Galcanezumab 120 mg	
−2.95 (−10.46 to 4.43)	−1.93 (−8.71 to 5.06)	−1.93 (−8.75 to 4.92)	1.99 (−5.23 to 9.11)	−1.54 (−9.02 to 5.87)	−1.24 (−7.91 to 5.52)	−0.62 (−7.51 to 6.17)	Topiramate 100 mg
7.28 (3.05 to 11.65)	**6.26 (2.96 to 9.49)**	**6.27 (3.09 to 9.28)**	**6.32 (2.51 to 9.95)**	**5.87 (2.03 to 9.87)**	**5.58 (2.68 to 8.54)**	**4.95 (1.91 to 8.08)**	4.33 (−1.88 to 10.50)	Placebo

Fremanezumab-M, fremanezumab monthly; fremanezumab-Q, fremanezumab quarterly.

Note
Mean differences more than 0 favour the column-defining treatment; CrIs not including 0 are highlighted in bold.

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TABLE 5 Head-to-head comparisons of treatments for mean change in MSQ-PR from baseline

Galcanezumab 120 mg							
−1.95 (−6.41 to 2.37)	BTA						
−1.89 (−5.15 to 1.44)	−0.07 (−4.56 to 4.41)	Galcanezumab 240 mg					
−2.04 (−6.59 to 2.51)	0.09 (−4.32 to 4.60)	−0.15 (−4.26 to 4.30)	Erenumab 140 mg				
2.68 (−1.42 to 6.73)	0.73 (−3.30 to 4.55)	0.79 (−3.28to 4.87)	0.64 (−3.44 to 4.63)	Fremanezumab-Q			
−2.88 (−7.34 to 1.49)	0.93 (−3.51 to 5.37)	−0.99 (−5.57 to 3.64)	0.84 (−2.69 to 4.29)	−0.20 (−4.47 to 3.81)	Erenumab 70 mg		
−3.19 (−10.04 to 3.51)	1.24 (−5.50 to 8.32)	−1.30 (−8.06 to 5.64)	−1.15 (−8.18 to 5.69)	−0.51 (−7.05 to 6.02)	−0.31 (−7.11 to 6.38)	Topiramate 100 mg	
3.08 (−1.06 to 7.14)	1.12 (−2.71 to 5.08)	1.19 (−2.87 to 5.17)	1.03 (−3.08 to 5.21)	−0.39 (−2.81 to 1.96)	0.20 (−3.88 to 4.30)	−0.11 (−6.76 to 6.27)	Fremanezumab-M
6.97 (3.79 to 10.24)	**5.01 (1.99 to 8.01)**	**5.08 (1.84 to 8.35)**	**4.93 (1.70 to 8.20)**	**4.29 (1.90 to 6.81)**	**4.09 (0.76 to 7.31)**	3.78 (−2.37 to 9.80)	**3.89 (1.39 to 6.41)**	Placebo

Fremanezumab-M, fremanezumab monthly; fremanezumab-Q, fremanezumab quarterly.

Note
Mean differences more than 0 favour the column-defining treatment; CrIs not including 0 are highlighted in bold.

TABLE 6 Head-to-head comparisons of treatments for mean change in MSQ-EF from baseline

Erenumab 140 mg							
0.59 (−5.82 to 7.14)	Erenumab 70 mg						
−1.55 (−8.60 to 5.55)	−0.97 (−8.49 to 6.75)	BTA					
1.99 (−4.84 to 8.74)	1.41 (−5.89 to 8.58)	0.44 (−5.48 to 6.13)	Galcanezumab 120 mg				
2.30 (−4.41 to 9.12)	1.71 (−5.70 to 9.30)	0.74 (−4.96 to 6.49)	−0.31 (−4.08 to 3.49)	Galcanezumab 240 mg			
−2.72 (−10.92 to 5.49)	−2.13 (−11.04 to 6.98)	1.17 (−6.56 to 8.78)	−0.73 (−7.79 to 6.61)	−0.42 (−7.52 to 6.94)	Topiramate 100 mg		
5.01 (−1.35 to 11.35)	4.42 (−2.31 to 11.35)	3.46 (−1.88 to 8.79)	3.02 (−1.73 to 7.69)	2.71 (−2.00 to 7.39)	2.29 (−4.60 to 9.13	Fremanezumab-Q	
5.58 (−0.77 to 11.65)	4.99 (−3.48 to 11.74)	4.03 (−1.10 to 9.18)	3.59 (−1.09 to 8.25)	3.28 (−1.31 to 7.72)	2.86 (−3.78 to 9.31)	−0.57 (−3.31 to 2.21)	Fremanezumab-M
8.89 (3.20 to 14.55)	**8.30 (2.10 to 14.63)**	**7.34 (2.90 to 11.72)**	**6.90 (3.42 to 10.57)**	**6.59 (2.87 to 10.23)**	**6.17 (0.02 to 12.52)**	**3.88 (1.06 to 6.75)**	**3.31 (0.69 to 5.95)**	Placebo

Fremanezumab-M, fremanezumab monthly; fremanezumab-Q, fremanezumab quarterly.

Note
Mean differences more than 0 favour the column-defining treatment; CrIs not including 0 are highlighted in bold.

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comparing the fit of NMA model and UME model is presented in *Appendix 3*, *Table 43*. There was no evidence of inconsistency in data points (see *Appendix 3*, *Figure 42*).

Mean change in headache impact test-6

Mean change in HIT-6 from baseline was reported in seven RCTs with a total of 5763 participants including a trial comparing BTA with placebo,[100] two trials evaluating eptinezumab versus placebo,[89,94] two trials comparing fremanezumab with placebo,[37,96] a trial investigating erenumab against placebo,[119] all of which have been measured at week 12, and a trial evaluating BTA versus topiramate[88,109] at week 30. As mentioned earlier, we considered the follow-up period of 12 weeks as a measurement point for NMA.

We analysed the first six trials with nine different doses of drugs compared with placebo as a reference treatment. The network plot is presented in *Figure 17*.

The most effective treatment in the reduction of HIT-6 estimated with the highest rank was eptinezumab 300 mg (MD: −3.22, 95% CrI: −3.59 to 2.09, SUCRA 0.93), followed by erenumab 140 mg (MD: −2.49, 95% CrI: −3.00 to −1.04, SUCRA 0.77), erenumab 70 mg (MD: −2.49, 95% CrI: −3.00 to −1.02, SUCRA 0.77), BTA (MD: −2.10, 95% CrI: −2.54 to −0.86, SUCRA 0.62), fremanezumab monthly (MD: −1.99, 95% CrI: −2.29 to −1.14, SUCRA 0.58), fremanezumab-quarterly (MD: −1.79, 95% CrI: −2.09 to −0.94, SUCRA 0.48), eptinezumab 100 mg (MD: −1.56, 95% CrI: −1.87 to −0.62, SUCRA 0.42), eptinezumab 10 mg (MD: −0.59, 95% CrI: −1.18 to 1.21, SUCRA 0.18), and the least efficacious drug was eptinezumab 30 mg (MD: −0.58, 95% CrI: −1.17 to 1.11, SUCRA 0.18) as shown in *Figures 18* and *19*.

Table 7 presents all head-to-head comparisons of treatment. The ranking probabilities and cumulative ranking probabilities for each treatment are tabulated in *Appendix 3*, *Tables 45* and *46*. Also plots can be found in *Appendix 3*, *Figures 43* and *44*. The result of comparing the fit of NMA model and UME model is presented in *Appendix 3*, *Table 47*. There was no evidence of inconsistency in data points as shown in *Appendix 3*, *Figure 45*.

Sensitivity analysis results

The results for two sensitivity analyses for the mean change in MHDs and MMDs from baseline, excluding eptinezumab 10 and 30 mg as they are not used in routine practice, are presented below. Further results are presented at *Appendix 3*, *Tables 48* and *49* and *Figures 46–49*.

Mean change in monthly headache days

The results of the MHD sensitivity analysis suggest that excluding eptinezumab 10 and 30 mg from the base-case analysis changed the observed effect size from −0.02 to +0.02. This has meant some of the ranking of treatments in the SUCRA have changed. However, the top two treatments (eptinezumab 300 mg and fremanezumab monthly) have remained the same. The reordering of the new treatments is provided in *Figure 20*.

Mean change in monthly migraine days

The results of the MMD sensitivity analysis suggest that the observed effect after excluding eptinezumab 10 and 30 mg changed from −0.02 to +0.02. This has meant some of the ranking of treatments in the SUCRA have changed, including for the top two treatments: the SUCRA for eptinezumab 300 mg and fremanezumab monthly switched from 0.77 to 0.73 and 0.70 to 0.73, respectively. The reordering of the new treatments is provided in *Figure 21*.

Risk of bias in included studies

RoB assessments were undertaken using the Cochrane RoB 2 tool for randomised trials. The results of the RoB ratings by trial are summarised across the studies below and are presented in *Figure 22* by RoB

TABLE 7 Head-to-head comparisons of treatments for mean change in HIT-6 from baseline

Eptinezumab 300 mg									
−0.72 (−1.34 to 1.10)	Erenumab 140 mg								
−0.73 (−1.36 to 1.15)	0.00 (−0.57 to 1.68)	Erenumab 70 mg							
1.11 (0.52 to 2.79)	0.39 (−0.30 to 2.32)	0.39 (−0.29 to 2.34)	BTA						
−1.23 (−1.72 to 0.17)	−0.50 (−1.09 to 1.15)	−0.50 (−1.09 to 1.16)	−0.11 (−0.64 to 1.43)	Fremanezumab-M					
−1.42 (−1.93 to 0.00)	−0.70 (−1.28 to 1.01)	−0.70 (−1.29 to 1.01)	−0.31 (−0.86 to 1.23)	−0.20 (−0.49 to 0.65)	Fremanezumab-Q				
−1.66 (−2.03 to −0.62)	0.93 (0.32 to 2.66)	0.93 (0.33 to 2.67)	−0.54 (−1.07 to 1.01)	0.43 (0.00 to 1.69)	0.23 (−0.23 to 1.51)	Eptinezumab 100 mg			
2.63 (2.01 to 4.44)	1.91 (1.12 to 4.19)	1.90 (1.14 to 4.20)	−1.52 (−2.24 to 0.54)	1.40 (0.73 to 3.36)	1.20 (0.52 to 3.19)	0.97 (0.37 to 2.70)	Eptinezumab 10 mg		
2.64 (2.04 to 4.39)	1.92 (1.13 to 4.11)	1.91 (1.17 to 4.11)	−1.52 (−2.24 to 0.54)	1.41 (0.76 to 3.27)	1.21 (0.55 to 3.07)	0.98 (0.41 to 2.67)	−0.01 (−0.67 to 1.95)	Eptinezumab 30 mg	
−3.22 (−3.59 to −2.09)	**−2.49 (−3.00 to −1.04)**	**−2.49 (−3.00 to −1.02)**	**−2.10 (−2.54 to −0.86)**	**−1.99 (−2.29 to −1.14)**	**−1.79 (−2.09 to −0.94)**	**−1.56 (−1.87 to −0.62)**	−0.59 (−1.18 to 1.21)	−0.58 (−1.17 to 1.11)	Placebo

Fremanezumab-M, fremanezumab monthly; fremanezumab-Q, fremanezumab quarterly.

Note
Mean differences lower than 0 favour the column-defining treatment; CrIs not including 0 are highlighted in bold.

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Base-case analysis Eptinezumab 300 mg		Sensitivity analysis	
Treatment ranking	**SUCRA**	**Treatment ranking**	**SUCRA**
1 Eptinezumab 300 mg	0.88	1 Eptinezumab 300 mg	0.82
2 Fremanezumab-Monthly	0.71	2 Fremanezumab-Monthly	0.66
3 Eptinezumab 30 mg	0.71	3 Eptinezumab 100 mg	0.57
4 OnabotulinumtoxinA	0.59	4 OnabotulinumtoxinA	0.57
5 Galcanezumab 120 mg	0.57	5 Galcanezumab 120 mg	0.54
6 Eptinezumab 100 mg	0.57	6 Fremanezumab-Quarterly	0.53
7 Fremanezumab-Quarterly	0.55	7 Galcanezumab 240 mg	0.47
8 Galcanezumab 240 mg	0.47	8 Topiramate 100 mg	0.31
9 Topiramate 100 mg	0.30	9 Placebo	0.03
10 Eptinezumab 10 mg	0.14		
11 Placebo	0.03		

FIGURE 20 Illustrative sensitivity analysis results for mean change in MHDs from baseline.

Base-case analysis		Sensitivity analysis	
Treatment ranking	**SUCRA**	**Treatment ranking**	**SUCRA**
1 Eptinezumab 300 mg	0.77	1 Fremanezumab-Monthly	0.73
2 Fremanezumab-Monthly	0.70	2 Eptinezumab 300 mg	0.73
3 Erenumab 70 mg	0.70	3 Erenumab 70 mg	0.67
4 Erenumab 140 mg	0.69	4 Erenumab 140 mg	0.66
5 Fremanezumab-Quarterly	0.63	5 Fremanezumab-Quarterly	0.59
6 Eptinezumab 30 mg	0.62	6 Galcanezumab 120 mg	0.49
7 Eptinezumab 100 mg	0.52	7 Eptinezumab 100 mg	0.47
8 Galcanezumab 120 mg	0.44	8 OnabotulinumtoxinA	0.40
9 OnabotulinumtoxinA	0.44	9 Galcanezumab 240 mg	0.38
10 Galcanezumab 240 mg	0.43	10 Topiramate 100 mg	0.27
11 Topiramate 100 mg	0.29	11 Placebo	0.00
12 Eptinezumab 10 mg	0.19		
13 Placebo	0.01		

FIGURE 21 Illustrative sensitivity analysis results for mean change in MMDs from baseline.

category. Overall, there were no major concerns that the studies were not applicable to the research question for this assessment.

Randomisation process

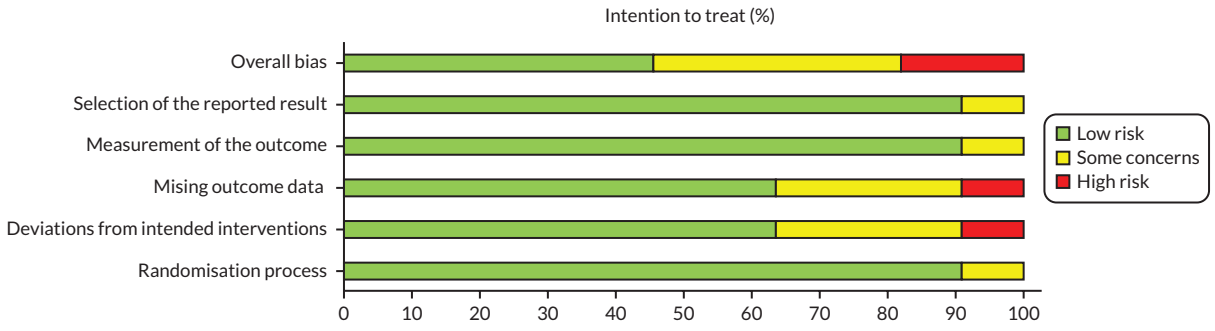
Only the open label trial[88] was rated as having some concerns for this domain, and other trials (10 studies) were assessed at being at low risk of bias (91%).[28,37,45,89–95]

Deviations from the intended interventions

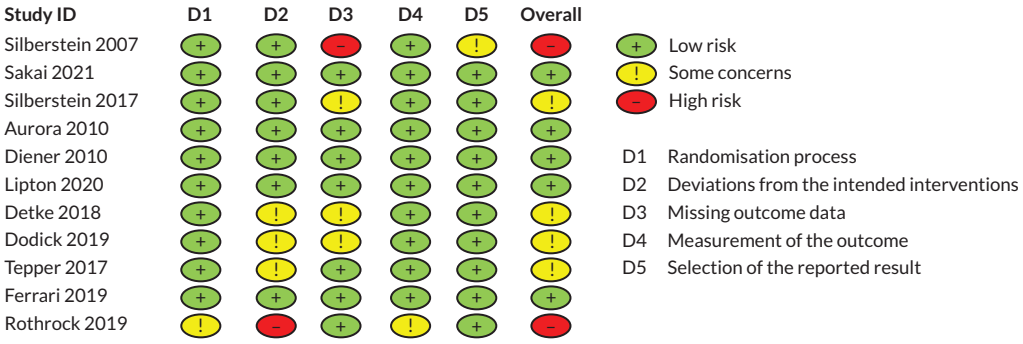
One trial (9%) was assessed as high risk of bias,[88] three trials (27%) rated as having some concerns of risk of bias,[45,89,95] and seven trials (64%) rated as being at low risk of bias.[28,37,90–94]

Missing outcome data

The result for assessing risk of bias due to the missing outcome data was considered the same as the previous domain: one trial (9%) (high risk of bias),[28] three trials (27%) (some risk of bias)[37,89,95] and seven trials (64%) (low risk of bias).[45,88,90–94]



a) Summary of risk of bias assessment



b) Traffic lights for the risk of bias for each included study

FIGURE 22 Risk of bias assessment result.

Measurement of the outcome

As the measurement or ascertainment of the outcome does not have to differ between intervention groups in all trials and outcome assessors were not aware of the intervention received by study participants in most of the trials, 10 (91%) trials were rated as being at low risk of bias.[28,37,45,89–95] Only the open-label study trial was rated as having some concerns of bias due to no masking of the outcome assessor.[88]

Selection of the reported result

Ten trials (91%) were in line with their pre-specified analysis plan and registered protocol, thus they were rated as being at low risk of bias,[37,45,88–95] and only one trial (9.1%) was considered to have some concerns and was unclear.[28]

Overall bias

Finally, the ratings for the overall risk of bias domain indicated that two trials (18%), four trials (36%) and five trials (46%) were rated as being at high,[28,88] some concerns,[37,45,89,95] and low risk of bias,[90–94] respectively.

In summary, the studies included in our systematic review and NMA had a relative good quality in terms of risk of bias.

Certainty of evidence assessment by GRADE approach

Using the GRADE approach, we found that the certainty of evidence for each estimate was judged to be low to high (see *Report Supplementary Material 2*). Some estimate points were rated down by one level when the studies with high risk of bias in at least one domain contributed to the comparisons. Imprecision of some results were downgraded when the null value (zero for continuous outcomes) lies within the 95% CrI. The summary of GRADE results for outcomes of interest separately is presented in *Table 8*. In brief, the GRADE assessments indicated a relative certainty of evidence. The robust certainty degree was particularly highlighted for those estimations when drugs were compared with placebo.

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TABLE 8 Summary of GRADE results for each outcome

	GRADE level			
Outcomes	High	Moderate	Low	Very low
MHDs	*	*	*	
MMDs	*	*		
MSQ-RR	*	*		
MSQ-PR	*		*	
MSQ-EF	*	*		
HIT-6	*	*		

Discussion

In our analysis of 11 RCTs[37,45,88–95,111] involving 7352 adult participants with chronic migraine, the results show that all pharmacological treatments for all outcomes of interest were beneficial in preventing migraine when compared to placebo. Evidence synthesis and treatments ranking was performed through a NMA, using pre-specified inclusion and exclusion criteria. The statistical analyses were conducted within a Bayesian framework using multinma package[80] in R software version 4.1.3[81] to synthesise relevant data for each outcome of interest.

We performed six NMA for MHDs, MMDs, the three dimensions of MSQ, and the six-item HIT-6. We considered different dosing regimens for fremanezumab, galcanezumab, eptinezumab, erenumab, topiramate and BTA as separate treatments.

The results from the NMA showed that eptinezumab 300 mg and fremanezumab monthly ranked in first place in both MHD and MMD analyses (SUCRA for MHD: 0.88 and 0.71; SUCRA for MMD: 0.77 and 0.70, respectively). Eptinezumab 300 mg was the most effective drug in reduction of MHDs and also ranked as the best treatment. It should also be noted that there were no considerable differences in MHDs between eptinezumab 300 mg and eptinezumab 30 mg (MD: −2.46, 95% CrI: −3.24 to −1.67 and MD: −2.19, 95% CrI: −3.63 to −0.74, respectively). However, for eptinezumab 30 mg, which resulted in higher effect size (MD: −2.19, 95% CrI: −3.63 to −0.74) than 100 mg (MD −1.84, 95% CrI −2.60 to −1.08), this may be partly explained by the smaller sample size and the wider CIs. For MMDs, the results showed were similar to MHDs, and the best ranked treatment was for eptinezumab 300 mg; however, the most effective treatment was fremanezumab monthly. The NMA results concluded that a lower dose of erenumab (70 mg) showed a similar reduction in the MMDs as with its higher dose (140 mg). However, our clinical colleagues have noted in clinical practice that erenumab 140 mg appears to come out better; however, this is anecdotal and not evidence-based.

Furthermore, the NMA results showed that BTA ranked better in the mean change in MHD (fourth place, SUCRA: 0.59) compared with the mean change in MMD (nineth place, SUCRA: 0.44). Topiramate is ranked bottom (by a reasonable margin) in both (SUCRA: 0.3 for MHDs and 0.29 for MMDs).

The results for the three dimensions of the MSQ, and HIT-6, were provided in a NMA and the other QoL outcomes, including MIDAS, EQ-5D, PHQ-9, WPAI:SHP and FIMQ, were reported narratively. Galcanezumab 120 mg provided the best improvement in QoL for the preventative role dimension of MSQ (MSQ-PR) (MD: 6.97, 95% CrI: 3.79 to 10.24, SUCRA 0.88), but for two other dimensions including restrictive role (MSQ-RR) and emotional function (MSQ-EF), erenumab 140 mg was superior to other interventions in terms of QoL (for MSQ-RR; MD: 7.28, 95% CrI: 3.05 to 11.65, SUCRA 0.75, and for MSQ-EF; MD: 8.89, 95% CrI: 3.20 to 14.55, SUCRA 0.79). However, it was noted that the

galcanezumab 120 mg showed superiority over galcanezumab 240 mg in the improvement of MSQ-PR and MSQ-EF dimensions. For the HIT-6, the results showed that eptinezumab 300 mg has the most effective treatment in reduction of the HIT-6 (MD: −3.22, 95% CrI: −3.59 to 2.09, SUCRA 0.93). It was noted that erenumab 140 mg had similar effect size with erenumab 70 mg (MD: −2.49, 95% CrI: −3.00 to −1.04, SUCRA 0.77 and MD: −2.49, 95% CrI: −3.00 to −1.02, SUCRA 0.77, respectively).

The results provided in this chapter are subject to the quality of the included studies. In this study, the results from the quality assessment found that approximately 46% of the included RCTs in this review had low RoB and 36% of the RCTs had some concerns of bias. The open label design data for BTA and topiramate carried a considerable risk of bias, but they were not incorporated into the NMA analysis due to a lack of information regarding week 12. However, the topiramate data that were included in the NMA were evaluated with a high risk of bias because it was unclear how to address the missing data. We found that the certainty of evidence for each estimate of GRADE was judged to be low to high, which highlighted the relative robustness of our findings for applying in the clinical decision-making. The main limitation of this study was the trial design for topiramate which led to grading down of certainty in MHDs, MMDs and the three dimensions of MSQ. Imprecision of estimations for eptinezumab 10 mg versus placebo resulted in downgrading in MHDs. In addition, the effect size of eptinezumab 10 and 30 mg compared with placebo gave some concerns to the imprecision.

Comparison to existing literature

To the best of our knowledge, this study is the first comprehensive NMA for pharmaceutical treatments currently available in the UK for adults with chronic migraine. Our findings for MHDs and MMDs are largely in line with a previous NMA.[72] The authors in this previous review aimed to investigate the effects of CGRP MAbs on 5164 chronic migraineurs in seven randomised trials.[72] Their focus was solely on CGRP MAbs drugs, whereas we took into account all pharmacological medications available in the UK. Our eligibility criteria allowed for the inclusion of not only CGRP MAbs, but also other drugs, such as BTA and topiramate.

In another paper, erenumab was more effective than BTA in the reduction of MMDs,[120] which is in line with our results. The effectiveness of different CGRP MAbs for 3052 adult migraine patients with prior treatment failure was investigated in another review.[121] Galcanezumab 240 mg was ranked first in reducing MMDs, followed by fremanezumab monthly and then eptinezumab 300 mg. However, these findings were not in line with ours and it seems that the population with the previous treatment failures may have resulted in this discrepancy. Moreover, erenumab in our findings was ranked as the second best treatment (jointly with fremanezumab monthly) in reduction of MMDs, while in their analyses erenumab was ranked as the least effective treatment for those participants with previous treatment failures.[121] Another review and NMA aimed to assess the effect of CGRP MAbs on disability related to migraine in 7095 adult patients from nine randomised trials.[122] Fremanezumab depicted slightly better improvement in disability compared with other CGRP MAbs at 12 weeks.[122] However, our finding in improvement of MSQ score in all dimensions had the same result. Although we also compared other medications including different doses of fremanezumab, eptinezumab and BTA in our analyses, this provides a comprehensive picture of the effectiveness of different classes of drugs on participants' QoL. Based on our results, erenumab 140 mg was the most effective treatment in the improvement of MSQ-RR and MSQ-EF but was ranked in fourth place in the effectiveness of the MSQ-PR. Our results illustrate that there are no significant differences between the two doses of erenumab in decreasing disability scores (measured by HIT-6); however, they were the second most effective treatment for MMDs.

Strengths and limitations

The main strength of this analysis is the range of migraine treatment classes including the latest treatments, such as CGRP MAbs, namely fremanezumab, eptinezumab, galcanezumab and erenumab, which are commonly used after other concurrent preventive treatments, such as BTA and topiramate have failed in the UK. This diversity can provide a comprehensive picture of the effectiveness profile of medications for decision-makers to compare migraine treatment alternatives. Therefore, this may

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better reflect current clinical practice. Another strength of this review is the comprehensiveness of the search strategy which was used. The search was run and updated across a broad range of electronic databases to ensure all relevant trials were included. Furthermore, we did not allow for any date or language restrictions.

However, the results of this analysis should be interpreted with caution due to its limitations. All trials included in the NMA were placebo-controlled; thus, we were not able to estimate any indirect comparisons and, hence, assess the local inconsistency. This means that there were no direct drug-to-drug comparisons in our included trials. We also included a trial which included participants who failed up to four migraine preventive drug classes[90] which might result in bias in our results. Finally, we excluded studies with fewer than 100 participants per arm to include better-quality studies and to avoid loss of precision on our NMA by including heterogenous studies;[55,56] hence, this excluded all other trials on oral migraine preventatives and restricted the analysis to topiramate, BTA and CGRP MAbs. This may have limited the NMA to more recently investigated treatments where the trial methodology is more precise, and which were undertaken after chronic migraine was introduced as a classification in 2007. Older trials did not separate out chronic migraine from episodic migraine or even define a difference – and including them would have resulted in a large degree of heterogeneity (e.g. between participant baseline characteristics) and results would have been at a high risk of bias and, thus, a NMA would not have been possible. Nevertheless, we might have also missed some important data by excluding these smaller trials. The quality of these older trials may be limited by a variety of factors, such as inadequate sample size, inadequate control groups and outdated methodologies. Conducting newer trials with adequate power, larger sample size and more rigorous designs can help improve our understanding of a treatment's effectiveness and can help address these limitations of the older trials and provide more reliable and accurate results. Due to the above-mentioned restrictions to the older trials or even newer trials with no efforts to distinguish between migraine subtypes, we believe our results may have less heterogeneity and, subsequently, more precise results.

After completion of the study, we reviewed papers that we had excluded on the size criterion and we identified just one that might have been included. This study randomised 72 people to BTA or amitriptyline. It did not report on MMD, MHD or headache-related QoL. No between-group difference was found in the measures reported.[123] Another trial, that randomised 191 participants from an original target of 250, tested the addition of propranolol to topiramate in people after failure of topiramate monotherapy. This trial was stopped early on the advice of the data safety and monitoring board for futility and provides conclusive evidence that it is not worth using propranolol in this situation.[124] In our protocol design we did not consider the inclusion of trials where additional drugs were added and by default we might have included this, if the trial had reached its recruitment target. Nevertheless, it would not have fitted in our NMA, and its effect estimate does not tell us what the effect of propranolol might be when used as monotherapy. This post hoc review of excluded studies does not indicate that any relevant data have been excluded from our NMA by setting a size criterion for inclusion. The total number of trials for which we eventually extracted data was substantially fewer than we anticipated at the scoping stage because of reporting different aspects of the trials across multiple, sometimes overlapping papers, with 51 individual papers reporting just 11 trials.

In summary, the NMA findings from the included 11 RCTs indicated that pharmacological treatments are more effective than placebo in managing chronic migraine across all outcomes of interest. This review provides supportive evidence for using prophylactic medications to improve both effectiveness and QoL in chronic migraine management. According to our results, some (but not all) MAbs are better than BTA and the remainder roughly equivalent to BTA. Topiramate is worst overall. However, it is important to consider some limitations in the analyses that may affect the certainty of the results, including the lower quality of some of the included trials and the focus on larger-scale trials.

Chapter 3 Adverse events review

Research question 2: What are the comparative incidences of AEs of prophylactic drugs used for migraine?

Introduction

This chapter will explore and systematically review all published evidence on the incidence of AEs and SAEs in people with both chronic and episodic migraine. Apart from the recent trials of CGRP MAbs, AEs are poorly reported. For this reason, we extended our inclusion criteria for this review (that met the inclusion criteria for the clinical effectiveness review) to include trials with mixed populations which included episodic migraine. Thus, this allows us to give a robust estimate of the incidence of AEs in the whole population with migraine. Therefore, the list of drugs in this chapter is different from the clinical effectiveness chapter.

In this review, we applied the Common Terminology Criteria for Adverse Events (CTCAE) v5.0[125] and considered the following standard definitions for AEs and SAEs.

> **Adverse event**: *An adverse event that is not a serious adverse event, meaning that it does not result in death, is not life-threatening, does not require inpatient hospitalisation or extend a current hospital stay, does not result in an ongoing or significant incapacity or interfere substantially with normal life functions, and does not cause a congenital anomaly or birth defect; it also does not put the participant in danger and does not require medical or surgical intervention to prevent one of the results listed above.*[125]
>
> **Serious adverse event**: *An adverse event that results in death, is life-threatening, requires inpatient hospitalisation or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalisation may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.*[125]

Methods

The AEs review followed the PRISMA guidelines for reporting systematic reviews[52] and the Cochrane Handbook for Systematic Reviews of Interventions.[53] The protocol for the AEs review was registered in the PROSPERO database. The registration number is CRD42021265993.

Search strategy

The search strategies for the AEs review were conducted jointly with those for the clinical effectiveness review and have already been reported in the previous chapter (see *Chapter 2*).

Assessing the relevance and inclusion of studies

Title and abstract screening was conducted by two reviewers (AB, SN). Screening was performed according to PICO criteria (see *Box 3* for inclusion criteria and *Box 4* for exclusion criteria). At this stage, the abstracts of the retrieved studies were reviewed independently by two out of four reviewers (MU, SN, AA, ND). The full texts of the remaining studies were retrieved, and the same combination of the reviewers conducted an additional round of full-text screening according to the pre-specified inclusion/exclusion criteria.

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BOX 3 Eligibility criteria – inclusion criteria

Inclusion criteria

Study design

- RCTs in any setting.
- RCTs with more than 100 participants per arm.

Population

- Adults (≥ 18 years old) with chronic or episodic migraine.

Intervention

- Available or anticipated to be available pharmacological medications in the UK: CGRP MAbs, BTA, antidepressants, ACE inhibitors and angiotensin receptor blockers, beta-blockers, calcium channel blockers, pizotifen, flunarizine and anti-convulsants (topiramate, valproate/divalproex, gabapentin).

Comparator

- Placebo, or
- Usual care, or
- Other prophylactic drugs.

Outcome(s) of interest

- Adverse events and treatment-related adverse events (TAEs).
- Serious adverse events and treatment-related serious adverse events (TSAEs).

BOX 4 Eligibility – exclusion criteria

Exclusion criteria

Study design

- Non-randomised trials, quasi-randomised trials, observational studies (e.g. case reports and case series), subgroup analysis and other designs.
- RCTs with fewer than 100 per arm.

Population

- Children and young people aged < 18 years.
- Participants with menstrual migraine, acute migraine, abdominal migraine, vestibular migraine, or any other conditions-related migraine.
- Trials that examined participants with other primary headaches including tension-type headaches, cluster headaches, and all sorts of secondary headaches.

Intervention and comparator

- Studies comparing cognitive–behavioural therapy, psychological interventions, exercise, dietary and relaxation.
- Studies which were dose–response trials.
- Studies comparing different preparations of the same drug in the absence of placebo.
- Laboratory studies without clinical outcomes.
- Chinese traditional medicines, that is, herbal medicine/drugs and other herbal remedies which are not prescribed in the UK.
- Drugs which are not prescribed by NHS or recommended by NICE or SMC.

Outcome(s) of interest

- Events data reported as discontinuation and withdrawal from trials.

Data extraction

Data for included studies were extracted by one reviewer (SN) and 20% randomly checked for accuracy by another reviewer (SK). Data extraction forms were developed in Microsoft Excel to capture the following information: ClinicalTrials.gov identifier (NCT number), study name, study characteristics

including first author, year, purpose, design, date, setting and country, treatments details, participant demographics, key inclusion and exclusion criteria, AEs and SAEs definition, and information on AEs, TAEs, SAEs and TSAEs.

Assessment of risk of bias for included trials

The Cochrane RoB 2 tool for RCTs[58] was applied for assessing the risk of bias of all trials independently by two members (SN, SK). The details of the tool in classifying the risk of bias in the various domains have been provided in *Chapter 2*.

Data synthesis

Information extracted from the included studies was summarised and tabulated. We applied the CTCAEs v5.0[125] to classify the events. In addition, AEs and SAEs were pooled and the proportion of AEs and SAEs for each system organ class (SOC) for each drug was calculated where the original paper used the standard definition for AEs and SAEs.

We reported the adverse and serious adverse events from the rest of the studies (AEs from 11 studies and SAEs from 6 trials) separately, as these studies did not report events according to standard definitions for AEs and SAEs.

Results

Included studies

Study selection

The PRISMA flow diagram in *Figure 23* summarises the results of our searches for the AE review. Of the 344 records which were assessed for eligibility, 277 records were excluded at full text. We identified 67 articles which described data from 40 trials[22,28,35–37,45,88–95,97,107,108,117,118,126–152] for the AEs review. Although these linked articles were cited, we used the main trial paper for the main citation, as the other linked papers only reported some subgroup analyses, were either repetitive or combined the data.

Study characteristics

Sixty-seven articles from 40 RCTs met the eligibility criteria to assess the AE and SAE incidences in adult with migraine (chronic or episodic). These trials evaluated 35 different dosing regimens of 12 drugs including:

- CGRP MAbs (eptinezumab 10, 30, 100 and 300 mg, erenumab 70 and 140 mg, fremanezumab 225 and 675 mg, and galcanezumab 120, 150 and 240 mg).
- BTA 7, 25, 40, 50, 75, 155 and 260U.
- Topiramate 100 and 200 mg.
- Flunarizine 5 and 10 mg.
- Propranolol 40 and 160 mg.
- Atogepant 10, 30 and 60 mg.
- Amitriptyline 50 and 100 mg.
- Divalproate 200 and 1000 mg.
- Rimegepant 75 mg.

The study-level characteristics of the included trials are summarised in *Table 9* and *Appendix 4*, *Table 50*. The participants randomised in all trials satisfied the diagnostic criteria of chronic or episodic migraine in accordance with the ICHD.[6]

Only two trials were conducted in a single site (Iran and India);[137,147] the remainder were multicentre studies from a list of countries. Twenty-seven trials included only participants with episodic migraine and nine trial studies included only participants with chronic migraine. Four trials had a mixed population of chronic and episodic migraine. The number of participants randomised across the 40 trials evaluating the

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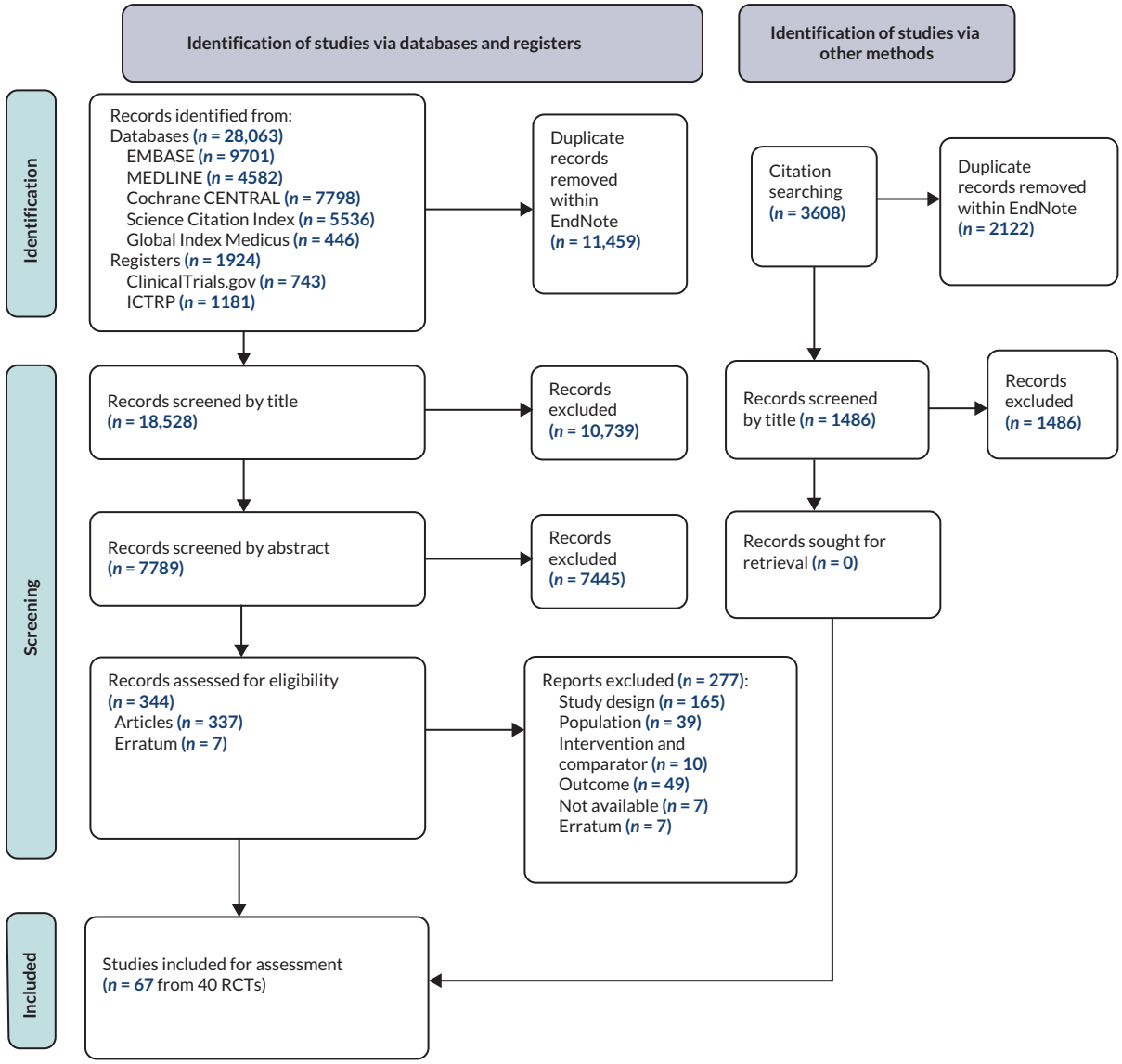

FIGURE 23 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram summarising the flow of studies for the AEs review.

safety of pharmacological treatment ranged from 217[133] to 1379[97] with a total of 25,891 participants. The mean age of trial participants ranged from 32[137] to 46[90] years; and the percentage of female participants ranged from 74%[150] to 91%.[151]

Only two trials were designed as open-label treatment trials.[88,137] Most trials were double-blind trials. Treatment duration varied across the trials, from 2 trials which had a 4-week treatment duration,[147,149] 3 trials reported 16 weeks,[28,128,136] 19 trials reported 12 weeks,[35,37,45,89–91,95,127,129,130,133,134,137,143–146,148,150] 1 trial reported 20 weeks,[22] 1 trial reported 22 weeks,[110] 10 trials reported 24 weeks,[36,88,94,97,127,131,140–142,151] 2 trials reported 26 weeks[139,152] and 2 final trials reported 36 weeks.[132,138]

In summary, the majority of included trials were conducted across multi sites in a list of countries for the episodic migraine population and the trials were double blind with a 12-week duration.

Risk of bias in included studies

Risk-of-bias ratings by trial are summarised across the studies below and are presented in *Figure 24*. For this purpose, the Cochrane RoB 2 tool for RCTs[58] was applied.

TABLE 9 Characteristics of included trials

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Couch, 2011[22]	To compare amitriptyline in doses of 25–100 mg/ day, depending on the tolerance of the patient, with a matched placebo	10 American centres	Episodic	20 DB	Placebo	–	–	–	197	83	35.7	26.9	0	AEs were seen roughly twice as often in the amitriptyline group
					Amitriptyline	25–100 mg	Oral	One to four pills per day	194	79	34.1	57.2	15.4	
Kalita, 2013[137]	To compare efficacy and safety of divalproex extended release (DVA-ER) and amitriptyline (AMT) in migraine	At a tertiary care teaching hospital, and patients enrolled from the neurology outpatient service, India	Episodic	12 OL	Divalproate	250–1000 mg	Oral	Daily	143	82	31.03	47.6	–	The composite side effects were also not different between the two groups
					Amitriptyline	12.5–50 mg	Oral	Daily	144	78.7	32.8	56.3	–	
Dodick, 2009[135]	To compare the efficacy and tolerability of topiramate and amitriptyline in the prophylaxis of EM	32 sites in the USA	Episodic	22 DB	Topiramate	100 mg	Oral	Twice daily	177	86.6	39.7	85.9 (68.4)	2.3 (0)	Both appeared to be well tolerated in this population with EM
					Amitriptyline	100 mg	Oral	Twice daily	169	83	37.9	88.8 (75.7)	4.7 (0.5)	

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TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Diener, 2002[136]	To assess the efficacy and tolerability of two doses of flunarizine in the prophylaxis of migraine, in comparison with slow-release propranolol	8 European countries	Episodic	16 DB	Flunarizine	5 mg	Oral	Once daily	263	79	–	33.5	0.4	No significant differences between the three treatments were found about safety: all three treatments were generally well tolerated and safe
						10 mg	Oral	Once daily	275	82	–	32	1.8	
					Propranolol	160 mg	Oral	Once daily	270	83	–	32.6	0.7	
Lucking, 1988[128]	To compare efficacy and tolerance of flunarizine and propranolol in the prophylaxis of migraine	99 medical practices in Germany	Episodic	16 DB	Flunarizine	10 mg	Oral	Once daily	166	83.7	42	24.6	0	Tolerance of flunarizine was similar to propranolol
					Propranolol	40 mg	Oral	Three times a day	170	80	42	29.6	0	
Diener,[a] 2007[152]	To assess the effects of discontinuation of topiramate after a treatment period of 6 months	88 neurology clinics in 21 European countries and the Middle East	Episodic	26 DB	Placebo	–	–	–	258	89	40.1	59	4	Satisfaction with tolerability was similar in both treatment groups
					Topiramate	200 mg	Oral	Twice per day	254	85	40.1	68	3	

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Lipton, 2011[139]	To evaluate whether topiramate would prevent the transformation of EM to chronic daily headache (CDH) in patients with a HFEM	At 81 sites in the USA	HFEM	26 DB	Placebo	–	–	–	185	91.2	40.9	73.5	2.7 (0.5)	Topiramate was generally well tolerated
					Topiramate	100 mg	Oral	Twice daily [two 25-mg tablets (50 mg)]	176	86.8	39.6	82.4	1.7 (1.1)	
Silberstein, 2007[28]	To evaluate the efficacy and safety of topiramate compared with placebo for the treatment of CM	46 clinics/ sites in the USA	Chronic	16 DB	Placebo	–	–	–	153	86.9	38.6	70.2	0	Topiramate is safe and generally well tolerated
					Topiramate	100 mg	Oral	Twice daily	153	83.7	37.8	82.5	0	
Fazlalizadeh, 2008[147]	To determine the comparative efficacy of topiramate and sodium valproate in the management of migraine headache	One hospital in Iran	Episodic	4 DB	Topiramate	100 mg	Oral	Daily	284	–	–	14	–	No statistically significant differences between therapeutic safety of sodium valproate and topiramate
					Sodium valproate	200 mg	Oral	Daily	285	–	–	14.4	–	

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TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Aurora, 2007[132]	To evaluate the safety and efficacy of multiple treatments of BTA for EM	20 North American study centres	Episodic	36 DB	Placebo	–	–	–	182	-	43.9	59.9 (21.4)	(0. 2)	Multiple treatments with BTA were shown to be safe and well tolerated over an active treatment period lasting 9 months
					BTA	105–260U	IM	Every 12 weeks	187	-	46	81.3 (60.4)	0	
Dodick, 2010[97] (pooled Aurora, 2010,[92] Diener, 2010[93])	To assess efficacy, safety and tolerability of BTA as headache prophylaxis in adults with CM.	56 sites in North America	Chronic	24 DB	Placebo	–	–	–	687	85.2	41.5	51.7 (13.7)	2.3 (0)	BTA treatments were safe and well tolerated
					BTA	155U +40U	IM at 39 sites	Every 12 weeks	692	87.6	41.1	62.4 (33.4)	4.8 (0.3)	
Elkind,[b] 2006[145]	To examine the effects of multiple treatments with low doses of BTA versus placebo for prophylaxis of EM	–	Episodic	12 DB	Study I	Placebo	–	–	106	84.9	43.8	47.2 (6.6)	(0)	AEs were similar among the groups within each study. BTA was safe and well tolerated
						BTA	7U	IM	Every 4 months	105	84.3	44.3	49.5 (6.7)	(0)
							25U	IM	Every 4 months	101	82.2	43.6	46.5 (21.8)	(0)
							50U	IM	Every 4 months	106	86.8	44.6	56.6 (30.2)	(0)
					Study II	BTA	25U	IM	Every 4 months	173	–	–	78 (24.9)	(0)
							50U	IM	Every 4 months	180	–	–	77.2 (29.4)	(0)
					Study III	Placebo	–	–	–	100	–	–	60	(0)
						BTA	25U	IM	Every 4 months	50	–	–	70	(0)
							50U	IM	Every 4 months	51	–	–	68.6	(0)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Relja, 2007[138]	To evaluate the safety and efficacy of onabotulinumtoxinA for prophylaxis of EM	At 37 study centres in 9 countries	Episodic	36 DB	Placebo	–	–	–	118	–	42.4	54.2 (31.4)	1.7 (0)	BTA was safe and well tolerated but did not result in significantly greater improvement than placebo
					BTA	225U	IM	Every 12 weeks	129	–	42..8	76.7 (67.4)	1.5 (0)	
						150U	IM	Every 12 weeks	125	–	44.9	77.6 (63.2)	1.62 (0)	
						75U	IM	Every 12 weeks	123	–	42.8	77.2 (62.6)	0.81 (0)	
Rothrock, 2019[88]	To compare the effectiveness of BTA and topiramate for CM prevention	USA (number of sites is not reported)	Chronic	24 OL	BTA	155U	IM	Every 12 weeks	140	84	40.2	48 (17)	2 (0)	BTA is safe; (51% of patients discontinued topiramate due to AEs)
					Topiramate	100 mg	Oral	Twice daily	142	86	39.4	79 (70)	4 (1)	
Ashina, 2020[131]	To evaluate the efficacy and safety of eptinezumab in the preventive treatment of EM	84 sites in the USA and the Republic of Georgia	Episodic	24 DB	Placebo	–	–	–	222	83.8	39.9	59.5	0. 4	Eptinezumab was well tolerated, and had an acceptable safety profile
					Eptinezumab	30 mg	IV	Every 12 weeks	219	84.5	39.1	58.4	1.83 (0)	
						100 mg	IV	Every 12 weeks	223	80.3	40	63.2	1.79 (0)	
						300 mg	IV	Every 12 weeks	224	88.8	40.2	57.6	1.34 (0)	
Ashina, 2022[151]	To investigate the safety and efficacy of eptinezumab for migraine prevention in adults with migraine and two to four previous failures	96 study locations across Europe (n = 93) and the USA (n = 3)	Episodic and chronic	24 DB	Placebo	–	–	–	298	88	43.8	40	1.3 (0)	The safety and tolerability of eptinezumab were similar to placebo
					Eptinezumab	100 mg	IV	Every 12 weeks	299	93	44.6	42	1.7 (0)	
						300 mg	IV	Every 12 weeks	294	89	43.1	41	2.4 (0.7)	

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TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Dodick, 2019[89]	To determine the safety, tolerability and effectiveness of four dose levels of eptinezumab and to inform the phase 3 development programme	92 clinics/ sites in the USA, Australia, New Zealand and the Republic of Georgia	Chronic	12 DB	Placebo	–	–	–	121	90	37.2	56.2 (14)	0.8 (0)	Eptinezumab appeared effective and well tolerated
					Eptinezumab	300 mg	IV	Single dose	121	81	37.2	63.6 (17.4)	5.8 (0)	
						100 mg	IV	Single dose	122	85	36.7	57.5 (19.8)	3.3 (0)	
						30 mg	IV	Single dose	122	91	35.7	45.9 (14.8)	0	
						10 mg	IV	Single dose	130	87	36.4	56.9 (16.2)	0.8 (0)	
Lipton, 2020[94]	To evaluate the efficacy and safety of eptinezumab, in the preventive treatment of CM	128 sites in 13 countries across the USA and Europe	Chronic	24 DB	Placebo	–	–	–	366	88.8	39.6	46.7	0.81	The day after IV administration through week 12, was well tolerated, and demonstrated an acceptable safety profile
					Eptinezumab	300 mg	IV	Single dose	350	89.7	41	52	1.1	
						100 mg	IV	Single dose	356	86.2	41	43.5	0.84	
Winner, 2021[149]	To evaluate the efficacy and safety of the preventive migraine treatment, eptinezumab, initiated during a migraine attack	47 sites in the USA and the Republic of Georgia	Episodic	4 DB	Placebo	–	–	–	242	83.1	44.1	10.3	0	No notable safety findings were identified
					Eptinezumab	100 mg	IV	Single dose on day 0	238	84.9	44.9	10.9	0	

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Dodick, 2018[134]	To evaluate the efficacy and safety of AMG 334 in migraine prevention	69 sites (neurology clinics, and clinical research sites) across North America and Europe (including Russia)	Episodic	12 DB	Placebo	–	–	–	289	84.9	42	54.7	1.7	AEs were similar in both, and did not suggest any particular safety risk with erenumab administration
					AMG 334 (erenumab)	70 mg	SC	Once a month	283	85.7	42	48.1	1.1	
Goadsby, 2017[36]	To compare the efficacy and safety of erenumab for the preventive treatment of EM	121 sites across North America, Europe and Turkey	Episodic	24 DB	Placebo	–	–	–	319	85.9	41.3	63	2.2	The overall safety profile of erenumab was similar to that of placebo
					Erenumab	70 mg	SC	Monthly	314	84.5	41.1	57.3	2.5	
						140 mg	SC	Monthly	319	85.3	40.4	55.5	2.5	
Reuter, 2018[143]	To compare the efficacy and tolerability of erenumab with placebo in a well-defined group of patients with EM	59 sites in 16 countries	Episodic	12 DB	Placebo	–	–	–	124	82	44.2	54	1	The tolerability and safety profiles of erenumab and placebo were similar
					Erenumab	140 mg	SC	Monthly	119	80	44.6	55	2	
Reuter, 2022[142]	To compare the tolerability and efficacy of erenumab to topiramate for migraine in adults	82 sites in Germany	Episodic and chronic	24 DB	Erenumab	140 mg	SC	Monthly	388	85.3	40.8	65.21 (55.4)	2.58 (0.3)	Erenumab demonstrated a favourable tolerability and efficacy profile compared to topiramate
					Topiramate	100 mg	Oral	Daily	388	86.3	40.7	85.31 (81.2)	4.9 (0.5)	

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TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Sun, 2016[130]	To assess the safety and efficacy of erenumab (AMG 334) for the prevention of migraine	59 headache and clinical research centres in North America and Europe	Episodic	12 DB	Placebo	–	–	–	153	83	41.4	54	0	No apparent association was recorded between patients with positive anti-AMG 334 antibodies and AEs
					AMG 334 (Erenumab)	7 mg	SC	Monthly	108	81	40.3	50	1 (0)	
						21 mg	SC	Monthly	105	81	39.9	51	0	
						70 mg	SC	Monthly	106	77	42.6	54	1 (0)	
Tepper, 2017[45]	To assess the safety and efficacy of erenumab 70 mg and 140 mg in CM patients	69 headache and clinical research centres in Canada, the USA and Europe	Chronic	12 DB	Placebo	–	–	–	286	79	42.1	39	2	Erenumab 70 and 140 mg have a safety profile similar to placebo
					Erenumab	70 mg	SC	Monthly	191	87	41.4	44	3	
						140 mg	SC	Monthly	190	84	42.9	47	1	
Wang, 2021[144]	To evaluate the efficacy and safety of erenumab in adults with EM	83 sites in Asia, the Middle East and Latin America	Episodic	12 DB	Placebo	–	–	–	335	83.1	38	36.7 (9.6)	1.5 (0)	The safety profile of erenumab was comparable with placebo; no new safety signals were observed
					Erenumab	70 mg	SC	Monthly	335	80.5	37.3	34.9 (11.3)	2.9 (0.3)	
						140 mg	SC	Monthly	224	82.1	37.1	34.4 (10.7)	0	
Dodick, 2018[35]	To compare the efficacy and safety of fremanezumab for the preventive treatment of EM	123 investigative sites in 9 countries	Episodic	12 DB	Placebo	–	–	–	293	84	41.3	58.4 (37.2)	2.4	The most common AE reported was injection site pain, greater incidence with fremanezumab than with placebo
					Fremanezumab	675 mg	SC	Single dose	291	86.3	41.1	66.3 (47.1)	1	
						225/225/ 225 mg	SC	Monthly	289	84.1	42.9	66.2 (47.6)	1	

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Ferrari, 2019[90]	To investigate the efficacy and tolerability of fremanezumab in patients with difficult-to-treat epi-sodic or chronic migraine	104 sites in Europe and the USA	Chronic and episodic	12 DB	Placebo	–	–	–	279	84	46.8	48 (20)	1 (0)	Fremanezumab was well tolerated in patients with difficult-to-treat migraine who had previously not responded to up to four classes of migraine preventive medications
					Fremanezumab	675 mg	SC	Single dose	276	83	45.8	55 (21)	0.7 (0)	
						225 + 225 + 225 mg	SC	Monthly	283	84	45.9	45 (19)	1 (0)	
Sakai, 2021[91]	To determine the efficacy and safety of fremanezumab administration in Japanese and Korean patients with CM	67 institu-tions in Japan and Korea	Chronic	12 DB	Placebo	–	–	–	191	85.3	42.1	61.8 (28.3)	0.5 (0)	Fremanezumab was well tolerated. No safety signal was detected
					Fremanezumab	675 mg	SC	Single dose	191	86.4	43.5	61.1 (32.1)	0.5 (0)	
						225 + 225 + 225 mg	SC	Monthly	189	86.2	42.7	61.7 (29.3)	1.6 (0)	
Sakai, 2021[126]	To evaluate the efficacy and safety of fremanezumab in Japanese and Korean patients with EM	57 insti-tutions in Japan and 10 institutions in Korea	Episodic	12 DB	Placebo	–	–	–	117	85.5	44.2	65.8 (23.9)	0	No new safety concerns for fremanezumab in Japanese and Korean patients with EM
					Fremanezumab	675 mg	SC	Single dose	118	84.9	41.9	62.7 (28.9)	0	
						225 + 225 + 225 mg	SC	Monthly	121	83.5	44.4	57 (26.4)	0	

continued

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TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Silberstein, 2017[37]	To compare two fremanezumab dosing regimens with placebo for the prevention of CM	132 sites in 9 countries across the USA and Europe	Chronic	12 DB	Placebo	–	–	–	375	88	41.4	64	1.7 (0)	Injection-site reactions to fremanezumab were common. The long-term durability and safety of fremanezumab requires further study
					Fremanezumab	675 mg	SC	Single dose	376	88	42	70	0.8 (0)	
						225 + 225 + 225 mg	SC	Monthly	379	87	40.6	71	1.3 (0)	
Bo Hu, 2022[150]	To assess the efficacy and safety of galcanezumab in patients with EM from China, India and Russia	40 centres in China (n = 26), India (n = 10), and Russia (n = 4)	Episodic	12 DB	Placebo	–	–	–	259	75.7	36.8	43.2	1.54	Galcanezumab 120 mg once monthly was well tolerated in patients with episodic migraine
					Galcanezumab	120 mg (240 mg in the first month followed by 120 mg)	SC	Monthly	261	72	37.2	49.8	0.76	
Detke, 2018[95]	To evaluate the efficacy and safety of Galcanezumab in the preventive treatment of CM	116 headache and clinical research centres in Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, UK and USA	Chronic	12 DB	Placebo	–	–	–	558	87	41.6	50	0.71	Galcanezumab appears safe, and well tolerated for the preventive treatment of CM
					Galcanezumab	120 mg	SC	Monthly	278	85	39.7	58	0.18	
						240 mg	SC	Monthly	277	82	41.1	57	1.8	

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Dodick, 2014[133]	To assess the safety and efficacy of galcanezumab (LY2951742) for migraine prevention	35 centres in the USA	Episodic	12 DB	Placebo	–	–	–	110	87	41.9	67	3.6	AEs were reported to a similar extent in both groups
					Galcanezumab	150 mg	SC	Every 2 weeks	107	82	40.9	72	1.9	
Mulleners, 2020[146]	To assess the safety and efficacy of galcanezumab in patients with migraine who had not benefited from preventive medications from two to four categories.	64 sites (hospitals, clinics or research centres) in 12 countries	Episodic and chronic	12 DB	Placebo	–	–	–	230	88	45.7	53 (15)	1	Galcanezumab was safe and well tolerated in patients for whom multiple previous standard-of-care preventive treatments had failed
					Galcanezumab	120 mg	SC	Monthly	232	84	45.9	51 (16)	1	
Sakai, 2020[127]	To assess the efficacy and safety of galcanezumab in comparison with placebo for the prevention of migraine in Japanese patients with EM	40 sites in Japan	Episodic	24 DB	Placebo	–	–	–	230	85.2	44.2	64.8	0	Galcanezumab was safe and well tolerated in Japanese patients with episodic migraine
					Galcanezumab	120 mg	SC	Monthly	115	82.6	43.2	85.2	2.6	
						240 mg	SC	Monthly	114	84.2	44.8	81.6	0.9	

continued

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TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Skljarevski, 2018[141]	To evaluate the efficacy and safety of two dosing regimens of galcanezumab in patients with EM	109 study sites in 12 countries	Episodic	24 DB	Placebo	–	–	–	461	85.3	42.3	62.3	1.1	Galcanezumab 120 or 240 mg given once monthly was safe and well tolerated
					Galcanezumab	120 mg	SC	Monthly	226	85.3	40.9	65.0	2.2	
						240 mg	SC	Monthly	228	85.7	41.9	71.5	3.1	
Stauffer, 2018[140]	To demonstrate that Galcanezumab is superior to placebo in the prevention of EM with or without aura	90 sites in North America	Episodic	24 DB	Placebo	–	–	–	432	83.6	41.3	60.4	1.16 (0)	The incidence rate of AEs was low, showing the favourable tolerability profile of galcanezumab
					Galcanezumab	120 mg	SC	Monthly	206	85	40.9	65.5	2.91 (0)	
						240 mg	SC	Monthly	220	82.6	39.1	67.7	0 (0)	
Ailani, 2021[129]	To examine the efficacy and safety of atogepant compared with placebo for the prevention of migraine in participants with EM	128 sites in the USA	Episodic	12 DB	Placebo	–	–	–	222	89.2	40.3	56.8 (9)	0.9 (0)	Most common AEs were constipation and nausea across atogepant
					Atogepant	10 mg	Oral	Once daily	221	90.5	41.4	52.9 (23.1)	0.9 (0.5)	
						30 mg	Oral	Once daily	228	89.5	42.1	52.2 (14.9)	0	
						60 mg	Oral	Once daily	231	86.1	42.5	53.7 (19.5)	0	

TABLE 9 Characteristics of included trials (*continued*)

Author, year	Purpose	Country and setting	Chronic/ episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean age	% any AEs (% TAEs)	% any SAEs (% TSAEs)	Conclusion
					Name	Dose	Route of administration	Frequency						
Croop, 2021[148]	To compare the efficacy of rimegepant with placebo for preventive treatment of migraine.	92 sites in the USA	Episodic	12 DB	Placebo	–	–	–	371	84	41.1	36 (9)	1 (0.26)	Tolerability was similar to that of placebo, and no unexpected or serious safety issues were noted
					Rimegepant	75 mg	Oral	Daily	370	81	41.3	36 (11)	1 (0)	

AMG334, erenumab; AMT, amitriptyline; BTA, onabotulinumtoxinA; CM, chronic migraine; DB, double blind; DVA-ER, divalproex extended release; EM, episodic migraine; IM, intramuscular; IV, intravenous; OL, open label; SC, subcutaneous.

a In this trial, patients received topiramate in a 26-week open label phase. Daily dose was increased from 25 to 100 mg in steps of 25 mg every week; the dose could be adjusted further in the range 50–200 mg/day but was stable for the final 4 weeks. Patients were randomly assigned to continue this dose or switch to placebo for a 26-week double-blind phase.

b This study is a series of three sequential RCTs. In study I, patients were randomised to treatment with placebo or BTA (7.5U, 25U or 50U) in predetermined fixed injection sites on the front and sides of the head only. In study II, patients continued to receive, or were randomised to, 2 consecutive treatments with 25U or 50U. In study III, patients were randomised to placebo or continuation of 25U or 50U. Injection cycles were each 4 months long.

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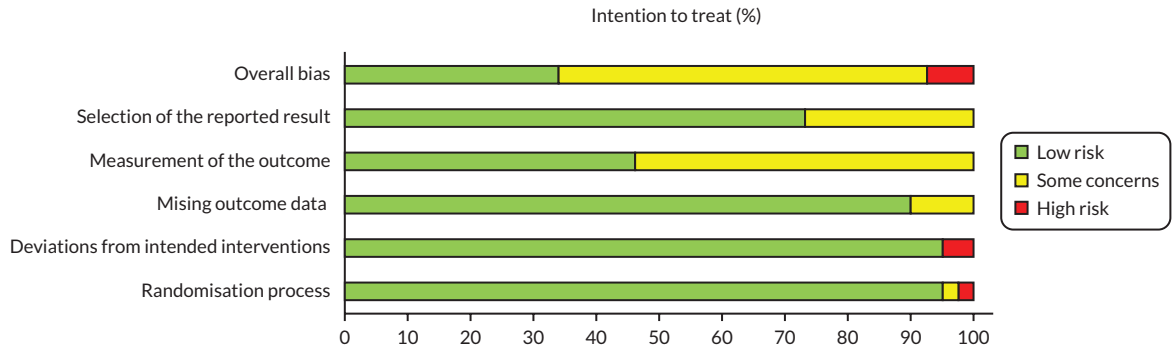

a) Summary of risk of bias assessment

Study ID	D1	D2	D3	D4	D5	Overall
Silberstein 2007	+	+	+	+	!	!
Sakai 2021	+	+	+	+	+	+
Silberstein 2017	+	+	!	+	+	!
Dodick 2010	+	+	+	+	+	+
Lipton 2020	+	+	+	+	+	+
Detke 2018	+	+	!	+	+	!
Dodick 2019	+	+	+	!	+	!
Tepper 2017	+	+	+	+	+	+
Ferrari 2019	+	+	+	+	+	+
Rothrock 2019	!	–	+	!	+	–
Lucking 1988	–	+	+	!	!	–
Ailani 2021	+	+	+	+	+	+
Sun 2016	+	+	+	+	+	+
Ashina 2020	+	+	!	+	+	!
Aurora 2007	+	+	+	!	+	!
Couch 2011	+	+	+	!	+	!
Dodick 2014	+	+	+	!	+	!
Dodick 2018	+	+	+	+	+	+
Dodick 2009	+	+	+	!	!	!
Diener 2002	+	+	+	+	+	!
Dodick 2018	+	+	+	+	+	+
Goadsby 2017	+	+	+	+	+	+
Kalita 2013	+	–	+	!	!	–
Relja 2007	+	+	+	!	!	!
Lipton 2011	+	+	+	!	!	!
Sakai 2021	+	+	+	+	+	+
Stauffer 2018	+	+	+	!	+	!
Skljarevski 2018	+	+	+	!	+	!
Reuter 2018	+	+	+	!	+	!
Reuter 2022	+	+	+	!	+	!
Wang 2021	+	+	+	+	+	+
Mulleners 2020	+	+	+	!	+	!
Fazlalizadeh 2008	+	+	!	!	!	!
Elkind 2006	+	+	+	!	!	!
Diener 2007	+	+	+	!	!	!
Croop 2021	+	+	+	!	+	!
Winner 2021	+	+	+	+	+	+
Bo Hu 2022	+	+	+	!	+	!
Ashina 2022	+	+	+	!	+	!
Sakai 2020	+	+	+	+	+	+

+ Low risk
! Some concerns
– High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

b) Traffic lights for the risk of bias for each included study

FIGURE 24 Risk of bias assessment result.

Randomisation process
Two trials[88,128] were rated as having some concerns (3%) and high level of risk (3%) for this domain, and the other trials (*n* = 38) were assessed at being at low risk of bias (94%).[22,28,35–37,45,89–91,94,95,97,126,127,129–152]

Deviations from the intended interventions
Two trials (5%)[88,137] were assessed as high risk of bias, and 38 trials (95%) were rated as being at low risk of bias.[22,28,35–37,45,89–91,94,95,97,126–136,138–152]

Missing outcome data
Assessment for missing outcome data showed four trials (10%)[37,95,131,147] had some concerns, and 36 trials (90%) trials were assessed as low risk of bias.[22,28,35,36,45,88–91,94,97,126–130,132–146,148–152]

Measurement of the outcome
Outcome assessors were aware of the intervention received by study participants in the 21 trials, hence, 53% of trials were rated as having some concerns[22,88,89,128,132,133,135,137–143,145–148,150–152] and 19 trials (47%) were rated as being at low risk of bias.[28,35–37,45,90,91,94,95,97,126,127,129–131,134,136,144,149]

Selection of the reported result
Twenty-nine trials (73%) adhered to their pre-specified analysis plan and registered protocol. Thus, they were rated as being at low risk of bias,[35–37,45,88–91,94,95,97,126,127,129–134,140–144,146,148–151] and 11 trials (27%) were considered to have some concerns and were assessed as 'unclear' as the trial protocol was unavailable.[22,28,128,135–139,145,147,152]

Overall risk of bias assessment
The ratings for the overall risk of bias domain indicated that 3 trials (7%), 23 trials (58%) and 14 trials (35%) were rated as being at high,[88,128,137] some concerns,[22,28,37,89,95,131–133,135,136,138–143,145–148,150–152] and low risk[35,36,45,90,91,94,97,126,127,129,130,134,144,149] of bias, respectively (see *Figure 24*).

In brief, most of the included RCTs were assessed with some concerns regarding the risk of bias.

Adverse events results
Of the 40 included trials, 29 trials with 20,694 participants applied a standard definition for AEs which we use in our review. We used SOC to classify and illustrate the proportion of attributed AEs to each drug. A list of classified AEs are presented in *Appendix 5*, *Table 51*. *Appendix 5*, *Table 68* shows the percentage of total incidence of any AEs reported for 20 different dosing regimens of 9 drugs. Among them, the most reported AEs belonged to amitriptyline 25–100 mg and galcanezumab 150 mg with 89%[133,135] and 72.0%,[133] respectively. The lowest number of any AEs is for erenumab 140 mg (33%).[36,45,142–144] Arm level AEs incidence are presented in *Appendix 5*, *Tables 52–67*.

Table 10 provides a detailed summary of classified AEs reported in 29 trials. The table illustrates the percentage of attributed AEs of each SOC.

- **Investigations:** amitriptyline 25–100 mg (14%), atogepant 60 mg (4%), atogepant 30 mg and galcanezumab 240 mg (2%), fremanezumab quarterly and galcanezumab 120 mg (1%).
- **Skin and subcutaneous:** galcanezumab 150 mg (5%), galcanezumab 240 mg (2%), galcanezumab 120 mg and Fremanezumab monthly (1%).
- **Gastrointestinal disorders:** amitriptyline 25–100 mg (59%), topiramate 100 mg (27%), galcanezumab 150 mg (14%), atogepant 60 and 10 mg (13%), erenumab 140 mg (12%), atogepant 30 mg (11%), eptinezumab 300, 30 and 10 mg (5%), erenumab 70 mg, galcanezumab 120 and 240 mg and fremanezumab quarterly (4%), eptinezumab 100 mg, erenumab 7 mg, rimegepant 75 mg and placebo (3%), erenumab 21 mg and fremanezumab monthly (2%).
- **Ear and labyrinth disorders:** topiramate 100 mg (3%), erenumab 140 mg, galcanezumab 120 and 240 mg (1%).

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TABLE 10 Adverse events from 29 trials classified by SOC (%)

Treatments	Doses	Participants (*N*)	Investigations (%)	Skin and subcutaneous (%)	Gastrointestinal disorders (%)	Ear and labyrinth disorders (%)	Eye disorders (%)	Psychiatric disorders (%)	Metabolism and nutrition disorders (%)	Vascular disorders (%)	Renal and urinary disorders (%)	Musculoskeletal and connective tissue disorders (%)	Nervous system disorders (%)	Infection and infestation (%)	General disorders and administration site conditions (%)	Respiratory, thoracic and mediastinal disorders (%)
Amitriptyline[135]	25–100 mg	169	23 (13.6)	0	100 (59.2)	0	0	0	8 (4.7)	0	0	0	73 (43.4)	40 (23.7)	41 (24.3)	7 (4.1)
Atogepant[129]	10 mg	221	8 (3.7)	0	28 (12.7)	0	0	2 (0.9)	0	0	0	0	7 (3.2)	25 (11.4)	3 (1.4)	1 (0.5)
	30 mg	228	4 (1.8)	0	26 (11.4)	0	0	1 (0.4)	0	0	0	0	4 (1.8)	40 (17.5)	7 (3.1)	2 (0.9)
	60 mg	231	9 (3.9)	0	30 (13)	0	0	5 (2.2)	0	0	0	0	4 (1.7)	39 (17)	9 (3.9)	4 (1.7)
BTA[88,97]	150U	907	0	0	1 (0.1)	0	29 (3.2)	5 (0.5)	0	0	0	141 (15.6)	5 (5.0)	14 (1.5)	23 (2.5)	0
Eptinezumab[89,94,131,149,151]	100 mg	1238	5 (0.4)	0	32 (2.6)	0	0	0	0	0	0	19 (1.5)	38 (3.1)	148 (12)	26 (2.1)	19 (1.5)
Eptinezumab[89,94,131,151]	300 mg	989	0	0	47 (4.8)	0	0	0	0	0	0	9 (0.9)	18 (1.8)	191 (19.3)	20 (2)	17 (1.7)
Eptinezumab[89]	10 mg	130	0	0	6 (4.6)	0	0	0	0	0	0	0	13 (10)	23 (17.7)	0	4 (3.1)
Eptinezumab[89,131]	30 mg	341	0	0	17 (5)	0	0	0	0	0	0	4 (1.2)	14 (4.2)	65 (19.1)	5 (1.5)	10 (3)
Erenumab[130]	21 mg	105	0	0	2 (2)	0	0	0	0	0	0	0	4 (4)	12 (11)	2 (2)	1 (1)
Erenumab[130]	7 mg	108	0	0	3 (3)	0	0	0	0	0	0	4 (4)	5 (5)	12 (11)	5 (5)	2 (2)
Erenumab[36,45,130,134,144]	70 mg	1228	0	0	50 (4.1)	0	0	0	0	5 (0.4)	0	15 (1.2)	23 (1.9)	161 (13.1)	59 (4.8)	0
Erenumab[36,45,142–144]	140 mg	1238	4 (0.3)	0	144 (11.6)	17 (1.4)	0	42 (3.4)	9 (0.7)	0	0	28 (2.3)	87 (7)	110 (8.9)	68 (5.5)	0
Fremanezumab[35,37,90,91,126]	Monthly	1263	4 (0.3)	8 (0.6)	24 (1.9)	0	0	8 (0.6)	0	1 (0.1)	0	11 (0.9)	19 (1.5)	155 (12.3)	794 (62.9)	63 (5)
	Quarterly	1251	8 (0.6)	4 (0.3)	48 (3.8)	0	0	9 (0.7)	0	3 (0.2)	0	13 (1)	18 (1.4)	170 (13.6)	762 (60.9)	8 (0.6)
Galcanezumab[95,127,140,141,146,150]	120 mg	1313	13 (1)	8 (0.6)	56 (4.3)	7 (0.5)	0	5 (0.4)	0	0	7 (0.5)	32 (2.4)	34 (2.6)	197 (15)	284 (21.6)	11 (0.8)
Galcanezumab[95,127,140,141]	240 mg	844	2 (0.2)	13 (1.5)	37 (4.4)	4 (0.5)	0	0	0	0	0	19 (2.3)	20 (2.4)	101 (12)	272 (32.2)	18 (2.1)
Galcanezumab[133]	150 mg	107	0	5 (5)	15 (14)	0	3 (3)	0	0	5 (5)	0	18 (17)	5 (5)	28 (26)	28 (26)	0
Placebo[35–37,45,89–91,94,95,97,126,127,129–131,133,134,140,141,143,144,146,148–151]	-	7569	16 (0.2)	8 (0.1)	228 (3)	0.0	8 (0.1)	6 (0.1)	0.0	7 (0.1)	0.0	132 (1.7)	150 (2)	874 (11.5)	996 (13)	55 (0.7)
Rimegepant[148]	75 mg	370	0	0	11 (3)	0	0	0	0	0	0	0	0	30 (8)	0	0
Topiramate[88,135,142]	100 mg	707	22 (3.1)	0	194 (27.4)	23 (3.2)	21 (2.9)	88 (12.5)	63 (8.9)	0	0	3 (0.4)	426 (60.2)	52 (7.3)	115 (16.3)	9 (1.3)

- **Eye disorders:** onabotulinumtoxinA 150U and galcanezumab 150 mg and Topiramate 100 mg (3%).
- **Psychiatric disorders:** topiramate 100 mg (13%), erenumab 140 mg (3%), atogepant 60 mg, fremanezumab monthly and quarterly, atogepant 10 mg and OnabotulinumtoxinA 150U (1%).
- **Metabolism and nutrition disorders:** topiramate 100 mg (9%), amitriptyline 25–100 mg (5%), erenumab 140 mg (1%).
- **Vascular disorders:** galcanezumab 150 mg (5%).
- **Renal and urinary disorders:** galcanezumab 120 mg (1%).
- **Musculoskeletal and connective tissue disorders:** galcanezumab 150 mg (17%), onabotulinumtoxinA 150U (16%), erenumab 7 mg (4%), erenumab 140 mg, galcanezumab 120 and 240 mg, eptinezumab 100 mg and placebo (2%), eptinezumab 300 and 30 mg, erenumab 70 mg, fremanezumab monthly and quarterly (1%).
- **Nervous system disorders:** topiramate 100 mg (60%), amitriptyline 25–100 mg (44%), eptinezumab 10 mg (10%), erenumab 140 mg (7%), onabotulinumtoxinA 150U, galcanezumab 150 mg and erenumab 7 mg (5%), eptinezumab 30 mg and erenumab 21 mg (4%), atogepant 10 mg, galcanezumab 120 mg and eptinezumab 100 mg (3%), atogepant 30 and 60 mg, eptinezumab 300 mg, fremanezumab monthly, galcanezumab 240 mg, erenumab 70 mg and placebo (2%), fremanezumab quarterly (1%).
- **Infection and infestation:** galcanezumab 150 mg (26%), amitriptyline 25–100 mg (24%), eptinezumab 300 and 30 mg (19%), atogepant 30 mg and eptinezumab 10 mg (18%), atogepant 60 mg (17%), galcanezumab 120 mg (15%), fremanezumab quarterly (14%), erenumab 70 mg (13%), eptinezumab 100 mg, fremanezumab monthly, galcanezumab 240 mg and placebo (12%), atogepant 10 mg, erenumab 7 and 21 mg (11%), erenumab 140 mg (9%), rimegepant 75 mg (8%), topiramate 100 mg (7%), onabotulinumtoxina 150U (2%).
- **General disorders and administration site conditions:** fremanezumab monthly (63%), fremanezumab quarterly (61%), galcanezumab 240 mg (32%), galcanezumab 150 mg (26%), amitriptyline 25–100 mg (24%), galcanezumab 120 mg (22%), topiramate 100 mg (16%), placebo (13%), erenumab 140 mg (6%), erenumab 7 and 70 mg (5%), atogepant 60 mg (4%), atogepant 30 mg and onabotulinumtoxina 150U (3%), eptinezumab 30, 100 and 300 mg and erenumab 21 mg (2%), atogepant 10 mg (1%).
- **Respiratory, thoracic and mediastinal disorders:** topiramate 100 mg (9%), fremanezumab monthly (5%), amitriptyline 25–100 mg (4%), eptinezumab 10 and 30 mg (3%), atogepant 60 mg, eptinezumab 100 and 300 mg, erenumab 7 mg and galcanezumab 240 mg (2%), atogepant 10 and 30 mg, erenumab 21 mg, galcanezumab 120 mg, fremanezumab quarterly and placebo (1%).

Eleven of the forty included trials did not mention what criteria they considered as AEs and just reported the incidence of AEs accrued. *Appendix 5*, *Tables 69* and *75* present the AEs reported in these trials as per publication.

Serious adverse events results

From the 40 RCTs, 30 trials reporting data from 21,529 participants have applied a standard definition for SAEs. These trials evaluated 20 different dosing regimens of 9 drugs. Among them, one study (a series of three sequential, randomised, controlled studies of repeated treatments with BTA for migraine prophylaxis)[145] did not explicitly report the number of people with SAEs, however, the results showed that there were no treatment-related SAEs. Thus, SAEs from 29 trials with 20,557 participants were combined. *Appendix 6*, *Table 98* shows the percentage of any SAEs reported for each dosing regimen of these drugs. *Table 11* provides more details of classified SAEs and illustrates the percentage of attributed SAEs of each SOC.

From the 40 trials included to assess the safety data, 4 trials have not reported any SAEs data. These four trials evaluated efficacy and safety of topiramate for the treatment of chronic migraine,[28] flunarizine versus propranolol in the prophylaxis of migraine,[128] amitriptyline versus divalproate in migraine,[137] and a comparative study of topiramate versus sodium valproate in the prevention of migraine headaches.[147]

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TABLE 11 Serious adverse events from 29 trials classified by SOC (%)

Treatments	Doses	Total participants (*n*)	Neoplasms benign malignant and unspecified (%)	Nervous system disorders (%)	Injury, poisoning and procedural complications (%)	Respiratory, thoracic and mediastinal disorders (%)	Gastrointestinal disorders (%)	Renal and urinary disorders (%)	Infections and infestations (%)	Cardiac disorders (%)	Congenital, familial and genetic disorders (%)	Hepatobiliary disorders (%)	Psychiatric disorders (%)	Musculoskeletal and connective tissue disorders (%)	Investigations (%)	Metabolism and nutrition disorders (%)	Reproductive system and breast disorders (%)	Skin and subcutaneous tissue disorders (%)	Vascular disorders (%)	General disorders and administration site conditions (%)	Eye disorders (%)	Ear and labyrinth disorders (%)	Immune system disorders (%)
Amitriptyline[135]	25–100 mg	169	2 (1.18)	1 (0.59)	0	0	1 (0.59)	1 (0.59)	1 (0.59)	0	0	1 (0.59)	0	0	0	0	1 (0.59)	0	0	0	0	0	0
Atogepant[129]	10 mg	221	0	0	0	1 (0.45)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.45)	0	0
	30 mg	228	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	60 mg	231	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BTA[88,92]	150U	907	11 (1.21)	5 (0.55)	2 (0.22)	7 (0.77)	3 (0.33)	1 (0.11)	1 (0.11)	5 (0.55)	0	0	4 (0.44)	1 (0.11)	0	1 (0.11)	1 (0.11)	0	1 (0.11)	1 (0.11)	0	0	0
Eptinezumab[89]	10 mg	130	0	0	0	0	0	0	0	0	0	1 (0.77)	1 (0.77)	0	0	0	0	0	0	0	0	0	0
Eptinezumab[89,131]	30 mg	341	0	0	1 (0.29)	0	0	2 (0.59)	0	0	0	0	0	1 (0.29)	0	0	0	0	0	0	0	0	0	0
Eptinezumab[89,94,131,149,151]	100 mg	1238	1 (0.08)	3 (0.24)	6 (0.48)	0	2 (0.16)	0	1 (0.08)	1 (0.08)	0	3 (0.24)	5 (0.40)	0	0	0	0	0	0	0	1 (0.08)	0	0
Eptinezumab[89,94,131,151]	300 mg	989	1 (0.98)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.98)
Erenumab[36,45,142–144]	140 mg	1238	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.96)	0	0	0	0	0
Erenumab[36,45,130,134,144]	70 mg	1228	2 (1.18)	1 (0.59)	0	0	1 (0.59)	1 (0.59)	1 (0.59)	0	0	1 (0.59)	0	0	0	0	1 (0.59)	0	0	0	0	0	0
Erenumab[130]	7 mg	108	0	0	0	1 (0.45)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.45)	0	0
Erenumab[130]	21 mg	105	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fremanezumab[35,37,90,91,126]	Monthly	1262	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Quarterly	1251	11 (1.21)	5 (0.55)	2 (0.22)	7 (0.77)	3 (0.33)	1 (0.11)	1 (0.11)	5 (0.55)	0	0	4 (0.44)	1 (0.11)	0	1 (0.11)	1 (0.11)	0	1 (0.11)	1 (0.11)	0	0	0
Galcanezumab[95,127,140,141,146,150]	120 mg	1313	0	0	0	0	0	0	0	0	0	1 (0.77)	1 (0.77)	0	0	0	0	0	0	0	0	0	0

TABLE 11 Serious adverse events from 29 trials classified by SOC (%) (*continued*)

Treatments	Doses	Total participants (*n*)	Neoplasms benign malignant and unspecified (%)	Nervous system disorders (%)	Injury, poisoning and procedural complications (%)	Respiratory, thoracic and mediastinal disorders (%)	Gastrointestinal disorders (%)	Renal and urinary disorders (%)	Infections and infestations (%)	Cardiac disorders (%)	Congenital, familial and genetic disorders (%)	Hepatobiliary disorders (%)	Psychiatric disorders (%)	Musculoskeletal and connective tissue disorders (%)	Investigations (%)	Metabolism and nutrition disorders (%)	Reproductive system and breast disorders (%)	Skin and subcutaneous tissue disorders (%)	Vascular disorders (%)	General disorders and administration site conditions (%)	Eye disorders (%)	Ear and labyrinth disorders (%)	Immune system disorders (%)
Galcanezumab[95,127,140,141]	240 mg	844	0	0	1 (0.29)	0	0	2 (0.59)	0	0	0	0	0	1 (0.29)	0	0	0	0	0	0	0	0	0
Galcanezumab (LY2951742)[133]	150 mg	107	1 (0.08)	3 (0.24)	6 (0.48)	0	2 (0.16)	0	1 (0.08)	1 (0.08)	0	3 (0.24)	5 (0.40)	0	0	0	0	0	0	0	1 (0.08)	0	0
Placebo[35–37,45,89–91,94,95,97,126,127,129–131,133,134,140,141,143,144,146,148–151]	-	7570	11 (0.14)	12 (0.15)	18 (0.23)	11 (0.14)	8 (0.1)	2 (0.03)	17 (0.22)	4 (0.05)	1 (0.01)	5 (0.06)	3 (0.04)	9 (0.12)	1 (0.01)	2 (0.03)	9 (0.12)	0	1 (0.01)	3 (0.04)	1 (0.01)	0	4 (0.05)
Rimegepant[148]	75 mg	370	1 (0.27)	0	0	0	0	0	1 (0.27)	0	0	0	1 (0.27)	0	0	0	0	0	0	0	0	0	0
Topiramate[88,135,142]	100 mg	707	1 (0.14)	1 (0.14)	1 (0.14)	2 (0.28)	2 (0.28)	1 (0.14)	8 (1.13)	1 (0.14)	0	1 (0.14)	1 (0.14)	1 (0.14)	1 (0.14)	2 (0.28)	4 (0.57)	0	2 (0.28)	0	4 (0.42)	0	1 (0.14)

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Six trials did not provide any definitions used to identify SAEs. We have reported them separately from those trials with a standard definition:

1. A trial evaluated BTA (105–260U) prophylactic treatment of episodic migraine for 369 participants.[132] Only four participants (three in the BTA group and one in the placebo group) experienced four SAEs, of which none were reported by the investigator to be related to study medication.
2. A study of multiple treatments of BTA (75, 150 and 225U) for the prophylaxis of episodic migraine headaches in 495 participants[138] reported that seven participants experienced SAEs. No further details were provided.
3. Amitriptyline 25–100 mg in the prophylactic treatment of migraine in 393 participants found that no serious events occurred.[22]
4. Efficacy and tolerability in migraine prophylaxis of flunarizine (5 and 10 mg) in comparison with propranolol 160 mg daily were evaluated in 808 participants with episodic migraine.[136] The results depicted one participant in the flunarizine 5 mg group experienced malaise and vertigo. In the flunarizine 10 mg group, five participants reported a SAE: urinary incontinence (n = 1), injury (n = 1), cholelithiasis (n = 1), breast neoplasm (n = 1) and depression (n = 1). In the propranolol group, two participants reported a SAE: one injury and one menstrual disorder.
5. A trial evaluated whether topiramate (100 mg) would prevent the transformation of episodic migraine to chronic daily headache (CDH) in 361 participants with a high-frequency episodic migraine (HFEM).[139] Eight participants (three in the topiramate group and five in the placebo group) reported a total of nine SAEs including spontaneous abortion (x2), bradycardia, bipolar disorder, suicidal thoughts, neuropathy, fractured pelvis secondary to a motor vehicle accident, chest pain and worsening of migraine.
6. A trial assessed the effects of discontinuation of topiramate (200 mg) after a treatment period of 6 months in 512 participants with episodic migraine.[152] Six of the 25 reported SAEs were judged by investigators to be possibly (urinary calculus, dyspnoea, pyrexia and urticaria), probably (depressed mood), or very likely to be (nephrolithiasis) related to the use of topiramate.

List of classified SAEs are presented in *Appendix 6*, *Table 76*. Arm level SAE incidence of the 36 trials can be found in *Appendix 6*, *Tables 77–97*.

Discussion

We systematically reviewed and narratively synthesised the incidences of AEs and SAEs from 40 RCTs[22,28,35–37,45,88–95,97,107,108,117,118,126–151] which investigated pharmacological interventions to manage chronic or episodic migraine. These trials included 25,891 participants. Results suggest that all the pharmacological interventions included in this review were found to be tolerable, although it was apparent that the rate of AEs on a particular organ is different for each drug. For example, nervous system disorders occurred more frequently with amitriptyline and topiramate drugs, whereas rimegepant was not responsible for these disorders in any of the included trials. Psychiatric disorders were more frequent in participants taking topiramate. Infection and infestation were reported for all included pharmacological interventions, among them, BTA had the least infection rate; however, musculoskeletal, and connective tissue disorders were highly reported for BTA than any of the other medications. Amitriptyline and topiramate had a major role in contributing to gastrointestinal disorders in participants, while participants who were taking fremanezumab suffered more from general disorders and administration site conditions than any of the other medications.

The number of included trials and subsequently the number of participants for those AEs and SAEs are different. Among them, the safety profiles for erenumab at different doses,[36,45,130,134,142–144] topiramate 100 mg,[28,88,135,139,142,147,152] and galcanezumab at three different doses[95,127,133,140,141,146,150] have been investigated more than the other medications, with seven trials for each of these medications. Then there are five RCTs for each of the following medications: eptinezumab at different ranges

of doses,[89,94,131,149,151] BTA at different ranges of doses[88,97,132,138,145] and fremanezumab monthly and quarterly.[35,37,90,91,126] Then we have three RCTs for amitriptyline at two doses,[22,135,137] two RCTs for divalproate extended release (250–1000 mg) and sodium valproate (200 mg);[137,147] flunarizine at two doses,[128,136] and propranolol at two doses.[128,136] The lowest amount of evidence about the AEs and SAEs are for rimegepant and atogepant at different ranges of doses.

Thus, it is important to note that the AEs and SAEs for erenumab at different doses, topiramate 100 mg, and galcanezumab may be better established and have a long history of records and documentation rather than the other medications. It is also important to consider that most of the included trials have some concerns in terms of the risk of bias (see below for further details).

For the drugs, with different doses of administration the results vary based on the drug of interest. For example, the safety profiles for erenumab, atogepant, BTA, galcanezumab, amitriptyline, propranolol, eptinezumab and flunarizine were all analysed at different doses. The included evidence showed that the higher doses for erenumab (140 mg) and atogepant (30 mg) had a lower incidence of the AEs and SAEs. However, for BTA, galcanezumab, amitriptyline and propranolol the lower doses seem to be associated with lower incidences of AEs and SAEs. Eptinezumab at a mid-dose (100 mg) also benefits from a lower incidence of AEs. Finally, for flunarizine (5 and 10 mg), there is a marginal difference in the incidence of the AEs and its safety profile does not seem to vary among the different doses.

Another interesting finding from our review is that placebo-related AEs in the included RCTs are more than erenumab at different doses, rimegepant, topiramate, and eptinezumab at doses 100 and 300 mg. The percentage of reported AEs for placebo is similar to that of atogepant, while it is lower for all other medications.

It is also important to note that in some trials the safety profiles for the medications have been investigated solely for episodic migraine, while in other trials, it is solely for chronic migraine or a combination of both episodic and chronic migraine. For example, for rimegepant, atogepant, amitriptyline, divalproate extended release (250–1000 mg), sodium valproate (200 mg), flunarizine and propranolol, the AEs and SAEs profiles have been among patients with episodic migraine only; while for eptinezumab, the participants have chronic migraine only; and for the rest of the medications the participants included in the trials are a combination of episodic and chronic migraineurs. However, regardless of the type of migraine, it seems that the medications generally have a satisfactory incidence of AEs and SAEs, and the type of the migraine does not seem to be a crucial determinant for the safety profiles of these medications.

Comparison with previous literature

When comparing with other studies, we have found some review studies that support our findings and a few reviews which may not be aligned with the conclusions we have reached about the AEs and SAEs in this review. Comparisons by each of the drugs are:

- Topiramate 100 mg: One open-label trial was assessed as having a high risk of bias,[88] and the rest were considered as having some concerns.[28,135,139,142,147,152] Overall, topiramate was reported as well tolerated with the most common AEs related to the nervous system and gastrointestinal disorders, although erenumab demonstrated a favourable tolerability profile compared to topiramate in a trial.[142] In another crossover trial, 51% of patients discontinued topiramate due to AEs and swapped to the BTA group.[88] Although these trials have been conducted with relatively similar inclusion and exclusion criteria and design, AEs incidences reported for topiramate 100 mg in a trial are meaningfully lower than others.[147] This gap might be justified by the short treatment duration, 4 weeks compared with at least 12 weeks. In another meta-analysis, the safety profile was in favour of the CGRP MAbs, with a higher likelihood to help than to harm compared with topiramate.[153]
- BTA at different ranges of doses: The safety profile of BTA at doses between 7.5 and 260 mg was investigated in five RCTs with 2237 subjects with chronic or episodic migraine. Two studies were

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rated as having a high[88] or a low risk of bias,[97] and three were rated as having some concerns.[132,138,145] The results showed that lower doses of BTA have a safer AEs profile than higher doses. It is worth mentioning that the lower doses are only prescribed for episodic migraine. Musculoskeletal and connective tissue disorders were the most common AEs for BTA. A pairwise meta-analysis shows that total AEs for BTA was higher than placebo with a relative risk ratio of 1.22 (95% CI 1.07 to 1.14).[154] This is in line with our results which show that BTA has a higher rate of AEs compared with placebo.

- Eptinezumab at different ranges of doses: The safety profile of eptinezumab at doses 10, 30, 100 and 300 mg was investigated in five RCTs with 2696 subjects with chronic or episodic migraine. Two studies were rated as being at low risk of bias,[89,94] and three were rated as having some concerns.[131,149,151] However, all doses of eptinezumab were generally reported to be tolerable and acceptable. Eptinezumab 100 mg showed a more desirable AE profile (a smaller proportion of AEs), which may be due the short treatment duration (4 weeks).[149] Hou *et al.* synthesised results from five trials and found that total AEs in migraine patients with CGRP MAbs therapy were not significantly different from those observed in placebo groups (OR 1.17, 95% CI 0.91 to 1.51).[155] The most common AEs for all doses were depicted for infection and infestation in the SOC. These results align with the other review results, which presented upper respiratory tract infection and urinary tract infection as the frequent AEs.[155] For SAEs, it appears from the data reviewed that a lower dose has a more favourable profile rather than higher doses.
- Erenumab at different ranges of doses: The results of two meta-analyses, one by Lattanzi *et al.* and another by Zhu *et al.*, align with our review and concluded that there were no differences in the occurrence of AEs and SAEs between the erenumab and placebo groups.[156,157] In our results for erenumab 21 mg, no SAEs were reported.[130] Our results showed that the least AEs incidence belonged to erenumab 140 mg by SOC, although AEs for gastrointestinal disorders were high. While participants who underwent erenumab 70 mg reported a higher number of infections and infestations, the results were in line with another review.[155] Two erenumab RCTs had some concerns regarding the risk of bias;[142,143] the rest were rated as having a low risk of bias.[36,45,130,134,144]
- Fremanezumab monthly and quarterly: The safety profile of fremanezumab was investigated in five RCTs with 2514 subjects with chronic or episodic migraine. Four studies were assessed as being at low risk of bias,[35,90,91,126] and one had some concerns.[37] There were differences in terms of participants who were included in the trials, that is, subjects with medication overuse, history of failed treatment, and those using preventive migraine medications. AEs incidence in monthly groups was reported to be lower than in quarterly groups.
- Galcanezumab at three doses: The results for evaluating the safety of galcanezumab 120, 150 and 240 mg were reported in seven trials with 2264 participants with chronic or episodic migraine. Of these studies, one trial was rated as being low risk of bias,[127] and six trials as having some concerns.[95,133,140,141,146,150] There were differences in eligibility criteria, for example, including participants with a history of documented treatment failure of two to four migraine preventive medications,[146] while another trial excluded participants having failed treatment with three or more migraine prevention medications.[141] Overall, galcanezumab for all doses was tolerable and accepted, although it appears from the data reviewed that the AEs incidence in the studies with 12 weeks of treatment occurred in a lower proportion than at 24 weeks. General disorders and administration site conditions, followed by infection and infestations, were the most frequent AEs for all doses. However, for Hou *et al.* they presented upper respiratory infections and viral infections (infections and infestations) as their most common AEs.[155] This discrepancy may be because they only included one trial.
- Rimegepant 75 mg: The results for rimegepant 75 mg were reported in one trial with 375 participants with episodic migraine which had some concerns in terms of risk of bias, although it showed similar tolerability to placebo, and there were no unexpected or serious safety issue noted.[148,158] Gao *et al.* included four RCTs (3827 subjects) and their results showed that rimegepant 75 mg had good safety for episodic migraine. Similar to our finding, there was no statistically significant increase in AEs compared with the placebo.[159]
- Atogepant at different ranges of doses: The safety profile of atogepant at doses 10, 30 and 60 mg was investigated in a low risk of bias trial with 680 episodic migraine subjects.[129] The AEs for all doses

were approximately the same and well tolerated, although atogepant 30 mg had fewer treatment-related AEs incidences. No SAEs were reported for atogepant 30 and 60 mg. A systematic review found that atogepant was well tolerated and had a low frequency of AEs.[160]

- Amitriptyline at two doses: The results for evaluating the safety of amitriptyline 50 and 100 mg were reported in three trials with 504 subjects with episodic migraine. An open label trial was assessed as being at high risk of bias,[137] and the other two trials as having some concerns.[22,135] AEs experienced the most by the participants were for gastrointestinal disorders followed by nervous system disorders. The results showed that a lower dose of amitriptyline had more AEs. We could not find any evidence for the safety profile of amitriptyline that had been synthesised through systematic review or meta-analysis.
- Divalproate extended release (250–1000 mg) and sodium valproate (200 mg): Two RCTs with 428 episodic migraine subjects. One trial was rated as having a high risk of bias,[137] and the other trial was rated as having some concerns.[147] Both were found to be tolerable, which is supported by two reviews.[161,162]
- Flunarizine at two doses: Two RCTs with 698 episodic migraine subjects investigated the safety profile of flunarizine at two doses (5 and 10 mg). One trial was rated as having a high risk of bias,[128] and the other was rated as having some concerns.[136] Both doses were well tolerated and acceptable. There were no considerable safety differences between the doses. Anker *et al.*'s systematic review on flunarizine efficacy and safety for episodic migraine supports our findings.[163]
- Propranolol at two doses (40 and 160 mg): The results from two trials with 440 subjects suffering from episodic migraine showed that the lower dose had a more desirable safety profile than the higher dose. One of these trials was rated as having a high risk of bias,[128] and the other was rated as having some concerns.[136] Gastrointestinal disorders, general disorders and administration site conditions were reported as the most frequent AEs.

Wang *et al.*[144] compared the different MAbs against CGRP or its receptor for adult patients with migraine; however, this NMA was limited to direct comparisons between placebo and eptinezumab, erenumab, fremanezumab and galcanezumab, for both AEs and SAEs.[164] The results of this NMA showed that galcanezumab ranked the highest for causing at least one SAE, followed by eptinezumab, erenumab and fremanezumab. However, this result is constrained by massive variations in reported SAEs among the included RCTs. Also, there was no available indirect comparisons between the trials.[164]

Strengths and limitations

Almost all the available evidence from the systematic reviews focused on one drug or fewer drugs than what we have considered in this review. Therefore, one of the key strengths of this analysis is the inclusion of a range of migraine treatments, including the latest therapies, such as CGRPs, specifically fremanezumab, eptinezumab, galcanezumab and erenumab, which are commonly used after other concurrent preventive treatments, such as BTA and topiramate have failed. As the inclusion criteria for this chapter comprised both episodic and/or chronic migraine, we have also included some oral medications which were not included in the clinical effectiveness chapter. This diversity provides a comprehensive overview of the medication effectiveness profile, allowing decision-makers to compare alternative treatments and obtain a better reflection of clinical practice. Another main strength of this review is the comprehensiveness of the search strategy employed. The search was conducted and updated across a wide range of electronic databases, without any restrictions on dates or language, to ensure that all relevant trials were included in the analysis.

It is important to note that all the systematic reviews that we have compared to our review have mentioned that there are shortcomings in their included RCTs and that further head-to-head RCTs are required for more robust results for AEs. We recommend further head-to-head RCTs to assess the safety profile of oral medications in the chronic migraine population because our review only found data evaluating the AEs incidence in chronic migraine participants which is limited to newer CGRP treatments, BTA and topiramate. In addition, for some of the considered drugs in our review including amitriptyline, divalproate, sodium valproate and Propranolol, our searches couldn't identify any relevant

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systematic reviews to enable us to compare our results. Hence, further studies are needed to have a clear understanding of the safety profile of these drugs.

We should also note that there are further limitations of some of the trials included in this review. For example, the trials which included the drugs atogepant and rimegepant – even though they have product licences, they have not yet been approved by NICE or SIGN; the trial for BTA for episodic migraine patients used non-standard doses, whereas the current standard dose for chronic migraine patients is 155U; and galcanezumab 150 mg dose is not used in standard practice and had a significantly higher AEs profile.

Finally, the results of this analysis should be interpreted with caution due to its limitations. We used CTCAE Version 5.0 for classifying the AEs and SAEs. However, there are some reported AEs and SAEs in the included studies which are not in the CTCAE, thus as a solution for this issue our clinical experts discussed what would be the best respective category for those events. For instance, panic attack was categorised as a psychiatric disorder. The included studies were not consistent in terms of the reporting of AE and SAE definitions, and due to this limitation, our clinical advisers reached a consensus on pooling the results for those studies with the same definitions and reporting the results for the other studies by each study narratively.

In summary, all medications were tolerable, but they had different side effects. Rimegepant had a favourable AEs profile. Amitriptyline and topiramate were associated with a higher occurrence of nervous system disorders and gastrointestinal disorders. Topiramate also was linked to a higher prevalence of psychiatric disorders. All medications had infections and infestations as a side effect. However, the medications did not follow a similar incidence pattern; BTA had the least infection rate, while it had a higher incidence of musculoskeletal and connective tissue disorders than other medications. Participants taking fremanezumab and galcanezumab experienced more general disorders and administration site conditions, while erenumab and eptinezumab had a higher rate of infection and infestation, similar to atogepant.

Chapter 4 Cost-effectiveness review

Research question 3: What is known about the cost-effectiveness of prophylactic drugs for chronic migraine?

Introduction

This chapter will explore and review all published cost-effectiveness studies including economic models of the use of different pharmacological treatments for adult patients with chronic migraine. Studies providing information on resource use, costs, utilities and probabilities, useful to inform the economic model in *Chapter 5*, were also identified.

Methods

The protocol for the cost-effectiveness review has been registered in the PROSPERO database. The registration number is CRD42021265995.

Search strategy

The search strategy was constructed by an information specialist (AB), in consultation with the project team. MEDLINE and EMBASE searches were based on those used in the searches for *Chapters 2* and *3*, with the addition of filters for economic and costs studies (instead of a RCTs filter) and search terms for prophylactic drug treatments of migraine in general (as well as specific named interventions). Search strategies in economics/Health Technology Assessment (HTA) specific sources included only terms for migraine/headache, with the addition of general terms for drug treatment or prevention in some cases. No language or date limits were applied. Full search strategies including bibliographic database names and dates searched can be found in *Appendix 7*, *Table 99*, along with the targeted internet searches using Google and Google Scholar. Furthermore, *Appendix 7* also contains information on the websites of the government agencies which were also searched for publications relating to migraine or headache.

Records retrieved by the database searches were exported into EndNote X9, to enable systematic removal of duplicates.[54] In addition, we did forward and backward citation tracking from included journal articles, using Web of Science Core Collection (and the Citation Finder tool or Google Scholar where articles were not available in Web of Science). Searches were re-run in November 2022 to identify any new studies or publications since the original searches, and we also ran searches to check for any retractions, errata or similar relating to included journal articles. Additional searches for utility data to inform the economic model were also undertaken at this time.

Assessment of eligibility

The citations including title and abstracts were first assessed against the eligibility criteria by two reviewers (HM, SK). Full-text articles meeting the eligibility criteria were then obtained and reviewed. Any disagreements between the reviewers were resolved by discussion or by a third reviewer if necessary (MU). No language restrictions were applied.

Inclusion criteria

Only studies meeting the following inclusion criteria were included:

- Study type: Full economic evaluations in which both the costs and the outcomes of interventions and comparators are examined, including both trial-based and model-based evaluations.
- Population: Adults with chronic migraine, where the headache occurred for 15 or more days/month for more than 3 months.

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- Interventions: Prophylactic drugs to treat chronic migraine as listed in *Box 1* (see *Chapter 2*).
- Comparators: Placebo, usual care, or other prophylactic drugs as in *Box 1* (see *Chapter 2*).
- Outcomes: Measures included headache/migraine days, headache-related QoL, MSQ and incremental cost-effectiveness ratios (ICERs) amongst others.

Exclusion criteria

Studies meeting the following exclusion criteria were excluded:

- Partial economic evaluations
- Systematic reviews and/or meta-analyses
- Qualitative studies
- Study protocols
- Conference abstracts
- Editorials and short commentaries
- Articles comparing pharmacotherapy with non-pharmacological interventions.

Data extraction

Using a pre-specified data extraction form, data extraction for full-text studies was carried out by one reviewer (SK) and then checked by a second reviewer (SN). Data extracted included:

- Study context – authors, publication year, country, setting, study population, intervention and comparators.
- Economic evaluation methods – economic evaluation type, model type, study perspective, time horizon, currency and price year, discount rate, resource use/costs, outcome measures and analytical methods.
- Economic evaluation results – study results, sensitivity analyses, generalisability and conclusion.
- Other – funding sources and conflicts of interest.

Data synthesis

Information extracted from the included studies was summarised and tabulated. Findings from individual studies were compared narratively. We summarised the published journal articles separately to the reports, as the latter will not have had a formal peer-reviewed process.

Quality appraisal of economic evaluations

The quality of both the trial-based and model-based economic evaluations was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist.[165] The Philips checklist was also used to assess the quality of each model based economic evaluation.[166] Quality assessment was undertaken by one reviewer (SK) and was checked for completeness and accuracy by a second reviewer (SN).

Results

Search results

A total of 7309 citations were retrieved from the database searches. After deduplication and title and abstract review, 88 articles were reviewed at the full-text stage. Nine articles met the inclusion criteria for published peer-reviewed journal articles.[167–175] The excluded studies with their reasons for exclusions are provided in *Report Supplementary Material 3*. Two articles were translated into English language.[173,175] The targeted internet and website searches identified an additional 72 reports, and after the screening we included 7 of these reports.[176–182] The PRISMA diagram is shown in *Figure 25*. We have narratively synthesised the reporting of the nine published journal articles separately from the seven reports.

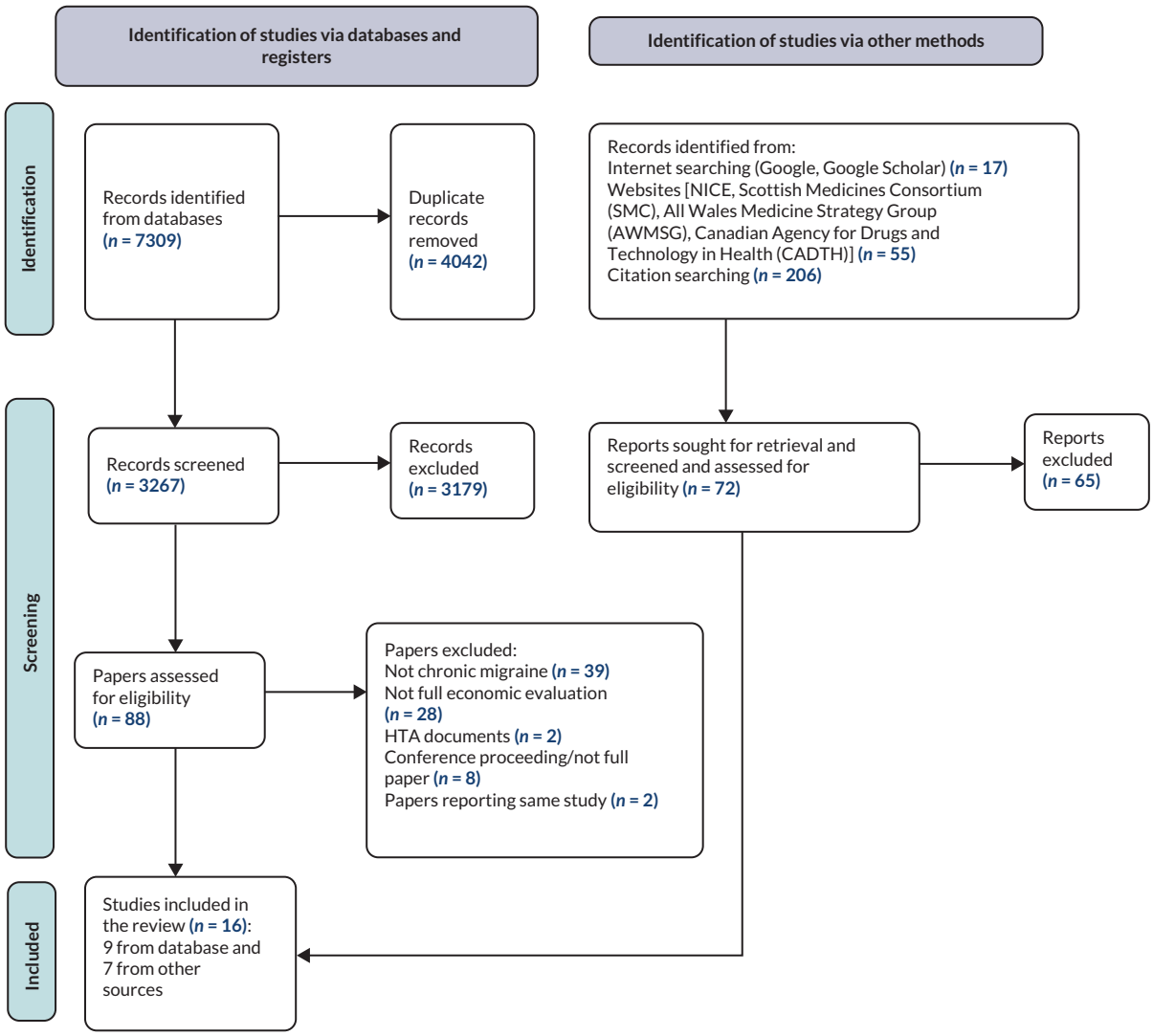

FIGURE 25 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for cost-effectiveness studies. CADTH, Canadian Agency for Drugs andTechnology in Health.

Journal articles (n = 9)

All journal based studies were model based cost-utility analyses and were from high-income countries including two from the UK.[167,170] Four studies[167,169,170,173] evaluated BTA and the remaining five studies evaluated erenumab.[168,171,172,174,175] All studies evaluating BTA compared the treatment with placebo or best supportive care; and studies evaluating erenumab compared their outcomes with placebo or BTA (see *Appendix 8*, *Table 100*).

Five studies[167,169–171,173] utilised a Markov state-transition model structure (see *Appendix 8*, *Table 101*). The Markov models included health states which were stratified by the number of migraine or headache days. Of the other four studies, one used a decision tree,[168] and the other three developed hybrid models.[172,174,175] The majority of studies used a 2-year time horizon in the economic models. An NHS perspective was adopted for the UK studies, the European studies were based on the societal perspective and the American studies were based on societal and payers' perspectives.

The majority of studies included the direct costs of the prophylactic and comparator drugs plus administration costs, and any associated costs for general practitioner (GP) visits, consultant, neurology or specialist nurse appointments and/or accident and emergency department visits (see *Appendix 8*, *Table 101*).

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The study by Vekov and Izmaylov[175] only included the costs of the drugs as they assumed all other healthcare costs for both arms were equal. For studies adopting a societal perspective, indirect costs were reported, such as wages lost as a result of not working. Some studies explicitly presented the productivity costs associated with presenteeism and absenteeism.[171,172] Resource use data for three studies[167,170,173] were obtained from the International Burden of Migraine Studies (IBMS), and for other studies, resource use was obtained from published studies including trial data or other local databases. For the UK studies,[167,170] the NHS reference costs were the main source of cost inputs, and for the non-UK studies the main source of cost inputs were previously published studies, publicly available local databases or published price lists. All nine studies reported the currency and price year in which the unit costs were calculated and reported (see *Appendix 8*, *Table 101*).

All studies longer than the 1-year time frame used discounting. The two UK studies in line with the NICE guidelines[183] used a 3.5% discount rate for both costs and outcomes.[167,170] All other studies discounted costs and outcomes at a rate of 3%, except one study which used a 5% discount rate.[175] The two UK studies[167,170] used a £20,000–30,000 per quality-adjusted life- year (QALY) as the willingness-to-pay (WTP) threshold, whereas the other studies had different WTP thresholds (see *Appendix 8*, *Table 102* for more information).

All studies used the EQ-5D as the main outcome measure to estimate QALYs (see *Appendix 8*, *Table 102*). The EQ-5D scores were mapped from the MSQ to produce utility values in six studies.[167–169,171–173] Hollier-Hann *et al.*[170] administered the EQ-5D-5L as part of the REPOSE trial, and utility values were estimated using a UK tariff. Sussman *et al.*[174] used EQ-5D-5L scores from the erenumab and BTA trials to estimate utility values; however, they did not state whose values or what tariff was used to estimate them.[174] Other outcomes measures included the number of headache days or migraine days avoided.

All studies[167,169,170,173] which used BTA as the treatment found BTA to be more cost-effective than placebo, with ICERs ranging from £15,028 (€17,720) to £16,598 (€19,572). Erenumab was found to be cost-effective in two studies in participants for whom previous preventive treatments had not worked,[168,171] and erenumab dominated placebo in two studies.[172,174] When erenumab was compared to BTA from a societal perspective, the ICER was above the most common WTP thresholds £182,128 (€218,870).[168] One study found erenumab not cost-effective compared to placebo.[175] All of the studies conducted deterministic and/or probabilistic sensitivity analysis (PSA). In most cases, the results were sensitive to changes in MMDs, health utilities and treatment costs, but were cost-effective overall – see *Appendix 8*, *Table 101* for more information.

Other reports (n = 7)

Four of the seven reports were from the UK,[179–182] two from Canada[176,177] and one from the USA[178] (see *Appendix 8*, *Table 100*). All reports were cost-utility model based analyses. The key interventions assessed for cost-effectiveness were: BTA,[176,182] erenumab,[177,178,180] fremanezumab[178,179] and galcanezumab.[181] All reports compared the intervention to placebo (best supportive care) and four reports also compared the main intervention to BTA.[177,179–181]

Two main models were employed (see *Appendix 8*, *Table 101*): a Markov model with health states stratified by number of headache days per 28 days or hybrid model with decision tree and Markov model using 12-week cycle lengths. The time horizon ranged from 2 years to a lifetime. The UK-based studies adopted an NHS perspective, and a healthcare payer perspective was adopted for the three North American studies.

All studies reported similar resource usage data. All studies reported the currency and price year for unit costs and also the discount rate (see *Appendix 8*, *Table 101*). All the studies used the MSQ scores which were mapped on to the EQ-5D to estimate utility values (see *Appendix 8*, *Table 102*).[176–182]

All CGRP inhibitors like erenumab, galcanezumab and fremanezumab were found to be cost-effective in the chronic migraine population for whom the previous treatments did not work under the widely accepted WTP thresholds[177,179–181] and have been recommended for such group of participants (see *Appendix 8*, *Table 102* for more information). The sensitivity analyses reported in each of the reports was more comprehensive than what was reported in the journal articles.

Generalisability

To assess the level of generalisability, all studies were classified as: (1) generalisable; (2) transferable; and (3) context-specific. Three journal articles[167,170,173] were transferable, and the remaining six studies were considered to be context-specific. Two journal articles did not report the source of funding.[168,175] All of the reports were considered to be context-specific and none of them declared any conflicts of interest, although they were all funded by the pharmaceutical industries except one report[182] (see *Appendix 8*, *Table 103*).

Quality appraisal of economic evaluations

None of the included studies fulfilled all of the quality criteria for the CHEERS 2022 checklist[165] (see *Appendix 8*, *Table 104*); however, the majority of studies fulfilled a large number of quality criteria. The criteria that were the least well addressed were the items on heterogeneity and generalisability. Most of the studies fulfilled a large number of the quality criteria according to the Phillips checklist.[166] The criteria that were least well addressed were whether the data has been assessed appropriately, the principles of uncertainty, heterogeneity, and assumption about the continuity of treatment and its effect, including sensitivity analysis around the assumption of different alternatives of treatment effect.

Discussion

We undertook a systematic search for economic evaluation studies for the cost-effectiveness of chronic migraine medications in the adult population and identified nine peer-reviewed journal articles and seven published reports. All articles were model based and were generally classed as high quality when appraised by the CHEERS reporting tool. None of the studies were trial-based economic evaluations.

The main strength of this review is that it included the latest CGRPs which have been approved for the treatment of chronic migraine. Although these newer drugs are more costly than the oral preventatives, they were cost-effective. Another strength is the comprehensiveness of the search strategy used and that the search was performed using a broad range of electronic databases of published studies. Furthermore, there were no country and language restrictions. The main limitation of our review is that we only included full economic evaluations and therefore important data contained within partial economic evaluations might have been missed. Another limitation of the included studies is that they did not define the comparators (i.e. best supportive care, placebo and preventative treatment) clearly.

Our review is more comprehensive and provides more worldwide evidence than the review published by Mahon and colleagues in 2020.[184] Their review only included eight studies which compared BTA or topiramate as the main intervention and is limited to studies published in the UK.[184]

In summary, based on the findings from the review, BTA and CGRPs were cost-effective compared to placebo, although the CGRPs had more incremental economic benefits compared to BTA. CGRPs might provide an acceptable cost-effective prophylactic medication for chronic migraine including for participants for whom the other treatments including BTA have been unsuccessful.

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Chapter 5 Economic model

Research question 4: Which prophylactic drugs for the management of chronic migraine are the most cost-effective?

Introduction

We built a Markov model to assess the cost-effectiveness of different pharmacological medications compared to usual care (placebo) to treat or prevent chronic migraine in the adult population. The economic model has only compared the drugs for which the trials were included in the NMA (see *Chapter 2*). The following seven treatments were compared in the base-case analysis: (1) onabotulinumtoxinA (BTA), (2) eptinezumab 100 mg, (3) eptinezumab 300 mg, (4) fremanezumab (monthly dose), (5) fremanezumab (quarterly dose), (6) galcanezumab and (7) topiramate with placebo. We also compared erenumab (70 and 140 mg) with placebo in a sensitivity analysis. This chapter describes the structure of the model, the model inputs, the assumptions made, the various scenarios which have been evaluated, the results and key sensitivity analyses.

Model structure and assumptions

To assess the cost-effectiveness of the different pharmacological medications for chronic migraine, we developed a Markov (state-transition) model in Microsoft Excel. The model structure was informed by the cost-effectiveness review (see *Chapter 4*)[167,182] and inputs from clinical and non-clinical team members. A Markov model was considered to be the most appropriate choice because progression of chronic migraine can evolve over time, and during this time patients can move between various states of headache severity based on the number of headache days (health states) or can die (due to all-cause mortality).

The model comprised 13 health states (as shown by the ovals), including death which is an absorbing state, once you have entered you cannot leave (*Figure 26*). The remaining 12 states were split into 2 parallel levels: on treatment and off treatment. Each health state was subdivided into categories based on the number of headache days per 28 days: 0–3, 4–9, 10–14 (episodic migraine) or 15–19, 20–23, 24–28 (chronic migraine) headache days per 28 days (see *Figure 26*). The arrows represent the transitions that patients can make in the model, and any recurring arrows show that the patients can stay in that health state for more than one cycle.

The model starts by assigning a hypothetical cohort of 1000 people presenting with chronic migraine into one of the three chronic migraine health states. The proportion of people starting the model in the three health states was based on the PREEMPT trial as it is one of the largest chronic migraine trials: 15–19 MHDs – 530 patients; 20–23 MHDs – 280 patients and 24–28 MHDs – 190 patients.[92,93] In the first cycle, the patient can stay in that health state, or move to a lesser headache severity health state, or move to a more headache severity health state, or move to the corresponding ‘off treatment’ health state or move to the death health state. For example, if a patient started in the 15–19 MHD health state, they can stay in this health state, or move to any of these ‘on treatment’ health states (0–3, 4–9, 10–14, 20–23 or 24–28 MHDs), or move to the 15–19 MHD ‘off treatment’ health state or die. In the second cycle and onwards, this pattern continues. If someone transitions to an ‘off treatment’ health state, we have assumed that they cannot move back to an ‘on treatment’ health state. The cycle length for the model is 3 months (12 weeks) and transitions between each health state occur at the end of each cycle.

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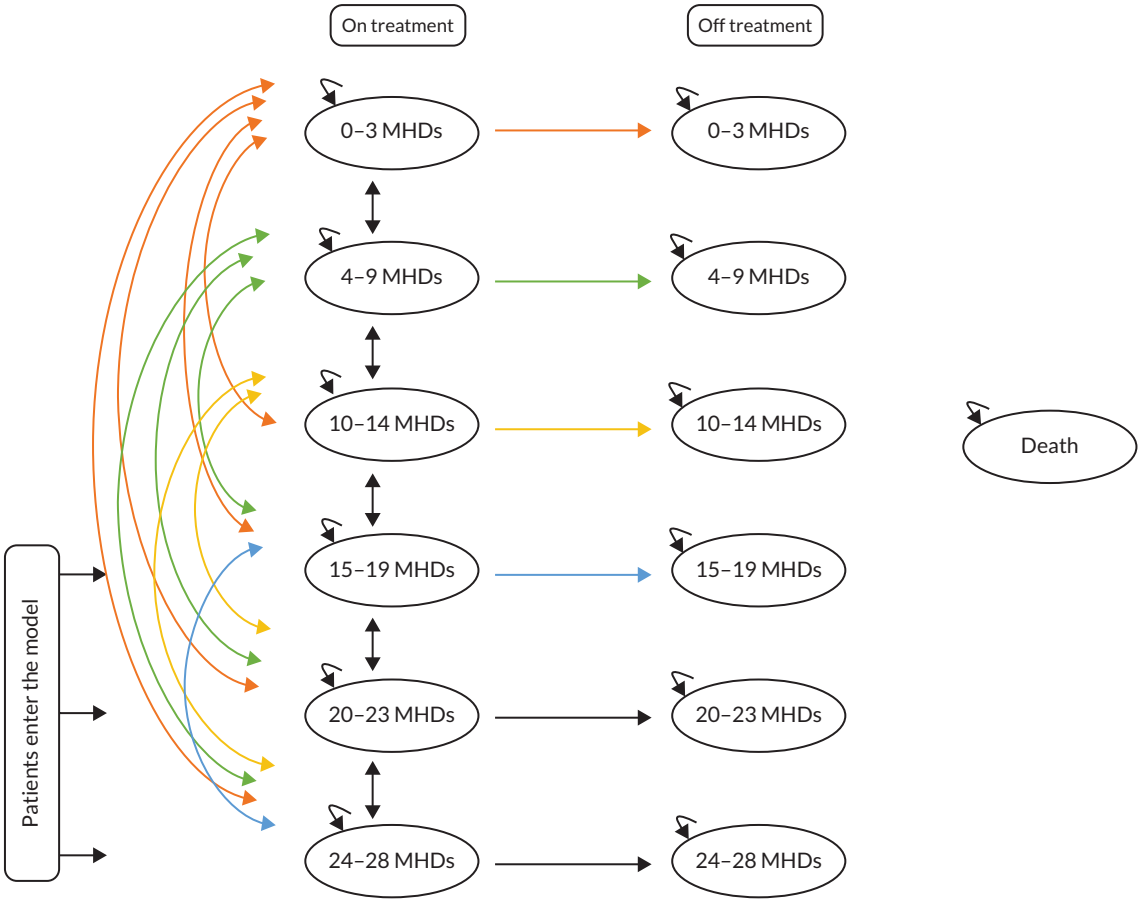

FIGURE 26 Economic model structure.

Model inputs

Transition probabilities

For the base-case analysis, the transition probabilities were calculated in the following way: for the placebo group, the transition probabilities were calculated by digitising the transition probability image (see *Figure 2* in the Batty *et al.* paper) which showed a visual representation of transition probabilities.[167] These transition probabilities were based on the PREEMPT trial.[92,93]

For the different prophylactic medications, transition probabilities were estimated using treatment effect estimates from the NMA (see *Figure 2*). Since treatment effects were parameterised as MD in MHDs, we derived transition probabilities from these as follows: we assumed that the number of headache days was uniformly distributed across the range covered by each state, and that the mean and variance of the treatment effect was independent of baseline disease severity. This allowed us to derive the post-treatment distribution of MHDs for each state, and therefore the proportion arriving in each state post-treatment. Based on advice from clinical members of the team and following NICE guidance, we also applied a discontinuation rate for each medication. For those who were on BTA we applied a 10% discontinuation rate and for all other medications we applied a 20% discontinuation rate.[39–41]

These probability matrices for each prophylactic medication were then multiplied with the placebo's transition probability matrix mentioned earlier (a two-step transition) to obtain transition probabilities for each individual prophylactic drug. The transition probabilities used for each drug are shown in *Appendix 9*, *Table 105*.

Utilities

The utility values for each of the health states were based on the EQ-5D-5L data from a RCT for educational and supportive self-management intervention for people with chronic headaches (CHESS).[12] We categorised participants in the CHESS trial regardless of their treatment group, based on the 'number of days over the last 4 weeks that they had a migraine/headache' to obtain MHD health states. The EQ-5D-5L data from the CHESS trial were obtained from the participants at 4 time points (baseline, 4, 8 and 12 months). These EQ-5D-5L responses were converted into health state utilities based on values mapped on to the EQ-5D-3L descriptive system[185] using the Hernandez-Alava crosswalk algorithm[186] for the baseline time point. In consultation with our clinical colleagues, we assumed that the utility is the same for all prophylactic drugs, but they differ by the MHD health states that the patient is in (*Table 12*).

Resource use and costs

The costs of the drugs for a 3-monthly cycle were obtained from the BNF.[51] For each of the drugs (except for BTA and eptinezumab as these are administered in hospitals/clinics and topiramate as this is an oral drug) we assumed that the first injection/infusion would be administered by a nurse (30 minutes) and in this appointment they would show the patient how to administer the drug by themself. In the NICE appraisals for these drugs, the manufacturers for these prophylactic drugs assumed that patients would then be able to self-administer these drugs; however, based on the information and guidance provided by NICE we have assumed that 10% of patients would not be able to self-administer and we have included a cost for this in each subsequent cycle.[179,181] For the drugs which are administered in a hospital/clinic setting we have assumed that this would be a 15-minute appointment with a nurse. The hourly cost of the nurse's time was obtained from the Unit Costs of Health and Social Care 2021.[187] These unit costs are shown in *Table 13* and further information is provided in *Appendix 9*, *Table 106*. The price year for costs is 2021/22 and any costs not in this financial year were bought in line using the NHS cost inflation index.[187]

For each 12-week cycle (regardless of the prophylactic medication), we assumed that there was a cost of care associated for each health state. This included GP visits, accident and emergency (A&E) visits, hospital admissions and triptan use. The frequency of usage for these resource items was obtained from

TABLE 12 Utility values used in the base-case analysis using the Hernandez-Alava algorithm

Health states	Mean	SE
0–3 MHD	0.7573	0.1662
4–9 MHD	0.6449	0.2817
10–14 MHD	0.6764	0.2458
15–19 MHD	0.6420	0.2543
20–23 MHD	0.5916	0.2549
24–28 MHD	0.5040	0.2835
0–3 Off TX	0.7573	0.1662
4–9 Off TX	0.6449	0.2817
10–14 Off TX	0.6764	0.2458
15–19 Off TX	0.6420	0.2543
20–23 Off TX	0.5916	0.2549
24–28 Off TX	0.5040	0.2835

Off TX, off treatment; SE, standard error.

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the IBMS for UK patients.[190] In addition, we checked the NICE guidance for the various prophylactic medications and we also included any additional neurology consultant and nursing visits (see *Table 13* and *Appendix 9*, *Table 107*).

All-cause mortality

Age-specific mortality rates used in the model were based on the UK general population lifetime tables from the Office for National Statistics (ONS).[191] Using the ONS data, the average probability of death for males and females were combined. As the cohort ages, mortality rates generally increase throughout the time horizon in the model.

Base-case and sensitivity analysis

We developed a Markov model from a UK NHS and personal social service (PSS) perspective to estimate the costs and QALY gains associated with the different prophylactic drugs for chronic migraine compared with placebo. For the base-case analysis, we have adopted a 2-year time horizon and the

TABLE 13 Resource use and unit costs

Resource use item	Unit cost (£)	Source
Prophylactic drugs (3-monthly cycle) – 2022 prices		
BTA	276.40	https://bnf.nice.org.uk/[51]
Eptinezumab 100 mg	1350.00	
Eptinezumab 300 mg	4050.00	
Fremanezumab – monthly	1350.00	
Fremanezumab – quarterly	1350.00	
Galcanezumab	1350.00[a]	
Topiramate	5.10	
Staff time in 2021–2 prices		
Nurse (hourly cost)	42.00	Unit Costs of Health and Social Care, 2021[187]
Specialist consultant – neurologist (hourly cost)	122.00[b]	Latest tariff did not include costs for neurology outpatient therefore assumed to be a follow-up attendance – single professional (WF01A) for a neurology outpatient visits (code 400).[188]
Other resource items in 2021–2 prices		
GP visit	39.23	Unit Costs of Health and Social Care, 2021[187]
A&E visit	165.00	A&E worksheet. 'VB08Z', Emergency Medicine, Category 2 Investigation with Category 1 Treatment.[189]
Hospital admission	618.00	Non-elective tariff for code AA31E (Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0–6) in worksheet '1 APC & OPROC' HRG code: AA31E.[189]
Triptan usage	3.99	The cost of triptans per attack was based on the weighted average of triptan costs in the UK, taken from NHS Prescriptions Cost Analysis.[167,182]

a The cost of maintenance dose in each subsequent cycle.
b Uprated to 2021–2 prices.

starting age for the patient cohort is 30 years. Costs are in 2021–2 prices and health outcomes are expressed in terms of QALY gains. Cost-effectiveness was measured in terms of an incremental cost per QALY gained (ICER). Discount rates of 3.5% were applied to both costs and outcomes.

We present both deterministic and probabilistic results. To represent the uncertainty in the parameters used in the model and to illustrate sampling uncertainty, a PSA was implemented via Monte Carlo simulations involving 1000 draws for all model inputs except the drug costs which were entered as deterministic values. We used a gamma distribution for costs and the beta distribution was used for utility values. These bootstrapped simulations enabled us to simulate 1000 replicates of the base-case ICER (displayed on cost-effectiveness planes) and to calculate the probability of cost-effectiveness at threshold values ranging from £0 to £50,000 per QALY gained [cost-effectiveness acceptability curves (CEACs)]. When comparing all prophylactic medications, we used a cost-effectiveness acceptability frontier (CEAF) which summarises the uncertainty around the cost-effectiveness of the various medications by indicating which strategy is preferred at different threshold values for cost-effectiveness.

Scenario and sensitivity analyses

We conducted scenario and sensitivity analyses by altering base-case inputs into the model. We did the following analyses:

1. Changing time horizon – in the base-case analysis we chose a 2-year time horizon, in the sensitivity analyses we have used a 5-year and a lifetime horizon.
2. Utility inputs – in the base-case analysis we chose to use utility values as recommended by NICE, currently using the Hernandez-Alava crosswalk algorithm,[186] in the sensitivity analyses we have used the van Hout crosswalk algorithm.[192]
3. Drug administration – in the base-case analysis we assumed that 10% of patients would not be able to self-administer (in line with NICE guidance); however, in practice our clinical colleagues said that all patients should be able to self-administer, and we have changed this assumption to only 1% of patients not being able to self-administer their medications.
4. MMDs – in the base-case analysis our main outcome was using MHDs, however, in this sensitivity analysis we have used MMDs as the outcome measure. This has enabled the addition of another medication for the analysis (erenumab – 70 and 140 mg). Furthermore, we have also used utility values from the Lipton *et al.* study which estimated utility values using MMDs.[171]
5. Reducing drug costs for MAbs – we know that there are confidential discounts agreed via the Patient Access Scheme between the NHS and manufacturers, however, we do not know what these discounts are. In this sensitivity analysis, we have reduced the drugs costs by 25% and 50% for eptinezumab 100 and 300 mg, fremanezumab monthly and quarterly and galcanezumab.
6. Eptinezumab – using MHDs as the primary outcome we compared eptinezumab 100 versus 300 mg.
7. BTA versus topiramate – using MHDs as the primary outcome we compared BTA versus topiramate.

Expected value of perfect information

Value-of-information analyses explore the likelihood that additional evidence might alter the recommendation by reducing decision uncertainty, and determine parameters of study design (e.g. choice of comparator(s), length of follow-up, choice of outcome measures) that maximise the value of any future RCTs. The expected value of perfect information (EVPI) is the maximum expected gain in net benefit per patient that can be obtained from reducing uncertainty in model parameters.[193] To estimate the maximum expected gain in net benefit across the whole population, we can multiply the individual EVPI by the expected future population to benefit from the interventions.

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To estimate the total population that would benefit from these prophylactic drugs, we need to know the incidence of chronic migraine per year in the UK. To the best of our knowledge, we could not find any reasonable estimate for the UK. We know that 2–4% of the world population meets the definition for chronic migraine;[10,11] and 15% of the UK population have a migraine,[3] but this is not split into migraine type. The annual global incidence of migraine is 1142.5 per 10,000 population.[194] Assuming that 2% of the UK population[195] are at risk of chronic migraine, the incidence of migraine per year is 153,095.

If the population EVPI is not significantly greater than the cost of doing a specific piece of research, then there is no value in doing that research.

Results

Base-case analysis: cost-effectiveness results

In the base-case analysis we compared the cost-effectiveness of the different medications for chronic migraine using data from the NMA based on MHDs. The time horizon was 2 years, with a starting age of 30 years for the patient cohort. Costs are in 2021–2 prices and utility was estimated using the Hernandez-Alava crosswalk algorithm. *Table 14* shows the deterministic (undiscounted and discounted) and probabilistic (discounted) results. The results are presented in terms of increasing costs.

When comparing each of the medications separately against placebo, the deterministic discounted results showed that topiramate was cheaper (£104 less expensive) and more effective (0.0464 more QALYs) than placebo, therefore topiramate dominated placebo. Each of the other medications, when compared separately, were more expensive than placebo, however, they generated more QALY gains than placebo. In terms of the cost per QALY gained, BTA was more cost-effective than placebo with an ICER of £25,238 per QALY gained. The other five medications (fremanzumab monthly, fremanzumab quarterly, eptinezumab 100 mg, eptinezumab 300 mg and galcanuzmab) when compared with placebo had ICERs which would not be considered cost-effective if using a £20,000–30,000 per QALY threshold. Probabilistic results were in line with deterministic results (see *Table 14*).

The cost-effectiveness planes for each of the medications versus placebo are shown in *Appendix 10*, *Figures 50–56*. For topiramate versus placebo, the ICER points are scattered across the four quadrants, with the majority of points in the bottom two quadrants (indicating that toprimate is cheaper but the effectiveness is varied in terms of topiramate either being less or more effective than placebo). For the other medications versus placebo, the ICER points were in the top two quadrants, indicating that each medication was more expensive than placebo and the effectiveness also varied (being less or more effective).

Figures 57–63 show the CEACs for each medication against placebo. For any amount (up to £50,000 maximum as shown in the graph) that a decision-maker is willing to pay for an additional QALY, topiramate was always 60% more cost-effective than placebo. When comparing BTA with placebo, if a decision-maker is willing to pay anything above £23,700 per QALY, BTA was the more cost-effective option. For the other medications, when comparing with placebo, placebo always remained the most cost-effective option (up to £50,000 maximum a decision-maker is willing to pay as shown in the graph).

Table 15 shows the base-case results when comparing all medications for the 2-year time horizon, ranked by the least costly option. For the discounted deterministic results, topiramate was the least costly option and had slightly more QALY gains than placebo, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains. Options placebo (dominated by topiramate), fremanezumab quarterly, eptinezumab 100 mg and galcanezumab (all dominated by fremanezumab monthly) were all eliminated as they were dominated by other medications. Then we compared topiramate, BTA, fremanezumab monthly and eptinezumab 300 mg. Fremanezumab monthly was extendedly dominated by a linear combination of BTA and eptinezumab 300 mg and therefore was

TABLE 14 Base-case cost-effectiveness results

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Deterministic results – undiscounted					
Placebo	1784	1.4006	–	–	–
Topiramate	1675	1.4491	−109	0.0485	Dominated
Placebo	1784	1.4006	–	–	–
BTA	3766	1.4802	1982	0.0796	24,900
Placebo	1784	1.4006	–	–	–
Fremanezumab (monthly)	10,458	1.4815	8674	0.0809	107,187
Placebo	1784	1.4006	–	–	–
Fremanezumab (quarterly)	10,498	1.4719	8714	0.0723	120,526
Placebo	1784	1.4006	–	–	–
Eptinezumab 100	10,521	1.4745	8737	0.0739	118,235
Placebo	1784	1.4006	–	–	–
Galcanezumab	10,945	1.4734	9160	0.0728	125,795
Placebo	1784	1.4006	–	–	–
Eptinezumab 300	28,219	1.4916	26,435	0.0910	290,453
Deterministic results – discounted					
Placebo	1729	1.3531	–	–	–
Topiramate	1624	1.3995	−104	0.0464	Dominated
Placebo	1729	1.3531	–	–	–
BTA	3654	1.4294	1925	0.0763	25,238
Placebo	1729	1.3531	–	–	–
Fremanezumab (monthly)	10,155	1.4307	8427	0.0776	108,604
Placebo	1729	1.3531	–	–	–
Fremanezumab (quarterly)	10,193	1.4224	8465	0.0693	122,126
Placebo	1729	1.3531	–	–	–
Eptinezumab 100	10,216	1.4239	8487	0.0708	119,796
Placebo	1729	1.3531	–	–	–
Galcanezumab	10,640	1.4229	8912	0.0698	127,649
Placebo	1729	1.3531	–	–	–
Eptinezumab 300	27,401	1.4403	25,672	0.0873	294,151
Probabilistic results – discounted					
Placebo	1728	1.3460	–	–	–
Topiramate	1624	1.4045	−104	0.0584	Dominated
Placebo	1728	1.3460	–	–	–
BTA	3654	1.4270	1926	0.0810	23,775

continued

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TABLE 14 Base-case cost-effectiveness results (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Placebo	1728	1.3460	–	–	–
Fremanezumab (monthly)	10,161	1.4350	8433	0.0890	94,748
Placebo	1728	1.3460	–	–	–
Fremanezumab (quarterly)	10,196	1.4273	8467	0.0812	104,251
Placebo	1728	1.3460	–	–	–
Eptinezumab 100	10,221	1.4199	8492	0.0739	114,894
Placebo	1728	1.3460	–	–	–
Galcanezumab	10,646	1.4161	8917	0.0701	127,279
Placebo	1728	1.3460	–	–	–
Eptinezumab 300	27,411	1.4365	25,683	0.0904	284,030

Note
Dominated – cheaper and more effective.

eliminated. The ICER between BTA and topiramate and the ICER between eptinezumab 300 mg and BTA were not within plausible cost-effectiveness thresholds.

For the discounted probabilistic results, again topiramate was the least costly option and had slightly more QALY gains than placebo, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains, in line with the deterministic results. Options placebo (dominated by topiramate), fremanezumab quarterly, eptinezumab 100 mg and galcanezumab (all dominated by fremanezumab monthly) were all eliminated as they were dominated by other medications. Then we compared topiramate, BTA, fremanezumab monthly and eptinezumab 300 mg. Fremanezumab monthly was extendedly dominated by a linear combination of BTA and eptinezumab 300 mg and therefore was eliminated. The ICER between BTA and topiramate and the ICER between eptinezumab 300 mg and BTA were not within plausible cost-effectiveness thresholds. This is represented graphically using a CEAF, where topiramate is the most cost-effective medication if the decision-maker is willing to pay up to £50,000 per QALY (*Figure 27*).

Sensitivity analysis: cost-effectiveness results

The results for the discounted deterministic and discounted PSA when comparing each medication separately against placebo are shown in *Appendix 10*, *Table 108*. When changing the time horizon from 2 to 5 years, using van Hout crosswalk algorithm instead of the Hernandez-Alava crosswalk algorithm for utility values, and assuming that 1% of patients could not self-administer their medication, and reducing the drug costs for the MAbs to 25% and 50%, these results were are all in line with the base-case analyses. When a lifetime horizon was adopted, topiramate still dominated placebo; however, when the other medications (apart from eptinezumab 300 mg) were compared with placebo separately, they were all deemed cost-effective with the ICERs less than £20,000 per QALY gained. Using MMDs as an outcome measure instead of MHDs, only BTA was below the £20k cost per QALY gained threshold, all other medications did not fall below the recommended £20,000–30,000 threshold by NICE. When comparing eptinezumab 100 mg with 300 mg, and BTA with topiramate, the ICERs did not fall within a cost-effectiveness range (see *Appendix 10*, *Table 108*).

TABLE 15 Base-case results – comparing all medications

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison for
Deterministic results – discounted						
Topiramate	1625	1.3995	–	–	–	
Placebo	1729	1.3531	104	−0.0464	Dominated	Placebo vs. topiramate
BTA	3654	1.4294	2029	0.0298	68,002	BTA vs. topiramate
Fremanezumab (monthly)	10,155	1.4403	6501	0.0013	Extendedly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,193	1.4224	38	−0.0083	Dominated	Fremanezumab (quarterly vs. monthly)
Eptinezumab 100	10,216	1.4239	60	−0.0067	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	10,640	1.4229	485	−0.0078	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	27,401	1.4403	23,747	0.0110	2,160,037	Eptinezumab 300 vs. BTA
Probabilistic results – discounted						
Topiramate	1624	1.4045	–	–	–	
Placebo	1728	1.3460	104	−0.0584	Dominated	Placebo vs. topiramate
BTA	3654	1.4270	2030	0.0226	89,939	BTA vs. topiramate
Fremanezumab (monthly)	10,161	1.4350	6507	0.0080	Extendedly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,196	1.4273	34	−0.0078	Dominated	Fremanezumab (quarterly vs. monthly)
Eptinezumab 100	10,221	1.4199	59	−0.0151	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	10,646	1.4161	485	−0.0189	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	27,411	1.4365	23,757	0.0094	2,524,429	Eptinezumab 300 vs. BTA

Note
Dominated – cheaper and more effective; extendedly dominated – where any interventions that have an ICER which is greater than that of a more effective intervention is ruled out.

The results for the discounted deterministic and discounted PSA when comparing all medications together are shown in *Appendix 10*, *Table 109*. For all the different scenarios, and in line with the base-case results, topiramate was the least costly option and had slightly more QALY gains than placebo, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains (except for when using MMDs as an outcome measure, fremanezumab monthly generated slightly more QALY gains then eptinezumab 300 mg). Only for the lifetime horizon, when removing the dominated options, BTA was more cost-effective than topiramate and the cost per QALY gained was always within the £20,000 WTP threshold. When left with the non-dominated options – comparing either fremanezumab monthly or eptinezumab 300 mg with BTA, the ICERs were not within plausible cost-effectiveness threshold ranges.

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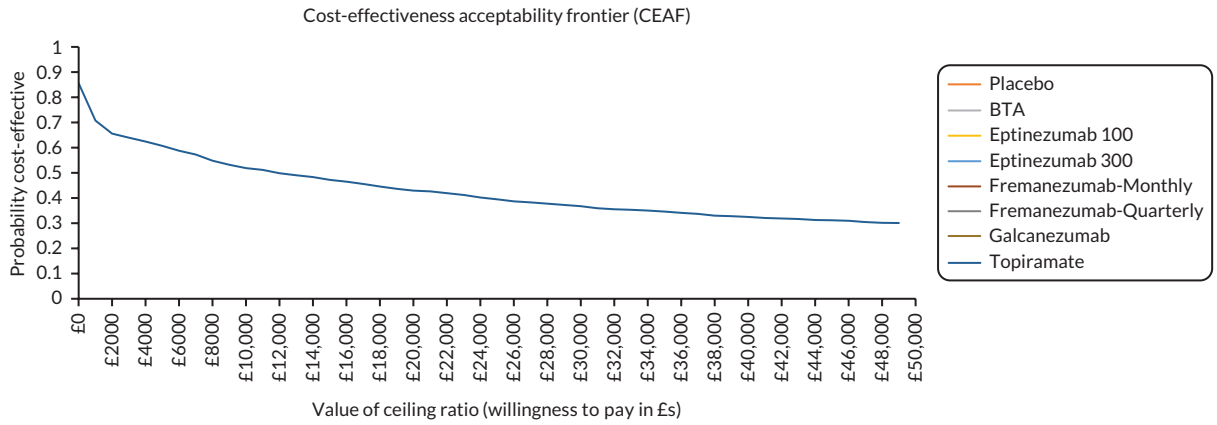

FIGURE 27 Base-case CEAF.

Expected value of perfect information results

The EVPI per person per year is £2374 at a cost-effectiveness threshold of £20,000 per QALY and £4047 at a cost-effectiveness threshold of £30,000 per QALY. To calculate the full EVPI for this decision, these figures need to be multiplied by the number of people whose treatment depends on the decision being made, and then aggregated (with discounting) over the time period until the decision is revisited. Assuming an annual decision population of 153,095, this gives an annual EVPI of £363 million at a cost-effectiveness threshold of £20,000 per QALY and £620 million at a cost-effectiveness threshold of £30,000 per QALY.

Assuming conservatively that the decision might be updated in 2 years, the total EVPI would therefore be £720 million at a cost-effectiveness threshold of £20,000 per QALY and at £1228 million at a cost-effectiveness threshold of £30,000 per QALY. This is an upper bound on the value of research, and the expected value of sample information of a specific trial would be less. The cost-effectiveness of further research will also depend on what treatment is offered in the interim. Nevertheless, the EVPI is substantial, suggesting there would be considerable value to further research in the form of a clinical trial to reduce decision uncertainty.

Discussion

We developed a Markov (state-transition) model to assess the cost-effectiveness of different pharmacological medications compared to usual care (placebo) to treat or prevent chronic migraine in the adult population based on evidence from the cost-effectiveness review in *Chapter 4* and in consultation with our clinical colleagues.

The model used the effectiveness data – the reduction in the MD in MHDs – for the different medications from the NMA in *Chapter 2*. In the base-case analysis, costs were in 2021–2 prices and calculated from an NHS and PSS perspective over a 2-year time horizon. EQ-5D-5L scores from the CHESS trial were converted into health state utility values using the Hernandez-Alava crosswalk algorithm. The health state utilities were expressed in terms of QALYs.

Our base-case deterministic results showed that when comparing each of the medications seperately against placebo, topiramate dominated placebo. Each of the other medications, when compared separately, were more expensive than placebo, however, they generated more QALY gains. In terms of the cost per QALY gained, BTA was more cost-effective than placebo with an ICER of £25,328 per QALY gained. When comparing all medications together, topiramate was the least costly option and had the fewest QALY gains, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains.

The ICER between BTA and topiramate, fremanezumab monthly and BTA, and eptinezumab 300 mg and fremanezumab monthly were not within plausible cost-effectiveness thresholds. Base-case probabilistic sensitivity analyses based on 1000 Monte Carlo simulations were in line with the base-case deterministic results; the CEAF showed that when comparing all medications, topiramate was the most cost-effective medication if the decision-maker is willing to pay up to £50,000 per QALY. Extensive sensitivity/scenario analyses were conducted, and when using MHDs as an outcome measure, the results were generally in line with the base-case results. The main exception was when using MMDs as an outcome measure instead of MHDs, fremanezumab monthly generated more QALY gains than eptinezumab 300 mg; and furthermore, when a lifetime horizon was adopted, all medications when compared separately against placebo were regarded as cost-effective as the cost per QALY gained fell below the £20,000 willingness-to-pay threshold, although eptinezumab 300 mg did not fall into this category.

A number of limitations apply to the model. Firstly, as there were not enough data in the literature, we assumed that once a participant enters the 'off treatment' health state, they cannot return to an 'on treatment' health state. However, in practice we know that a participant can come off a prophylactic medication if their migraines are better, or if they cannot tolerate a medication; however, their migraine may return sometime later, and they may be prescribed another medication for their migraine.

Secondly, there were no data on MHDs for erenumab, hence, we only compared erenumab when using MMDs as an outcome measure. However, erenumab may have the potential to be a cost-effective treatment as it generated more QALY gains than BTA, even though it was slightly more expensive. Furthermore, there was no effectiveness data on the cheaper oral drugs, such as amitriptyline and propranolol, and including these medications in the economic model may have changed the overall cost-effectiveness results.

Thirdly, the small differences in QALY gains between some of the medications, namely fremanezumab and BTA, meant that they produced huge ICERs and therefore these drugs may not appear to be cost-effective.

Fourthly, the length of follow-up used in the base-case model was 2 years as there is not enough long-term data on the success or failure of these medications. However, in a sensitivity analysis we used a lifetime horizon and nearly all of the medications, including the costly CGRP MAbs, were considered to be cost-effective against placebo and within plausible WTP thresholds.

Fifthly, we know that a lot of these medications are heavily discounted. We conducted a sensitivity analysis reducing the costs of these expensive CGRP MAbs by 25% and 50% and although the cost of these medications fell, the ICERs were still huge. This was mainly due to the small QALY gain differences between the prophylactic medications which were compared.

Sixthly, we used utility data based on MHDs based on the CHESS trial. There was very limited data in the literature on utility values which were based on MMDs. Also, there were no studies that mapped EQ-5D or SF-6D data to generate utility values for specific headache day health states which we have used in our model.

Seventhly, as the model is from an NHS and PSS perspective, we have not taken into account any broader societal costs, such as the costs to the patient for time off work and loss of pay (productivity). Finally, the model did not take into account any adverse effects associated with migraines as described in *Chapter 3*.

In summary, we found that topiramate was the least costly option and had the fewest QALY gains, whereas eptinezumab 300 mg was more costly but generated the most QALY gains. The CEAF showed that topiramate was the most cost-effective medication if the decision-maker is willing to pay up to £50,000 per QALY.

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Chapter 6 Consensus workshop and recommendations for research priorities

Research question 5: Based on our findings, what should the research recommendations be?

Introduction

In our final work package, we used consensus methodology to develop a set of research recommendations based on the results from the systematic reviews and the economic modelling.

Methods

Ethical approval

We obtained ethical approval for the consensus workshop from the University of Warwick's Biomedical and Scientific Research Ethics Committee (BSREC 49/22-23).

Design

Nominal Group Technique (NGT) is a method used in health research to enable a large diverse group to generate ideas and make decisions quickly.[196–199] The method facilitates everyone to participate and contribute to the decision-making. The workshop was designed together with our patient and public involvement (PPI) representative who suggested that we add a breakaway session, wherein people with migraine and headache experts meet separately, to share thoughts and reflect on any challenges in the mixed groups. This was an additional way of ensuring that all voices were heard at the workshop. Small group work facilitated discussion between patients and healthcare professionals, moderated by experienced facilitators. Facilitators were not members of the study team, minimising the possibility of influencing the conversation in a particular direction. At the end of the workshop, participants voted anonymously using an online polling software (Vevox).[200]

Sample and recruitment

We aimed to recruit around 15 people with chronic migraine and 10 healthcare professionals. People with migraine were approached through the National Migraine Centre (NMC) mailing list. An invitation was sent out by administrators of the NMC containing information about the workshop and a link to an online expression of interest (EoI) form and contact details for the study team. Healthcare professionals were approached directly by the study team using personal networks. We aimed for a mix of specialties and backgrounds, such as neurologists, GPs with a special interest and headache nurses. Clinicians were invited to express an interest by contacting the study team.

Results

Participants

We received 147 EoIs in response to the invitation shared by NMC. Nineteen people were sampled for maximum variation in terms of age, years living with chronic migraine and ethnicity, and were invited to the workshop. Eight people with chronic migraine attended on the day. Fourteen clinicians expressed an interest in response to information circulated by the team to their networks, and all were invited to the workshop. Eleven attended on the day; all of the eight neurologists worked in a secondary care setting and four of these worked solely as headache specialists (tertiary referral headache neurologists). Although we invited more people with migraine than health professionals, on the day the balance of

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attendees was tipped in favour of health professionals. Demographics of our sample are shown in *Table 16*.

The workshop

Prior to the workshop, we sent out a summary of the study findings (see *Report Supplementary Material 4*). The workshop took place online using Microsoft Teams. The workshop began with a presentation to summarise the research and the findings of work packages 1–4. We explained the aim of the workshop, and the scope of research recommendations. Our PPI representative spoke briefly about the importance of equal voice within the small groups. Following this, we split into three breakout groups with around seven participants (approximately four healthcare professionals and three people with migraine).

In the small groups, participants were asked to agree on their top five drug-placebo comparisons, and their top five drug-drug comparisons. They were asked to consider:

- how much evidence we have on the drug
- safety (side effects)
- efficacy (how effective the drugs were found to be in this study)
- feasibility (cost, availability, ease of administration).

We provided a crib sheet reporting the study findings to support the discussion and decision-making (see *Report Supplementary Material 4*). Participants could suggest comparisons of drugs not included in this study, and they were reminded that they held valid knowledge and perspectives to bring to the discussion.

We then split into two groups: one group with people with migraine and the other group with healthcare professionals, to reflect on the success of/any issues with equal voice in the small group sessions. During a break, the scribes sent their notes from the breakout group sessions to the team. We then held a plenary session to discuss the outcomes of the group discussions, took a break and prepared for the voting (to take place using Vevox, an anonymous polling website).[200] Voting took place in the last part of the workshop, followed by a brief discussion of the results and explanation of the next steps for the team. All attendees were provided with a certificate of attendance (health professionals) or thank you letter and payment (patients) by e-mail after the meeting.

TABLE 16 Consensus workshop attendees demographics

	Characteristic		Number
People with migraine	Age	18–39	3
		40–59	3
		60+	2
	Ethnicity	White British/other	4
		Mixed heritage	3
		Asian British/other	1
	Number of years with CM	0–9	4
		10–20	2
		20+	2
Health professionals	Role	Neurologists	8
		Specialist nurse	1
		GP with special interest	2

Results

Each group provided ten top comparisons [five drug vs. placebo (*Table 17*), and five drug vs. drug (*Table 18*)]. We removed duplicate questions to create the following two lists of top comparisons:

Participants then anonymously voted for their top five choices of the drug versus placebo (*Table 19*) and drug versus drug (*Table 20*) comparisons. The results were:

TABLE 17 The top drug vs. placebo research recommendations suggested by the small groups (in alphabetical order)

Beta-blocker	Placebo
Candesartan	Placebo
Doxycycline	Placebo
Flunarizine	Placebo
Melatonin	Placebo
Rimegepant	Placebo
SNRIs (duloxetine, venlafaxine)	Placebo
Tricyclic antidepressant	Placebo

TABLE 18 The top drug vs. drug comparisons suggested by the small groups (in alphabetical order)

All CGRP MAbs rotation	All CGRP MAbs rotation[a]
BTA + topiramate	CGRP MAbs
CGRP MAbs	BTA
CGRP MAbs	CGRP MAbs + gepant
CGRP MAbs + BTA	BTA
CGRP MAbs + BTA	CGRP MAbs
CGRP MAb receptor	MAb ligand
Flunarizine	BTA
Melatonin	Amitriptyline
Propranolol	BTA
Topiramate	Flunarizine

a This meant a study design whereby participants try one CGRP MAb, and if this fails, move on to another, and so on.

TABLE 19 The group's top five drug vs. placebo comparisons (in order of priority)

1	Candesartan	Placebo
2	Flunarizine	Placebo
3	Melatonin	Placebo
4	Beta-blocker	Placebo
5	Tricyclic antidepressant	Placebo

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We then combined these 10 and asked participants to rank them in order of priority (*Table 21*). The results were:

Discussion

The results indicate that comparisons of CGRP MAbs and BTA were a top priority for our group. They also raised the question of whether there might be additive effects of combining these medications, which was not something we anticipated. The effect sizes, in terms of MHDs/MMDs days for each of the drugs we included in our reviews, are at best modest; the largest being 2.76 days for fremanezumab monthly dose. As these drugs work through different pathways, it might be that more substantial effects are possible. Adding together the effects of BTA and a CGRP MAb, assuming no negative interaction, might have a mean effect size of 4–5 days that would be transformative for many people with chronic migraine. Candesartan and flunarizine were the top drugs the group wanted compared against placebo. There was no evidence for these drugs in our clinical and cost-effectiveness study, and the group felt strongly that these were important drugs to study.

TABLE 20 The group's top five drug vs. drug comparisons (in order of priority)

1	CGRP MAbs + BTA	CGRP MAbs
2	CGRP MAbs	BTA
3	CGRP MAb receptor	Mab ligand
4	CGRP MAbs + BTA	BTA
5	CGRP MAbs	CGRP MAbs + gepant

TABLE 21 The group's top 10 drug comparisons (in order of priority)

1	CGRP MAbs + BTA	CGRP MAbs
2	Candesartan	Placebo
3	Flunarizine	Placebo
4	CGRP MAbs	BTA
5	CGRP MAbs + BTA	BTA
6	CGRP MAb receptor	MAb ligand
7	Tricyclic antidepressant	Placebo
8	CGRP MAbs	CGRP MAbs + gepant
9	Melatonin	Placebo
10	Beta-blocker	Placebo

Chapter 7 Discussion and conclusions

Statement of principal findings

In *Chapter 2*, we identified 11 RCTs with more than 100 participants per arm from 51 publications which comprised 7352 adult participants with chronic migraine. We found that all pharmacological medications for all outcomes of interest were beneficial in preventing chronic migraine compared with placebo; however, there were no trials of sufficient quality of the commonly used drugs, such as propranolol or amitriptyline. Overall, the CGRP MAbs reduced headache/migraine days by 2.0–2.5 days per month. Eptinezumab 300 mg reduced MHDs by 2.46 days and fremanezumab monthly reduced MMDs by 2.76 days. BTA reduced headache/migraine days by fewer than 2 days per month. The NMA results showed that eptinezumab 300 mg had the highest probability ranking to reduce MHDs and MMDs; and BTA ranked better in the NMA in terms of the mean change in MHD compared with the mean change in MMD. Topiramate reduced headache/migraine days by less than 1.5 fewer days per month. The CGRP MAbs provided a worthwhile improvement on the HIT-6 measure – eptinezumab 300 mg reducing the HIT-6 by a score of 3.22 points and BTA had a worthwhile effect on the HIT-6 measure, reducing the HIT-6 score by 2.10 points. There was no convincing benefit of topiramate on the MSQ measure. Galcanezumab 120 mg provided the best improvement in QoL for the MSQ-PR dimension, but for two other dimensions of the MSQ-RR and MSQ-EF, erenumab 140 mg was superior to other treatments. The quality assessment results found that approximately 46% of the included RCTs in this review had a low RoB and 36% of the RCTs had some concerns of bias.

In *Chapter 3*, the incidence of AEs review found evidence from 40 RCTs reported across 67 articles, which investigated pharmacological interventions to manage chronic or episodic migraine. These trials included 25,891 participants and three additional drugs were included – amitriptyline, atogepant and rimegepant. There were very few SAEs – none of which were linked to the use of these drugs. Non-SAEs were common, and results suggested that all the pharmacological medications included in this review were found to be tolerable. There were differences in the incidence of AEs between the CGRP MAbs with most people using fremanezumab and one in four people using galcanezumab reporting injection site issues. These issues were much less common in people using eptinezumab or erenumab. Most people using topiramate or amitriptyline had nervous system or gastrointestinal side effects; topiramate was also linked to a higher prevalence of psychiatric disorders; and AEs related to BTA were uncommon.

In *Chapter 4*, the cost-effectiveness review identified nine peer-reviewed journal articles and seven published reports of economic evaluation studies of chronic migraine prophylactic medications in the adult population. All articles were model based evaluations, and none were trial-based economic evaluations. We found that although these newer drugs (BTA and CGRP MAbs) were more costly than the oral preventatives, they were however deemed cost-effective. Generally, the articles were classed as high quality when appraised by the CHEERS reporting tool.

In *Chapter 5*, our economic model to assess the cost-effectiveness of different pharmacological medications to treat chronic migraine found that when comparing each of the medications separately against placebo, topiramate dominated placebo (cheaper and more effective); and the best value medication was BTA, with the cost per QALY around £25,000. When comparing all medications together, the results showed that topiramate was the least costly option and had slightly more QALY gains than placebo, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains. Most medications were eliminated due to dominance. The ICER between BTA and topiramate, and the ICER between eptinezumab 300 mg and BTA weres not within plausible cost-effectiveness thresholds. Probabilistic results were similar to deterministic results. The CEAF showed that when comparing all medications topiramate was the most cost-effective medication if the decision-maker is willing to pay up to £50,000 per QALY. None of the CGRP MAbs represented good value for

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money in this comparative analysis. However, it is likely that CGRP MAbs will be cost-effective in people who have failed treatment with BTA.

In *Chapter 6*, our consensus workshop brought together 8 participants with chronic migraine and 11 health professionals with expertise in chronic migraine. The small groups found that the cheaper, oral medications, tricyclic antidepressants, SNRIs were ranked highly when compared with placebo; and when comparing the medications with each other, the CGRP MAbs and BTA separately or in combination with each other were ranked highly. The final (anonymised) rankings showed that the top three medications were: (1) candesartan, (2) flunarizine and (3) melatonin when compared with placebo; and (1) CGRP MAbs and BTA versus CGRP MAbs, (2) CGRP MAbs versus BTA and (3) CGRPs MAbs receptor (erenumab) versus CGRP MAbs ligand (eptinezumab, fremanezumab and galcanezumab), when all medications were compared together. In terms of priority, general consensus was reached on the top three choices of medications for chronic migraine: (1) CGRP MAbs and BTA versus CGRP MAbs, (2) candesartan versus placebo and (3) flunarizine versus placebo.

Strengths and limitations

To the best of our knowledge, this study is the first, most comprehensive NMA and economic model for pharmacological medications for chronic migraine in adult participants in the UK. A key strength of this project is the range of chronic migraine treatments we have included. These include the latest CGRP MAbs, namely fremanezumab, eptinezumab, galcanezumab and erenumab, which are commonly used after other concurrent preventive treatments, such as BTA and topiramate have failed in the UK.

A further strength of this project is that we applied a methodological approach following internationally recognised systematic review guidance for the systematic reviews and network meta-analyses. For example, we used a robust, comprehensive systematic search strategy, where the search was run on a broad range of electronic databases to identify all relevant trials, which did not allow for any date or language restrictions; and studies were selected by at least two reviewers independently and data extraction was performed by one reviewer and checked by a second to ensure accuracy and completion. We also conducted risk of bias and quality assessments of the included articles. For the clinical effectiveness review, we not only included the key outcomes in terms of headache days and migraine days, but we also looked at headache-related quality of life. For the AEs review, we widened our inclusion criteria to include episodic migraine participants as well as chronic migraine participants, this enabled us to include three more additional migraine medications. The economic model was based on a previous peer-reviewed published economic model which we adapted, and we conducted a fully probabilistic economic analysis, which meant that it avoids assuming that uncertain parameters are fixed. Finally, we held a consensus workshop and consensus was reached on the top three choices of medication for chronic migraine.

A potential limitation of this study is that we could not include all medications used to treat chronic migraine. This was due to excluding any RCTs with less than 100 participants per arm to ensure that we included better-quality studies and to avoid loss of precision on our NMA by including heterogeneous studies. We made this decision based on our initial scoping review where we found many studies that appeared to be of chronic migraine.

On further examination during the research process, it became clear that many studies apparently of chronic migraine were in fact of episodic migraine, of mixed populations. Additionally, the 11 trials we did include were reported across 51 papers meaning the pool of trials was very much smaller than it appeared at the start of the study.

Disappointingly, we did not identify any eligible studies for other commonly used drugs, recommended by NICE and/or SIGN, such as amitriptyline, candesartan, flunarizine or propranolol. This emphasises the need for high-quality trials on these older oral medications to ensure that we are appropriately using them.

Our post hoc re-examination of the characteristics of studies excluded on the basis of size identified just one small trial (n = 72) comparing amitriptyline and BTA that might have met our inclusion criteria.[123] This trial did not report on our outcomes of interest. One other trial, testing the addition of propranolol to topiramate (n = 191), would have met our size criterion except it was closed early for futility.[124] Furthermore, the trial would not have contributed to our NMA. Even though the trial did produce a very clear result on the futility of adding propranolol to topiramate, it does not tell us anything about how effective propranolol might be as monotherapy.

Furthermore, some of these older trials did not define whether the migraine was either chronic or episodic, or even define a difference, and including them would have resulted in a large degree of heterogeneity; this has limited our NMA to more recently investigated treatments when chronic migraine was introduced as a classification in 2007. Overall, this means that we only included the more recently investigated treatments where the trial methodology is more precise and excluded some of the pertinent data from smaller, usually older, trials such as the oral preventatives.

All of our included trials were industry funded, therefore caution is needed when interpreting these results. For the additional three drugs included in the AEs review, two of these drugs, atogepant and rimegepant, have product licences, but these have not yet been approved by NICE or SMC for the preventative treatment of CM. The main limitation of our cost-effectiveness review is that we only included full economic evaluations (i.e. studies which compared both costs and outcomes of the intervention and comparator), so we may have missed potential important information relating to the costs and outcomes of these medications. In our economic model, we did not have data on MHDs for one of the most commonly used MAbs, erenumab; hence, this medication was excluded from the main base-case analysis and including this medication may have resulted in slightly different findings as shown by the sensitivity analysis when erenumab was included when using MMDs as the outcome measure. Furthermore, we included eptinezumab 300 mg as a dose, but only the 100 mg dose for eptinezumab was approved by NICE and SMC, hence further caution is needed when interpreting these results.

Patient and public involvement

We would like to thank Andrew Cooklin for providing a patient and public perspective. He contributed to the design of the protocol, the study methods and findings, and the writing of the Plain Language Summary, and helped with the consensus workshop. Furthermore, we would like to thank the participants with chronic migraine and headache experts who took part in the consensus workshop. As a result of PPI involvement, we identified the need for trials where all medications currently used for chronic migraine can be compared concurrently, and this has contributed to our recommendations for future research.

Equality, diversity and inclusion

The report contains data from published peer-reviewed articles and reports. We cannot take responsibility for any information that does not abide by equality, diversity and inclusion in the inclusion of studies in this report.

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Implications for practice

Our clinical effectiveness results suggested that the CGRP MAbs overall were consistently the best choices for headache days, migraine days and headache-related quality of life. However, our economic model suggested that topiramate was the best value drug if you are prepared to pay up to £50,000 per QALY. However, there is uncertainty in these results as not all medications were included in the base-case economic analysis as we did not have information on MHDs for some of the medications; and thus, if all current chronic migraine medications were included, the cost-effectiveness results may have been different.

Topiramate is the only established oral drug we can make any observations for and compare with CGRP MAbs. The CGRP MAbs appear to be clinically superior, but even so, topiramate, despite its high incidence of AEs, represents the best value for money. Within the current care pathway, it is unlikely that BTA or CGRP MAbs will be recommended ahead of topiramate without a very substantial reduction in price. What is perhaps a more critical decision point is whether BTA or CGRP MAbs might be preferred as the first choice in patients where oral medications are not effective. Our findings support continuing with the current care pathway since our CEAF found that only topiramate met an acceptable threshold. However, as noted in our sensitivity analysis, if the price of the CGRPs MAbs was reduced then these medications are more likely to be cost-effective. Data from our health economics review, however, does support the use of CGRP MAbs for chronic migraine in patients where BTA is not effective.

It is disappointing that we did not find an evidence base to support the use of medications such as amitriptyline, candesartan, flunarizine and propranolol that are recommended by NICE and/or SIGN. Our consensus meeting identified the need for trials comparing candesartan and flunarizine with placebo as the top priorities for placebo-controlled trials. Furthermore, our consensus group identified the direct comparison of BTA and CGRP MAbs as a key research question. They also identified the question of whether the clinical effectiveness of these drugs might be additive. The effect sizes, in terms of mean monthly migraine/headache days for each of these drugs, are at best modest, the largest being 2.76 days for Fremanezumab monthly dose. As these drugs work through different pathways, it might be that more substantial effects are possible. Adding together the effects of BTA and a CGRP MAb, assuming no negative interaction, might have a mean effect size of 4–5 days that would be transformative for many people with chronic migraine. Our consensus group identified the comparative, and additive, effects of BTA and CGRP MAbs as high-priority research questions, although it should be noted that a previous study of multiple drugs for chronic migraine was terminated for futility.[124]

Recommendations for future research

Further research is needed where all medications currently used for chronic migraine can be compared concurrently, using common outcome measures, such as MHDs or MMDs. Head-to-head RCTs of these common medications for chronic migraine are very much needed to assess both the clinical and cost-effectiveness evidence for adults with chronic migraine in the UK.

Conclusions

The CGRP MAbs overall were consistently best choices for headache days, migraine days and headache-related quality of life. BTA was less likely to be the best choice than some (but not all) CGRP MAbs for headache days, migraine days and headache-related quality of life. Topiramate was very unlikely to be the best choice for headache days, migraine days and headache-related quality of life when compared to CGRP MAbs or BTA. The economic model found that topiramate was the best value drug if you are prepared to pay up to £50,000 per QALY. It is likely that CGRP MAbs are likely to be cost-effective in

people who have failed treatment with BTA. We reached general consensus on the top three choices of medication for preventing chronic migraine.

In conclusion, we have summarised the existing clinical and cost-effectiveness data on preventive drugs for chronic migraine and identified which directions future research on these drugs might take. We did not find convincing evidence that the CGRP MAbs are more clinically effective and cost-effective compared to topiramate or BTA.

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Additional information

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CRediT contribution statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/AYWA5297.

Primary conflicts of interest: Hema Mistry is a member of the NIHR HTA General Funding Commissioning Committee. She is co-investigator on NIHR grants.

Jason Madan is co-investigator on NIHR grants (NIHR award IDs: 14/199/14; 17/149/12; 17/84/07; 17/86/06; NIHR132871; NIHR200846; 14/25/05; RP-PG-1209-10071).

Amy Grove is a member of the NIHR HTA Commissioning Committee and a member of the NIHR DSE Fellowship Funding Committee. She is supported by NIHR Advanced Fellowship NIHR300060 and also by the NIHR Applied Research Collaboration (ARC) West Midlands NIHR200165. She is co-investigator on NIHR grants.

Callum Duncan is chair of Scottish Intercollegiate Guideline Network (SIGN) 155 and has provided advice on the use of BTA, CGRP monoclonal antibodies and CGRP antagonists to the Scottish Medicines Consortium and on eptinezumab to NICE. He was the Secretary for the British Association for the Study of Headache 2015–22 and he is a board member of Anglo Dutch Migraine Association. He is co-investigator on NIHR grants.

Manjit Matharu is the president of the medical advisory board of the CSF Leak Association. He has received consulting fees from AbbVie, TEVA, Lundbeck, Eli Lilly, Salvia and Pfizer. He has received payment for the development of educational presentations from AbbVie, Pfizer and Eli Lilly and support for attending a meeting from Pfizer. He is on the advisory board for AbbVie, TEVA, Lunbeck, Eli Lilly, Salvia and Pfizer. He has the following patent issued WO2018051103A1: System and method for diagnosing and treating headaches. He has stock options with Tesla, Adobe, Nvidia, META and Microsoft. He has received grants from Abbott, Medtronic and The Ehlers Danlos society. He is co-investigator on NIHR grants.

Martin Underwood is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health and Care Research (NIHR award IDs: 13/146/02; 14/224/04; 15/15/09; 16/61/18; 16/77/02; 17/129/02; NIHR128768; NIHR131316; NIHR131407; NIHR131629; NIHR132046; NIHR132871; 14/25/05; 17/60/22; NIHR134398; 16/167/56), and is a co-investigator on grants funded by the Australian NHMRC and Norwegian MRC. He was part of the NIHR Journals Library Editors Group 1 March 2016 to 31 March 2019. He was an NIHR senior investigator until March 2021. He is a director and shareholder of Clinvivo Ltd that provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd, funded by the European Social Fund, related to return to work initiatives. He receives some salary support from University Hospitals Coventry and Warwickshire NHS Trust. He is a co-investigator on two current and one completed NIHR-funded studies that have, or have had, additional support from Stryker Ltd. He has published multiple papers on headache disorders, some of which are cited in this monograph.

Data-sharing statement

All data requests should be submitted to the Warwick Clinical Trials Unit data accessing committee. Access to anonymised data may be granted following review.

Ethics statement

Ethical approval for the consensus workshop was obtained from the University of Warwick's Biomedical and Scientific Research Ethics Committee (BSREC 49/22-23) on 13 February 2023.

Information governance statement

University of Warwick is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University of Warwick is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: https://warwick.ac.uk/services/legalandcomplianceservices/dataprotection/privacynotices/research/.

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Appendix 1 Literature searches for clinical effectiveness review and adverse events review

TABLE 22 Overview of literature searches for clinical effectiveness and AEs review

Bibliographic databases and clinical trials registers		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	8 September 2021	4029
EMBASE (via Ovid)	8 September 2021	8404
Cochrane CENTRAL (via Cochrane Library)	8 September 2021	6754
Science Citation Index (via Web of Science)	8 September 2021	4737
Global Index Medicus (via World Health Organization)	14 September 2021	200
ClinicalTrials.gov	15 September 2021	338
ICTRP (World Health Organization)	15 September 2021	512
Total number of records retrieved: 24,974 **Duplicates removed (EndNote): 8368** **Final number for screening: 16,606**		
Bibliographic databases and clinical trials registers; additional search for riboflavin, magnesium and coenzyme Q10		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	8 February 2022	163
EMBASE (via Ovid)	8 February 2022	587
Cochrane CENTRAL (via Cochrane Library)	8 February 2022	331
Science Citation Index (via Web of Science)	8 February 2022	359
Global Index Medicus (via World Health Organization)	8 February 2022	24
ClinicalTrials.gov	8 February 2022	15
ICTRP (World Health Organization)	8 February 2022	38
Total number of records retrieved: 1517 **Duplicates removed within this set (EndNote): 481** **Duplicates removed against original search (EndNote): 448** **Final number for screening: 588**		
Pragmatic search for recent systematic reviews, to check reference lists/included studies		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	14 February 2022	114
EMBASE (via Ovid)	14 February 2022	164
Cochrane Database of Systematic Reviews (via Cochrane Library)	14 February 2022	4
Total number of records retrieved: 282 **Duplicates removed within this set (EndNote): 103** **Final number for screening: 179**		

continued

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TABLE 22 Overview of literature searches for clinical effectiveness and AEs review (*continued*)

Bibliographic databases and clinical trials registers; search update November 2022 (including all relevant drug terms)		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	7 November 2022	390
EMBASE (via Ovid)	7 November 2022	710
Cochrane CENTRAL (via Cochrane Library)	7 November 2022	713
Science Citation Index (via Web of Science)	7 November 2022	440
Global Index Medicus (via World Health Organization)	7 November 2022	222
ClinicalTrials.gov	8 November 2022	390
ICTRP (World Health Organization)	8 November 2022	631
Total number of records retrieved: 3496 **Duplicates removed within this set (EndNote): 1096** **Duplicates removed against previous searches (EndNote): 1066** **Final number for screening: 1334**		
Other sources; citation tracking		
Source	**Date searched**	**Number of records**
Reference lists – included studies (Web of Science)	23 November 2022	875
Forwards citation tracking: Science Citation Index (Web of Science)	22–23 November 2022	2710
Forwards citation tracking: Google Scholar (for studies not found in Web of Science only)	23 November 2022	23
Total number of records retrieved: 3608 **Duplicates removed (both within this set and against previous searches) (Endnote): 2122** **Final number for screening: 1486**		
Checking for retraction notices, errata and comments relating to included studies		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	22 November 2022	23
EMBASE (via Ovid)	22 November 2022	0
Retraction Watch website	22 November 2022	0
Total number of records retrieved: 23		

Search strategies: original searches, September 2021

MEDLINE (via Ovid)

Date searched: 8 September 2021

Database: Ovid MEDLINE(R) ALL <1946 to 7 September 2021>

Search Strategy:

_____ _____ _____ _____ _____

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. (112921)
2 Headache/ or exp Headache Disorders/ (61239)

3 1 or 2 [population: migraine/headache] (124144)
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. (216437)
5 Calcitonin Gene-Related Peptide/ai (436)
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ (217039)
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ (701)
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. (507)
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. (214)
10 exp Botulinum Toxins/ (17105)
11 (botulin* adj toxin*).ab,kf,ti,nm. (21943)
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. (25159)
13 (antidepress* or anti depress*).ab,kf,ti. (73890)
14 exp Antidepressive Agents/ (153122)
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. (17955)
16 exp 'Serotonin and Noradrenaline Reuptake Inhibitors'/ (5005)
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. (2908)
18 exp Angiotensin Converting Enzyme Inhibitors/ (45324)
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. (37937)
20 acei.ab,kf,ti. (4344)
21 lisinopril.ab,kf,ti,nm. (3086)
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. (14474)
23 (ARB or ARBs).ab,kf,ti. (7873)
24 exp Angiotensin Receptor Antagonists/ (25403)
25 candesartan.ab,kf,ti,nm. (3374)
26 ((beta adj3 block*) or betablock*).ab,kf,ti. (55697)
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. (34997)
28 exp Adrenergic beta-Antagonists/ (85444)
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. (67114)
30 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. (41676)
31 (CCB or CCBs).ab,kf,ti. (2619)
32 exp Calcium Channel Blockers/ (88532)
33 (flunarizine or verapamil).ab,kf,ti,nm. (27700)
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. (53599)
35 exp Anticonvulsants/ (147158)
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. (31200)
37 Pizotyline/ (250)
38 (pizotifen or pizotyline).ab,kf,ti,nm. (418)
39 (alpha adj4 agonist*).ab,kf,ti. (15369)
40 exp Adrenergic alpha-Agonists/ (164069)
41 (clonidine or guanfacine).ab,kf,ti,nm. (19180)
42 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [Interventions: named drugs/drug classes or types] (1098623)
43 randomized controlled trial.pt. (542809)
44 controlled clinical trial.pt. (94373)
45 randomized.ab. (533045)
46 placebo.ab. (221237)
47 clinical trials as topic.sh. (197235)
48 randomly.ab. (365421)
49 trial.ti. (247114)

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50 43 or 44 or 45 or 46 or 47 or 48 or 49 (1392358)
51 exp animals/ not humans.sh. (4882975)
52 50 not 51 [RCTs filter] (1281368)
53 3 and 42 and 52 [population and interventions and RCTs filter] (3949)
54 ('in data review' or in process or publisher or 'pubmed not medline').st. (4677722)
55 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. (1547833)
56 54 and 55 [pragmatic filter to pick up RCTs that have not been fully indexed for MEDLINE yet] (236445)
57 3 and 42 and 56 [population and interventions and non-MEDLINE RCT filter] (365)
58 53 or 57 (4029)

The migraine/headache search terms (lines 1–3) and botox search terms (lines 10–12) are based on those used in:

Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, *et al.* Botulinum toxins for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2018;**6**:CD011616. https://doi.org/10.1002/14651858.CD011616.pub2

The search filter for RCTs (lines 43–52) is the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format:

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, *et al.* Technical Supplement to Chapter 4: Searching for and Selecting Studies. In Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.2 (updated February 2021). Cochrane; 2021. URL: www.training.cochrane.org/handbook.

EMBASE (via Ovid)

Date searched: 8 September 2021

Database: EMBASE Classic+EMBASE <1947 to 7 September 2021>

Search strategy:

_____ _____ _____ _____ _____ _____

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kw,ti. (186,741)
2 'headache and facial pain'/ or exp chronic daily headache/ or headache/ or exp migraine/ or vascular headache/ (294,109)
3 headache/si not exp 'headache and facial pain'/dm, dt, pc, th (78,809)
4 (1 or 2) not 3 [population: headache/migraine, not indexed with headache only as a side effect] (253,432)
5 antimigraine agent/ (2568)
6 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kw,ti. (274,731)
7 exp calcitonin gene-related peptide receptor antagonist/ (3874)
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kw,ti,tn. (1446)
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kw,ti,tn. (465)
10 botulinum toxin/ or botulinum toxin A/ (39,617)
11 (botulin* adj toxin*).ab,kw,ti,tn. (23,049)
12 (botulinum* or botox* or onabotulinum*).ab,kw,ti,tn. (34,514)
13 (antidepress* or anti depress*).ab,kw,ti. (108,574)

14 exp antidepressant agent/ (515,170)
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kw,ti,tn. (22,239)
16 exp serotonin noradrenalin reuptake inhibitor/ (200,894)
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kw,ti. (4807)
18 exp dipeptidyl carboxypeptidase inhibitor/ (184,029)
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kw,ti. (55,292)
20 acei.ab,kw,ti. (9043)
21 lisinopril.ab,kw,ti,tn. (4456)
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kw,ti. (22,208)
23 (ARB or ARBs).ab,kw,ti. (15,639)
24 exp angiotensin receptor antagonist/ (100,628)
25 candesartan.ab,kw,ti,tn. (4072)
26 ((beta adj3 block*) or betablock*).ab,kw,ti. (83,019)
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kw,ti. (44,785)
28 exp beta adrenergic receptor blocking agent/ (316,412)
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kw,ti,tn. (69,432)
30 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kw,ti. (55,273)
31 (CCB or CCBs).ab,kw,ti. (4501)
32 exp calcium antagonist/ (289,500)
33 (flunarizine or verapamil).ab,kw,ti,tn. (29,550)
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kw,ti. (84,444)
35 exp anticonvulsive agent/ (451,887)
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kw,ti,tn. (43,826)
37 pizotifen/ (1970)
38 (pizotifen or pizotyline).ab,kw,ti,tn. (443)
39 (alpha adj4 agonist*).ab,kw,ti. (12,528)
40 exp alpha 2 adrenergic receptor stimulating agent/ (114,998)
41 (clonidine or guanfacine).ab,kw,ti,tn. (19,865)
42 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [Interventions: named drugs/drug classes or types] (1,819,814)
43 Clinical trial/ (1,033,371)
44 Randomized controlled trial/ (676,452)
45 Randomization/ (91,991)
46 Single blind procedure/ (43,673)
47 Double blind procedure/ (189,813)
48 Crossover procedure/ (68,369)
49 Placebo/ (381,079)
50 Randomi?ed controlled trial$.tw. (265,730)
51 Rct.tw. (43,428)
52 Random allocation.tw. (2293)
53 Randomly allocated.tw. (39,355)
54 Allocated randomly.tw. (2722)
55 (allocated adj2 random).tw. (993)
56 Single blind$.tw. (27,624)
57 Double blind$.tw. (228,282)
58 ((treble or triple) adj blind$).tw. (1438)
59 Placebo$.tw. (336,008)
60 Prospective study/ (711,345)
61 or/43-60 (2,456,634)
62 Case study/ (89,939)

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63 Case report.tw. (486,887)
64 Abstract report/ or letter/ (1,209,603)
65 or/62-64 (1,774,111)
66 61 not 65 [Ovid EMBASE RCTs filter, available from: https://tools.ovid.com/ovidtools/expertsearches.html] (2,397,874)
67 4 and 42 and 66 [population and interventions and RCTs filter] (11,374)
68 conference abstract.pt. (4,171,170)
69 67 not 68 (8404)

The search filter for RCTs (lines 43–66) is the Ovid search filter: RCT – EMBASE, available from: https://tools.ovid.com/ovidtools/expertsearches.html.

Cochrane CENTRAL (via www.cochranelibrary.com)

Date searched: 8 September 2021

Database: Cochrane Central Register of Controlled Trials. Issue 9 of 12, September 2021

ID Search Hits

#1 (headache* OR (head NEXT ache*) OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*):ti,ab,kw 36,987
#2 [mh Headache] OR [mh 'Headache Disorders'] 5399
#3 #1 or #2 36,987
#4 ((('calcitonin gene related peptide' OR CGRP) NEAR/5 (antibod* OR antagon* OR inhibit* OR block*)) OR 'anti CGRP' OR 'anti calcitonin gene-related peptide' OR (monoclonal NEXT antibod*) OR mAb OR mAbs OR moAb OR moAbs):ti,ab,kw 11,615
#5 [mh 'Calcitonin Gene-Related Peptide'/AI] 24
#6 [mh ^'Antibodies, Monoclonal'] OR [mh ^"Antibodies, Monoclonal, Humanized"] 8639
#7 [mh ^'Calcitonin Gene-Related Peptide Receptor Antagonists'] 55
#8 (erenumab OR galcanezumab OR fremanezumab OR eptinezumab):ti,ab,kw 879
#9 (rimegepant OR ubrogepant OR atogepant OR gepant*):ti,ab,kw 199
#10 [mh 'Botulinum Toxins'] 1981
#11 (botulin* NEXT toxin*):ti,ab,kw 4218
#12 (botulinum* OR botox* OR onabotulinum*):ti,ab,kw 4788
#13 (antidepress* OR (anti NEXT depress*)):ti,ab,kw 16,855
#14 [mh 'Antidepressive Agents'] 5919
#15 (amitriptyline OR venlafaxine OR mirtazapine OR duloxetine):ti,ab,kw 6344
#16 [mh 'Serotonin and Noradrenaline Reuptake Inhibitors'] 59
#17 (SNRI OR SNRIs OR ((serotonin NEAR/2 (noradrenaline OR norepinephrine)) NEXT ('reuptake inhibitor' OR 'reuptake inhibitors' OR 'reuptake inhibition'))):ti,ab,kw 832
#18 [mh 'Angiotensin Converting Enzyme Inhibitors'] 4056
#19 (('Angiotensin Converting Enzyme' NEXT Inhibit*) OR (ACE NEXT inhibit*)):ti,ab,kw 9206
#20 acei:ti,ab,kw 1658
#21 lisinopril:ti,ab,kw 1304
#22 (('angiotensin receptor' OR 'angiotensin II receptor') NEXT (block* OR antagon*)):ti,ab,kw 4639
#23 (ARB OR ARBs):ti,ab,kw 2490
#24 [mh 'Angiotensin Receptor Antagonists'] 2218
#25 candesartan:ti,ab,kw 1247
#26 ((beta NEAR/3 block*) OR betablock*):ti,ab,kw 11,414
#27 ((adrenergic OR adrenoreceptor* OR adrenoceptor*) NEAR/3 (antagon* OR block*)):ti,ab,kw 10,435
#28 [mh 'Adrenergic beta-Antagonists'] 4597

#29 (propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol):ti,ab,kw 13,764
#30 (calcium NEAR/2 (block* OR antagon* OR inhibit*)):ti,ab,kw 7875
#31 (CCB OR CCBs):ti,ab,kw 727
#32 [mh 'Calcium Channel Blockers'] 2877
#33 (flunarizine OR verapamil):ti,ab,kw 2752
#34 (anticonvuls* OR antiepilep* OR (anti NEXT convuls*) OR (anti NEXT epilep*)):ti,ab,kw 5822
#35 [mh Anticonvulsants] 2470
#36 (topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin):ti,ab,kw 6356
#37 [mh ^Pizotyline] 36
#38 (pizotifen OR pizotyline):ti,ab,kw 85
#39 (alpha NEAR/4 agonist*):ti,ab,kw 2130
#40 [mh 'Adrenergic alpha-Agonists'] 1145
#41 (clonidine OR guanfacine):ti,ab,kw 4432
#42 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 98,163
#43 #3 and #42 in Trials 6754

The Ovid MEDLINE search strategy was translated for use in the Cochrane Library with the aid of the Polyglot Search Translator:

Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, *et al.* Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc* 2020;**108**:195–207. https://doi.org/10.5195/jmla.2020.834

Science Citation Index Expanded (via Web of Science)

Date searched: 8 September 2021

SCI-EXPANDED – 1970–present

Search history

29 #27 AND #28 4737
28 TS = (random* OR 'controlled trial*' OR 'clinical trial*' OR rct OR placebo* OR ((single* OR doubl* OR trebl* OR tripl*) NEAR/0 (blind* OR mask* OR dummy))) 2,167,277
27 (#1) AND #26 10,871
26 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 713,606
25 TS = (clonidine OR guanfacine) 15,906
24 TS = (alpha NEAR/4 agonist*) 19,843
23 TS = (pizotifen OR pizotyline) 224
22 TS = (topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin) 37,381
21 TS = (anticonvuls* OR antiepilep* OR 'anti convuls*' OR 'anti epilep*') 55,882
20 TS = (flunarizine OR verapamil) 24,117
19 TS = (CCB OR CCBs) 2897
18 TS = (calcium NEAR/2 (block* OR antagon* OR inhibit*)) 46,563
17 TS = (propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol) 49,544
16 TS=((adrenergic OR adrenoreceptor* OR adrenoceptor*) NEAR/3 (antagon* OR block*)) 29,120
15 TS=((beta NEAR/3 block*) OR betablock*) 56,780
14 TS = (candesartan) 4054

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13 TS = (ARB OR ARBs) 8763
12 TS=((‘angiotensin receptor’ OR ‘angiotensin II receptor’) NEAR/0 (block* OR antagon*)) 14,815
11 TS = (lisinopril) 3148
10 TS=(‘Angiotensin Converting Enzyme Inhibit*’ OR ‘ACE inhibit*’ OR acei) 39,677
9 TS = (SNRI OR SNRIs OR (serotonin NEAR/2 (noradrenaline OR norepinephrine) NEAR/0 ‘reuptake inhib*’)) 2774
8 TS = (amitriptyline OR venlafaxine OR mirtazapine OR duloxetine) 18,231
7 TS = (antidepress* OR ‘anti depress*’) 80,971
6 TS = (botulinum* OR botox* OR onabotulinum*) 29,222
5 TS = (botulin* NEAR/0 toxin*) 19,563
4 TS = (rimegepant OR ubrogepant OR atogepant OR gepant$) 402
3 TS = (erenumab OR galcanezumab OR fremanezumab OR eptinezumab) 1260
2 TS=(((‘calcitonin gene-related peptide’ OR CGRP) NEAR/5 (antibod* OR antagon* OR inhibit* OR block*)) OR ‘anti-CGRP’ OR ‘anti-calcitonin gene-related peptide’ OR ‘monoclonal antibod*’ OR mAb OR mAbs OR moAb OR moAbs) 284,268
1 TS = (headache* OR ‘head ache*’ OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*) 106,395

The Ovid MEDLINE search strategy was translated for use in the Cochrane Library with the aid of the Polyglot Search Translator:

Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, *et al.* Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc* 2020;**108**:195–207. https://doi.org/10.5195/jmla.2020.834

The search filter for RCTs (line 28) incorporates some terms used in literature searches for the development of NICE clinical guideline CG155: Psychosis and schizophrenia in children and young people: recognition and management. NICE, 2013. *Appendix 8*: search strategies for the identification of clinical studies. Available from: www.nice.org.uk/guidance/cg155/evidence.

Global Index Medicus www.globalindexmedicus.net/

Date searched: 14 September 2021

Databases:

All the Regional Indexes Medici: African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asia Region (IMSEAR), Latin America and the Caribbean Literature on Health Sciences (LILACS), Western Pacific Region Index Medicus (WPRO).

Search screen: Advanced, available at: https://search.bvsalud.org/gim/advanced/?lang=en.

Search strategy: (note tw fields are Title, Abstract, Subject)

1.

tw:((tw:(headache* OR ‘head ache’ OR ‘head aches’ OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*))

AND

(tw:((('calcitonin gene related peptide' OR cgrp) AND (antibod* OR antagon* OR inhibit* OR block*)) OR 'anti-CGRP' OR 'anti-calcitonin gene-related peptide' OR 'monoclonal antibody' OR 'monoclonal antibodies' OR mab OR mabs OR moab OR moabs OR erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR rimegepant OR ubrogepant OR atogepant OR gepant* OR (botulin* AND toxin*) OR botulinum* OR botox OR onabotulinum* OR antidepress* OR 'anti depressant' OR 'anti depressants' OR 'anti depressive' OR amitriptyline OR venlafaxine OR mirtazapine OR duloxetine OR (serotonin AND (noradrenaline OR norepinephrine) AND reuptake AND inhibit*) OR snri OR snris OR ('angiotensin converting enzyme' AND inhibit*) OR 'ACE inhibitor' OR 'ACE inhibitors' OR acei OR lisinopril OR (('angiotensin receptor' OR 'angiotensin II receptor') AND (block* OR antagon*)) OR arb OR arbs OR candesartan OR 'beta blocker' OR 'beta blockers' OR 'beta blocking' OR 'beta blockade' OR betablock* OR ((adrenergic OR adrenoreceptor* OR adrenoceptor*) AND beta AND (antagon* OR block*)) OR propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol OR (calcium AND (block* OR antagon* OR inhibit*)) OR flunarizine OR verapamil OR anticonvuls* OR antiepilep* OR 'anti convulsive' OR 'anti convulsant' OR 'anti convulsives' OR 'anti convulsants' OR 'anti epileptic' OR 'anti epileptics' OR topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin OR pizotifen OR pizotyline OR (alpha AND agonist*) OR clonidine OR guanfacine))

AND

(tw:(random* OR placebo* OR sham OR trial* OR 'double blind' OR 'single blind' OR 'triple blind' OR 'treble blind' OR 'control group' OR 'control groups' OR allocat* OR 'phase 3' OR 'phase III' OR 'open label' OR quasirandom* OR rct)))

[uses free text sensitive filter for RCTs developed by the Information Specialist (Anna Brown)]

199 results

2.

tw:((tw:(headache* OR 'head ache' OR 'head aches' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*))

AND

(tw:((('calcitonin gene related peptide' OR cgrp) AND (antibod* OR antagon* OR inhibit* OR block*)) OR 'anti-CGRP' OR 'anti-calcitonin gene-related peptide' OR 'monoclonal antibody' OR 'monoclonal antibodies' OR mab OR mabs OR moab OR moabs OR erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR rimegepant OR ubrogepant OR atogepant OR gepant* OR (botulin* AND toxin*) OR botulinum* OR botox OR onabotulinum* OR antidepress* OR 'anti depressant' OR 'anti depressants' OR 'anti depressive' OR amitriptyline OR venlafaxine OR mirtazapine OR duloxetine OR (serotonin AND (noradrenaline OR norepinephrine) AND reuptake AND inhibit*) OR snri OR snris OR ('angiotensin converting enzyme' AND inhibit*) OR 'ACE inhibitor' OR 'ACE inhibitors' OR acei OR lisinopril OR (('angiotensin receptor' OR 'angiotensin II receptor') AND (block* OR antagon*)) OR arb OR arbs OR candesartan OR 'beta blocker' OR 'beta blockers' OR 'beta blocking' OR 'beta blockade' OR betablock* OR ((adrenergic OR adrenoreceptor* OR adrenoceptor*) AND beta AND (antagon* OR block*)) OR propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol OR (calcium AND (block* OR antagon* OR inhibit*)) OR flunarizine OR verapamil OR anticonvuls* OR antiepilep* OR 'anti convulsive' OR 'anti convulsant' OR 'anti convulsives' OR 'anti convulsants' OR 'anti epileptic' OR 'anti epileptics' OR topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin OR pizotifen OR pizotyline OR (alpha AND agonist*) OR clonidine OR guanfacine)))

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AND

(type_of_study:('clinical_trials'))

[uses the 'Type of study' filter available from the results page for 'Controlled clinical trial']

71 results, of which 1 unique (i.e. not found by search 1 – deduplicated on import into EndNote)

Final number of unique results from Global Index Medicus: **200**

ClinicalTrials.gov https://clinicaltrials.gov/

Date searched: 15 September 2021

Search screen: basic/home page

Search strategy:

Condition or disease	Other terms	Filter applied	Hits
headache OR migraine	'calcitonin gene related peptide' OR CGRP OR 'monoclonal antibody' OR 'monoclonal antibodies'	Study Type: Interventional	100
headache OR migraine	erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR rimegepant OR ubrogepant OR atogepant OR gepant OR gepants	Study Type: Interventional	115
headache OR migraine	botox OR 'botulinum toxin' OR onabotulinumtoxin	Study Type: Interventional	50
headache OR migraine	antidepressant OR amitriptyline OR venlafaxine OR mirtazapine OR duloxetine	Study Type: Interventional	38
headache OR migraine	'serotonin noradrenaline reuptake inhibitor' OR SNRI	Study Type: Interventional	8
headache OR migraine	'angiotensin converting enzyme inhibitor' OR lisinopril	Study Type: Interventional	2
headache OR migraine	'angiotensin receptor blocker' OR candesartan	Study Type: Interventional	5
headache OR migraine	'beta blocker' OR propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol	Study Type: Interventional	28
headache OR migraine	calcium AND (blocker OR antagonist)	Study Type: Interventional	32
headache OR migraine	flunarizine OR verapamil	Study Type: Interventional	18
headache OR migraine	anticonvulsant OR anticonvulsive OR topiramate OR valproate OR divalproex OR valproic acid OR gabapentin	Study Type: Interventional	99
headache OR migraine	alpha agonist OR clonidine OR guanfacine	Study Type: Interventional	5
headache OR migraine	pizotifen OR pizotyline	Study Type: Interventional	0
Total number of records retrieved: 500 Total number of unique records (after deduplication using EndNote): **338**			

International Clinical Trials Registry Platform (WHO ICTRP) https://trialsearch.who.int/

Date searched: 15 September 2021

Search screen: basic/home page

Search	Number of trials found
(migrain* OR headache*) AND (calcitonin gene related peptide OR CGRP OR monocolonal antibod*)	55
(migrain* OR headache*) AND (erenumab OR amg334 OR amg-334 OR galcanezumab OR LY2951742 OR fremanezumab OR TEV-48125 OR eptinezumab OR ALD403)	166
(migrain* OR headache*) AND (rimegepant OR BHV-3000 OR BHV3000 OR BMS-927711 OR ubrogepant OR MK-1602 OR atogepant OR AGN-241689 OR MK-8031 OR gepant*)	40
(migrain* OR headache*) AND (botulin* OR botox OR onabotulinum* OR AGN 191622 OR NT 201)	70
(migrain* OR headache*) AND (antidepress* OR anti depress* OR anti-depress* OR serotonin norepinephrine reuptake inhibitor OR serotonin noradrenaline reuptake inhibitor OR SNRI OR SNRIs)	2
(migrain* OR headache*) AND (amitriptyline OR venlafaxine OR mirtazapine OR duloxetine OR LY248686)	49
(migrain* OR headache*) AND (angiotensin converting enzyme inhibit* OR ACE inhibit* OR lisinopril)	1
(migrain* OR headache*) AND (angiotensin OR ARB OR ARBs OR candesartan)	7
(migrain* OR headache*) AND (beta block* OR beta-block* OR betablock*)	2
(migrain* OR headache*) AND (propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol)	64
(migrain* OR headache*) AND calcium AND (block* OR antagon* OR inhibit*)	0
(migrain* OR headache*) AND (flunarizine OR verapamil)	37
(migrain* OR headache*) AND (anticonvuls* OR antiepilep* OR anti convuls* OR anti epilep* OR anti-convuls* OR anti-epilep*)	6
(migrain* OR headache*) AND (topiramate OR RWJ-17021 OR USL255 OR valproate OR divalproex OR valproic acid OR gabapentin)	136
(migrain* OR headache*) AND (clonidine OR guanfacine OR SPD503 OR pizotifen OR pizotyline)	6
Total number of records retrieved: 641 Total number of unique records (after deduplication using EndNote): **512**	

Search strategies: additional searches for riboflavin, magnesium and coenzyme-Q10, February 2022

MEDLINE (via Ovid)

Date searched: 8 February 2022

Ovid MEDLINE(R) ALL <1946 to 7 February 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 115,846
2 Headache/ or exp Headache Disorders/ 62,888
3 1 or 2 [population: migraine/headache] 127,140
4 Riboflavin/ 9019
5 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 14,667
6 Ubiquinone/ 9986
7 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17,133
8 Magnesium/ or exp Magnesium Compounds/ 83,822
9 magnesium.ab,kf,ti,nm. 113,129
10 4 or 5 or 6 or 7 or 8 or 9 [interventions: 3 drugs added February 2022] 147,736
11 randomized controlled trial.pt. 558,117
12 controlled clinical trial.pt. 94,685

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13 randomized.ab. 550,007
14 placebo.ab. 225,467
15 clinical trials as topic.sh. 199,113
16 randomly.ab. 375,668
17 trial.ti. 256,318
18 11 or 12 or 13 or 14 or 15 or 16 or 17 1,425,517
19 exp animals/ not humans.sh. 4,955,382
20 18 not 19 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)] 1,311,348
21 3 and 10 and 20 [population + interventions + RCT filter] 161
22 ('in data review' or in process or publisher or 'pubmed not medline').st. 4,673,502
23 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 1,597,122
24 22 and 23 [filter to pick up RCTs that have not been fully indexed for MEDLINE yet] 231,267
25 3 and 10 and 24 [population + interventions + RCT filter for non indexed studies] 18
26 21 or 25 163

EMBASE (via Ovid)

Date searched: 8 February 2022

EMBASE Classic+EMBASE <1947 to 7 February 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kw,ti. 192,971
2 'headache and facial pain'/ or exp chronic daily headache/ or headache/ or exp migraine/ or vascular headache/ 304,535
3 headache/si not exp 'headache and facial pain'/dm, dt, pc, th 80,538
4 (1 or 2) not 3 263,170
5 exp riboflavin/ 22,643
6 (riboflavin or vitamin b2 or vitamin b 2).ab,kw,ti,tn. 15,440
7 ubidecarenone/ 9897
8 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kw,ti,tn. 18,062
9 magnesium/ or magnesium citrate/ or magnesium sulfate/ or magnesium oxide/ or magnesium derivative/ 125,171
10 magnesium.ab,kw,ti,tn. 83,078
11 5 or 6 or 7 or 8 or 9 or 10 198,610
12 Clinical trial/ 1047586
13 Randomized controlled trial/ 697,078
14 Randomization/ 93,174
15 Single blind procedure/ 45,106
16 Double blind procedure/ 194,609
17 Crossover procedure/ 69,726
18 Placebo/ 387,209
19 Randomi?ed controlled trial$.tw. 277,050
20 Rct.tw. 45,402
21 Random allocation.tw. 2364
22 Randomly allocated.tw. 40,516
23 Allocated randomly.tw. 2775
24 (allocated adj2 random).tw. 996
25 Single blind$.tw. 28,417
26 Double blind$.tw. 232,753
27 ((treble or triple) adj blind$).tw. 1530
28 Placebo$.tw. 343,527

29 Prospective study/ 746,134
30 or/12-29 2,526,798
31 Case study/ 92,743
32 Case report.tw. 502,347
33 Abstract report/ or letter/ 1,226,797
34 or/31-33 1,809,075
35 30 not 34 [Ovid EMBASE RCTs filter, available from: https://tools.ovid.com/ovidtools/expertsearch-es.html] 2,466,633
36 4 and 11 and 35 690
37 conference abstract.pt. 4,311,641
38 36 not 37 587

Cochrane CENTRAL (via www.cochranelibrary.com)

Date searched: 8 September 2021

Database: Cochrane Central Register of Controlled Trials. Issue 2 of 12 February 2022

ID Search Hits

#1 (headache* OR (head NEXT ache*) OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*):ti,ab,kw 38,109
#2 [mh Headache] OR [mh 'Headache Disorders'] 5556
#3 #1 or #2 38,109
#4 [mh ^Riboflavin] 370
#5 (riboflavin OR 'vitamin b2' OR 'vitamin b 2'):ti,ab,kw 1059
#6 [mh ^Ubiquinone] 585
#7 ((coenzyme NEXT q*) OR ('co enzyme' NEXT q*) OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10'):ti,ab,kw 1446
#8 [mh ^Magnesium] OR [mh 'Magnesium Compounds'] 2639
#9 (magnesium):ti,ab,kw 8245
#10 #4 or #5 or #6 or #7 or #8 or #9 10,644
#11 #3 and #10 in Trials 331

Science Citation Index Expanded (via Web of Science)

Date searched: 8 February 2022

SCI-EXPANDED – 1970–present

Search history

7 #6 AND #5 AND #1 359
6 TS = (random* OR 'controlled trial*' OR 'clinical trial*' OR rct OR placebo* OR ((single* OR doubl* OR trebl* OR tripl*) NEAR/0 (blind* OR mask* OR dummy))) 2,233,208
5 #2 OR #3 OR #4 203,563
4 TS = (magnesium) 171,475
3 TS=('coenzyme q*' OR 'co enzyme q*' OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10') 18,925
2 TS = (riboflavin OR 'vitamin b2' OR 'vitamin b 2') 13,950
1 TS = (headache* OR 'head ache*' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*) 109,965

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Global Index Medicus www.globalindexmedicus.net/

Date searched: 8 February 2022

Databases:

All the Regional Indexes Medici: African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asia Region (IMSEAR), Latin America and the Caribbean Literature on Health Sciences (LILACS), Western Pacific Region Index Medicus (WPRO)

Search screen: Advanced, available at: https://search.bvsalud.org/gim/advanced/?lang=en

Search strategy: (note tw fields are Title, Abstract, Subject)

1.

tw:((tw:(headache* OR 'head ache' OR 'head aches' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*)) AND (tw:(riboflavin OR 'vitamin b2' OR 'vitamin b 2' OR 'coenzyme q' OR 'coenzyme q10' OR 'co enzyme q' OR 'co enzyme q10' OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10' OR magnesium)) AND (tw:(random* OR placebo* OR sham OR trial* OR 'double blind' OR 'single blind' OR 'triple blind' OR 'treble blind' OR 'control group' OR 'control groups' OR allocat* OR 'phase 3' OR 'phase III' OR 'open label' OR quasirandom* OR rct)))

[uses free text sensitive filter for RCTs developed by the Information Specialist (Anna Brown)]

24 results

2.

tw:((tw:(headache* OR 'head ache' OR 'head aches' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*)) AND (tw:(riboflavin OR 'vitamin b2' OR 'vitamin b 2' OR 'coenzyme q' OR 'coenzyme q10' OR 'co enzyme q' OR 'co enzyme q10' OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10' OR magnesium))) AND (type_of_study:('clinical_trials'))

[uses the 'Type of study' filter available from the results page for 'Controlled clinical trial']

6 results, of which 0 unique (i.e. not found by search 1 – deduplicated on import into EndNote)

Final number of unique results from Global Index Medicus: **24**

ClinicalTrials.gov *https://clinicaltrials.gov/*

Date searched: 8 February 2022

Search screen: basic/home page

Search strategy:

Condition or disease	Other terms	Filter applied	Hits
headache OR migraine	riboflavin	Study Type: Interventional	3
headache OR migraine	'coenzyme Q10'	Study Type: Interventional	5

Condition or disease	Other terms	Filter applied	Hits
headache OR migraine	magnesium	Study Type: Interventional	14
Total number of records retrieved: 22 Total number of unique records (after deduplication using EndNote): 15			

International Clinical Trials Registry Platform (WHO ICTRP)
https://trialsearch.who.int/
Date searched: 8 February 2022

Search screen: basic/home page

Search	Number of trials found
(migrain* OR headache*) AND (riboflavin OR vitamin b2 OR vitamin b 2)	11
(migrain* OR headache*) AND (coenzyme q OR coenzyme q10 OR co enzyme q OR co enzyme q10 OR ubidecarenone OR ubiquino* OR coq10 OR co q10)	11
(migrain* OR headache*) AND magnesium	23
Total number of records retrieved: 45 Total number of unique records (after deduplication using EndNote): 38	

Search strategies: pragmatic search for recent systematic reviews, to check reference lists/included studies, February 2022

MEDLINE (via Ovid)
Date searched: 14 February 2022

Ovid MEDLINE(R) ALL <1946 to 11 February 2022>

1 exp Migraine Disorders/pc 2569
2 'migrain*'.ab,hw,kf,ti. 43,508
3 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kf,ti. 179,039
4 2 and 3 3218
5 (migrain* adj4 (prevent* or prophyla*)).ab,hw,kf,ti. 3883
6 1 or 4 or 5 5846
7 (metaanalys* or 'meta analys*').tw. 222,321
8 (systematic* adj3 review*).mp. 276,043
9 meta analysis.pt. 152,804
10 7 or 8 or 9 [pragmatic systematic review filter] 392,108
11 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 219,332
12 Calcitonin Gene-Related Peptide/ai 452
13 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 221,635
14 Calcitonin Gene-Related Peptide Receptor Antagonists/ 781
15 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 588
16 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 247
17 exp Botulinum Toxins/ 17,563
18 (botulin* adj toxin*).ab,kf,ti,nm. 22,444
19 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 25,677
20 (antidepress* or anti depress*).ab,kf,ti. 75,518

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21 exp Antidepressive Agents/ 155,320
22 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18,204
23 exp 'Serotonin and Noradrenaline Reuptake Inhibitors'/ 5141
24 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,-ti. 2996
25 exp Angiotensin-Converting Enzyme Inhibitors/ 45,974
26 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 38,458
27 acei.ab,kf,ti. 4519
28 lisinopril.ab,kf,ti,nm. 3114
29 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 14,830
30 (ARB or ARBs).ab,kf,ti. 8220
31 exp Angiotensin Receptor Antagonists/ 26,157
32 candesartan.ab,kf,ti,nm. 3407
33 ((beta adj3 block*) or betablock*).ab,kf,ti. 56,350
34 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. 35,141
35 exp Adrenergic beta-Antagonists/ 85,957
36 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,k-f,ti,nm. 67,483
37 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. 41,979
38 (CCB or CCBs).ab,kf,ti. 2692
39 exp Calcium Channel Blockers/ 89,276
40 (flunarizine or verapamil).ab,kf,ti,nm. 27,822
41 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 54,399
42 exp Anticonvulsants/ 149,062
43 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 31,789
44 Pizotyline/ 250
45 (pizotifen or pizotyline).ab,kf,ti,nm. 420
46 (alpha adj4 agonist*).ab,kf,ti. 15,482
47 exp Adrenergic alpha-Agonists/ 165,206
48 (clonidine or guanfacine).ab,kf,ti,nm. 19,260
49 Riboflavin/ 9020
50 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 14,670
51 Ubiquinone/ 9995
52 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,k-f,ti,nm. 17,147
53 Magnesium/ or exp Magnesium Compounds/ 83,845
54 magnesium.ab,kf,ti,nm. 113,174
55 or/11-54 1,249,348
56 6 and 10 and 55 182
57 limit 56 to yr='2017 - 2022' 114

EMBASE (via Ovid)

Date searched: 14 February 2022

EMBASE Classic+EMBASE <1947 to 11 February 2022>

1 exp migraine/pc [Prevention] 4944
2 'migrain*'.ab,hw,kf,ti. 82,866
3 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kf,ti. 254,616
4 2 and 3 6551
5 (migrain* adj4 (prevent* or prophyla*)).ab,hw,kf,ti. 7162
6 1 or 4 or 5 11,916
7 (metaanalys* or 'meta analys*').tw. 285,785

8 (systematic* adj3 review*).mp. 446,604
9 'systematic review'/ 331,996
10 exp meta analysis/ 238,368
11 7 or 8 or 9 or 10 587,214
12 antimigraine agent/ 2621
13 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kw,ti. 278,976
14 exp calcitonin gene-related peptide receptor antagonist/ 4505
15 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kw,ti,tn. 1846
16 (rimegepant or ubrogepant or atogepant or gepant?).ab,kw,ti,tn. 634
17 botulinum toxin/ or botulinum toxin A/ 40,825
18 (botulin* adj toxin*).ab,kw,ti,tn. 22677
19 (botulinum* or botox* or onabotulinum*).ab,kw,ti,tn. 35,359
20 (antidepress* or anti depress*).ab,kw,ti. 110,521
21 exp antidepressant agent/ 544,182
22 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kw,ti,tn. 22,630
23 exp serotonin noradrenalin reuptake inhibitor/ 205,435
24 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kw,ti. 4833
25 exp dipeptidyl carboxypeptidase inhibitor/ 188,015
26 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kw,ti. 56,131
27 acei.ab,kw,ti. 9324
28 lisinopril.ab,kw,ti,tn. 4542
29 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kw,ti. 21,397
30 (ARB or ARBs).ab,kw,ti. 16,145
31 exp angiotensin receptor antagonist/ 104,492
32 candesartan.ab,kw,ti,tn. 4099
33 ((beta adj3 block*) or betablock*).ab,kw,ti. 82,776
34 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kw,ti. 43,748
35 exp beta adrenergic receptor blocking agent/ 322,377
36 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kw,ti,tn. 70,087
37 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kw,ti. 53,952
38 (CCB or CCBs).ab,kw,ti. 4594
39 exp calcium antagonist/ 294,836
40 (flunarizine or verapamil).ab,kw,ti,tn. 29,749
41 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kw,ti. 85,741
42 exp anticonvulsive agent/ 473,685
43 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kw,ti,tn. 44,825
44 pizotifen/ 1985
45 (pizotifen or pizotyline).ab,kw,ti,tn. 447
46 (alpha adj4 agonist*).ab,kw,ti. 12,307
47 exp alpha 2 adrenergic receptor stimulating agent/ 119,247
48 (clonidine or guanfacine).ab,kw,ti,tn. 20,022
49 exp riboflavin/ 22,670
50 (riboflavin or vitamin b2 or vitamin b 2).ab,kw,ti,tn. 15,448
51 ubidecarenone/ 9906
52 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kw,ti,tn. 18,078
53 magnesium/ or magnesium citrate/ or magnesium sulfate/ or magnesium oxide/ or magnesium derivative/ 125,280
54 magnesium.ab,kw,ti,tn. 83,136

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55 or/12-54 2,046,652
56 6 and 11 and 55 513
57 limit 56 to yr='2017 - 2022' 267
58 conference abstract.pt. 4,317,835
59 57 not 58 164

Cochrane Database of Systematic Reviews (via www.cochranelibrary.com)

Date searched: 14 February 2022

ID Search Hits

#1 MeSH descriptor: [Migraine Disorders] explode all trees and with qualifier(s): [prevention&control - PC] 514
#2 (migrain*):ti,ab,kw 8739
#3 ((prevent* or prophyla*) NEAR/2 (treatment? or therap* or medication? or drug?)):ti,ab,kw 39,315
#4 #2 AND #3 1778
#5 (migrain* NEAR/4 (prevent* or prophyla*)):ti,ab,kw 2616
#6 #1 OR #4 OR #5 with Cochrane Library publication date Between Jan 2017 and Feb 2022, in Cochrane Reviews 4

Search strategies: update searches, November 2022

MEDLINE (via Ovid)

Date searched: 7 November 2022

Ovid MEDLINE(R) ALL <1946 to 4 November 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 121,076
2 Headache/ or exp Headache Disorders/ 64,821
3 1 or 2 [population: migraine/headache, based on Cochrane botox review] 132,425
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 224,346
5 Calcitonin Gene-Related Peptide/ai 463
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 227,720
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ 887
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 730
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 300
10 exp Botulinum Toxins/ 18,153
11 (botulin* adj toxin*).ab,kf,ti,nm. 23,232
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 26,565
13 (antidepress* or anti depress*).ab,kf,ti. 78,168
14 exp Antidepressive Agents/ 158,352
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18,641
16 exp 'Serotonin and Noradrenaline Reuptake Inhibitors'/ 5336
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,-ti. 3138
18 exp Angiotensin Converting Enzyme Inhibitors/ 46,764
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 39,244
20 acei.ab,kf,ti. 4749
21 lisinopril.ab,kf,ti,nm. 3155

22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 15,370
23 (ARB or ARBs).ab,kf,ti. 8687
24 exp Angiotensin Receptor Antagonists/ 27,181
25 candesartan.ab,kf,ti,nm. 3449
26 ((beta adj3 block*) or betablock*).ab,kf,ti. 57,470
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. 35,378
28 exp Adrenergic beta-Antagonists/ 86,663
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. 68,123
30 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. 42,541
31 (CCB or CCBs).ab,kf,ti. 2828
32 exp Calcium Channel Blockers/ 90,326
33 (flunarizine or verapamil).ab,kf,ti,nm. 28,045
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 55,690
35 exp Anticonvulsants/ 152,010
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 32842
37 Pizotyline/ 252
38 (pizotifen or pizotyline).ab,kf,ti,nm. 425
39 (alpha adj4 agonist*).ab,kf,ti. 15,644
40 exp Adrenergic alpha-Agonists/ 16,6795
41 (clonidine or guanfacine).ab,kf,ti,nm. 19,418
42 Riboflavin/ 9260
43 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 15,160
44 Ubiquinone/ 10,256
45 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17,694
46 Magnesium/ or exp Magnesium Compounds/ 85,028
47 magnesium.ab,kf,ti,nm. 115,926
48 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 [Interventions: named drugs/drug classes or types] 1,275,840
49 randomized controlled trial.pt. 579,949
50 controlled clinical trial.pt. 95,083
51 randomized.ab. 580,977
52 placebo.ab. 232,922
53 clinical trials as topic.sh. 200,534
54 randomly.ab. 394,586
55 trial.ti. 273,031
56 49 or 50 or 51 or 52 or 53 or 54 or 55 148,2588
57 exp animals/ not humans.sh. 5,060,853
58 56 not 57 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)] 1,364,006
59 3 and 48 and 58 [population and interventions and RCT filter] 4313
60 ('in data review' or in process or publisher or 'pubmed not medline').st. 4,897,386
61 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 1,688,331
62 60 and 61 [filter to pick up RCTs that have not been fully indexed for MEDLINE yet] 242,577
63 3 and 48 and 62 [population and interventions and non-MEDLINE RCT filter] 328
64 59 or 63 4390
65 limit 64 to ed = 20210908-20221107 303
66 limit 64 to ep = 20210908-20221107 211
67 limit 64 to dt = 20210908-20221107 259

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68 limit 64 to ez = 20210908-20221107 259
69 limit 64 to da = 20210908-20221107 366
70 65 or 66 or 67 or 68 or 69 390

EMBASE (via Ovid)

Date searched: 7 November 2022

EMBASE <1974 to 4 November 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kw,ti. 191,138
2 'headache and facial pain'/ or exp chronic daily headache/ or headache/ or exp migraine/ or vascular headache/ 308,443
3 headache/si not exp 'headache and facial pain'/dm, dt, pc, th 84,165
4 (1 or 2) not 3 264,484
5 antimigraine agent/ 2699
6 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kw,ti. 287,081
7 exp calcitonin gene related peptide receptor antagonist/ 5131
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kw,ti,tn. 2201
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kw,ti,tn. 796
10 botulinum toxin/ or botulinum toxin A/ 42,134
11 (botulin* adj toxin*).ab,kw,ti,tn. 23,263
12 (botulinum* or botox* or onabotulinum*).ab,kw,ti,tn. 35,729
13 (antidepress* or anti depress*).ab,kw,ti. 112,171
14 exp antidepressant agent/ 544,332
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kw,ti,tn. 22,582
16 exp serotonin noradrenalin reuptake inhibitor/ 202,776
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kw,ti. 5032
18 exp dipeptidyl carboxypeptidase inhibitor/ 195,131
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kw,ti. 57,476
20 acei.ab,kw,ti. 9813
21 lisinopril.ab,kw,ti,tn. 4703
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kw,ti. 22,228
23 (ARB or ARBs).ab,kw,ti. 17,008
24 exp angiotensin receptor antagonist/ 111,549
25 candesartan.ab,kw,ti,tn. 4178
26 ((beta adj3 block*) or betablock*).ab,kw,ti. 81,083
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kw,ti. 39,737
28 exp beta adrenergic receptor blocking agent/ 321,800
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kw,ti,tn. 67,224
30 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kw,ti. 54,558
31 (CCB or CCBs).ab,kw,ti. 4814
32 exp calcium antagonist/ 338,915
33 (flunarizine or verapamil).ab,kw,ti,tn. 29,819
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kw,ti. 83,876
35 exp anticonvulsive agent/ 465,496
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kw,ti,tn. 46,634
37 pizotifen/ 1959

38 (pizotifen or pizotyline).ab,kw,ti,tn. 430
39 (alpha adj4 agonist*).ab,kw,ti. 12,529
40 exp alpha 2 adrenergic receptor stimulating agent/ 122,600
41 (clonidine or guanfacine).ab,kw,ti,tn. 20,035
42 exp riboflavin/ 18,899
43 (riboflavin or vitamin b2 or vitamin b 2).ab,kw,ti,tn. 12,921
44 ubidecarenone/ 10,384
45 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kw,ti,tn. 17,792
46 magnesium/ or magnesium citrate/ or magnesium sulfate/ or magnesium oxide/ or magnesium derivative/ 111,389
47 magnesium.ab,kw,ti,tn. 76,887
48 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 2,044,855
49 Clinical trial/ 1,047,984
50 Randomized controlled trial/ 735,096
51 Randomization/ 95,413
52 Single blind procedure/ 48,155
53 Double blind procedure/ 200,384
54 Crossover procedure/ 71,963
55 Placebo/ 387,396
56 Randomi?ed controlled trial$.tw. 299,187
57 Rct.tw. 49,280
58 Random allocation.tw. 2441
59 Randomly allocated.tw. 42,860
60 Allocated randomly.tw. 2848
61 (allocated adj2 random).tw. 933
62 Single blind$.tw. 29,805
63 Double blind$.tw. 235,200
64 ((treble or triple) adj blind$).tw. 1684
65 Placebo$.tw. 350,987
66 Prospective study/ 806,517
67 or/49-66 2,623,005
68 Case study/ 89,478
69 Case report.tw. 50,970
70 Abstract report/ or letter/ 1,257,280
71 or/68-70 1,836,926
72 67 not 71 [Ovid EMBASE RCTs filter, available from: https://tools.ovid.com/ovidtools/expertsearch-es.html] 2,560,333
73 4 and 48 and 72 12,827
74 conference abstract.pt. 4,583,125
75 73 not 74 9141
76 limit 75 to dc = 20210908-20221107 710

Cochrane CENTRAL (via www.cochranelibrary.com)

Date searched: 7 November 2022

Database: Cochrane Central Register of Controlled Trials. Issue 10 of 12, October 2022

ID Search Hits

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#1 (headache* OR (head NEXT ache*) OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*):ti,ab,kw 39,419
#2 [mh Headache] OR [mh 'Headache Disorders'] 5788
#3 #1 or #2 39,419
#4 ((('calcitonin gene related peptide' OR CGRP) NEAR/5 (antibod* OR antagon* OR inhibit* OR block*)) OR 'anti CGRP' OR 'anti calcitonin gene-related peptide' OR (monoclonal NEXT antibod*) OR mAb OR mAbs OR moAb OR moAbs):ti,ab,kw 13,047
#5 [mh 'Calcitonin Gene-Related Peptide'/AI] 26
#6 [mh ^'Antibodies, Monoclonal'] OR [mh ^"Antibodies, Monoclonal, Humanized"] 9475
#7 [mh ^'Calcitonin Gene-Related Peptide Receptor Antagonists'] 80
#8 (erenumab OR galcanezumab OR fremanezumab OR eptinezumab):ti,ab,kw 1138
#9 (rimegepant OR ubrogepant OR atogepant OR gepant*):ti,ab,kw 339
#10 [mh 'Botulinum Toxins'] 2130
#11 (botulin* NEXT toxin*):ti,ab,kw 4497
#12 (botulinum* OR botox* OR onabotulinum*):ti,ab,kw 5138
#13 (antidepress* OR (anti NEXT depress*)):ti,ab,kw 17,488
#14 [mh 'Antidepressive Agents'] 6090
#15 (amitriptyline OR venlafaxine OR mirtazapine OR duloxetine):ti,ab,kw 6524
#16 [mh 'Serotonin and Noradrenaline Reuptake Inhibitors'] 62
#17 (SNRI OR SNRIs OR ((serotonin NEAR/2 (noradrenaline OR norepinephrine)) NEXT ('reuptake inhibitor' OR 'reuptake inhibitors' OR 'reuptake inhibition'))):ti,ab,kw 854
#18 [mh 'Angiotensin Converting Enzyme Inhibitors'] 4125
#19 (('Angiotensin Converting Enzyme' NEXT Inhibit*) OR (ACE NEXT inhibit*)):ti,ab,kw 9390
#20 acei:ti,ab,kw 1753
#21 lisinopril:ti,ab,kw 1331
#22 (('angiotensin receptor' OR 'angiotensin II receptor') NEXT (block* OR antagon*)):ti,ab,kw 4748
#23 (ARB OR ARBs):ti,ab,kw 2624
#24 [mh 'Angiotensin Receptor Antagonists'] 2308
#25 candesartan:ti,ab,kw 1256
#26 ((beta NEAR/3 block*) OR betablock*):ti,ab,kw 11,523
#27 ((adrenergic OR adrenoreceptor* OR adrenoceptor*) NEAR/3 (antagon* OR block*)):ti,ab,kw 10,392
#28 [mh 'Adrenergic beta-Antagonists'] 4648
#29 (propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol):ti,ab,kw 13,983
#30 (calcium NEAR/2 (block* OR antagon* OR inhibit*)):ti,ab,kw 7926
#31 (CCB OR CCBs):ti,ab,kw 732
#32 [mh 'Calcium Channel Blockers'] 2910
#33 (flunarizine OR verapamil):ti,ab,kw 2808
#34 (anticonvuls* OR antiepilep* OR (anti NEXT convuls*) OR (anti NEXT epilep*)):ti,ab,kw 6069
#35 [mh Anticonvulsants] 2555
#36 (topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin):ti,ab,kw 6651
#37 [mh ^Pizotyline] 36
#38 (pizotifen OR pizotyline):ti,ab,kw 86
#39 (alpha NEAR/4 agonist*):ti,ab,kw 2206
#40 [mh 'Adrenergic alpha-Agonists'] 1159
#41 (clonidine OR guanfacine):ti,ab,kw 4662
#42 [mh ^Riboflavin] 377
#43 (riboflavin OR 'vitamin b2' OR 'vitamin b 2'):ti,ab,kw 1112
#44 [mh ^Ubiquinone] 606
#45 ((coenzyme NEXT q*) OR ('co enzyme' NEXT q*) OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10'):ti,ab,kw 1507

#46 [mh ^Magnesium] OR [mh 'Magnesium Compounds'] 2714
#47 (magnesium):ti,ab,kw 8693
#48 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 113,318
#49 #3 and #48 with Cochrane Library publication date Between Sep 2021 and Nov 2022, in Trials 713

Science Citation Index Expanded (via Web of Science)

Date searched: 7 November 2022

	Query	Results
#33	#1 AND #31 AND #32 and Science Citation Index Expanded (SCI-EXPANDED) Timespan *[Index date]*: 2021-09-08 to 2022-11-07	440
#32	TS = (headache* OR 'head ache*' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*) Editions: WOS.SCI	114,776
#31	#26 OR #30	981,863
#30	#27 OR #28 OR #29 Editions: WOS.SCI	212,609
#29	TS = (magnesium) Editions: WOS.SCI	179,306
#28	TS=('coenzyme q*' OR 'co enzyme q*' OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10') Editions: WOS.SCI	19,547
#27	TS = (riboflavin OR 'vitamin b2' OR 'vitamin b 2') Editions: WOS.SCI	14,589
#26	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	772,406
#25	clonidine OR guanfacine (Topic)	17,184
#24	alpha NEAR/4 agonist* (Topic)	21,033
#23	pizotifen OR pizotyline (Topic)	236
#22	topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin (Topic)	41,733
#21	anticonvuls* OR antiepilep* OR 'anti convuls*' OR 'anti epilep*' (Topic)	62,154
#20	flunarizine OR verapamil (Topic)	25,018
#19	CCB OR CCBs (Topic)	3729
#18	calcium NEAR/2 (block* OR antagon* OR inhibit*) (Topic)	49,286
#17	propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol (Topic)	52,463
#16	(adrenergic OR adrenoreceptor* OR adrenoceptor*) NEAR/3 (antagon* OR block*) (Topic)	30,107
#15	(beta NEAR/3 block*) OR betablock* (Topic)	61,243
#14	candesartan (Topic)	4293
#13	ARB OR ARBs (Topic)	10,693
#12	('angiotensin receptor' OR 'angiotensin II receptor') NEAR/0 (block* OR antagon*) (Topic)	16,515

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	Query	Results
#11	lisinopril (Topic)	3398
#10	'Angiotensin Converting Enzyme Inhibit*' OR 'ACE inhibit*' OR acei (Topic)	42,930
#9	SNRI OR SNRIs OR (serotonin NEAR/2 (noradrenaline OR norepinephrine) NEAR/0 'reuptake inhib*') (Topic)	3230
#8	amitriptyline OR venlafaxine OR mirtazapine OR duloxetine (Topic)	20,245
#7	antidepress* OR 'anti depress*' (Topic)	92,351
#6	botulinum* OR botox* OR onabotulinum* (Topic)	32,959
#5	botulin* NEAR/0 toxin* (Topic)	22,325
#4	rimegepant OR ubrogepant OR atogepant OR gepant$ (Topic)	648
#3	erenumab OR galcanezumab OR fremanezumab OR eptinezumab (Topic)	1801
#2	TS = ((((‘calcitonin gene-related peptide’ OR CGRP) NEAR/5 (antibod* OR antagon* OR inhibit* OR block*)) OR ‘anti-CGRP’ OR ‘anti-calcitonin gene-related peptide’ OR ‘monoclonal antibod*’ OR mAb OR mAbs OR moAb OR moAbs))	301,595
#1	TS = (random* OR ‘controlled trial*’ OR ‘clinical trial*’ OR rct OR placebo* OR ((single* OR doubl* OR trebl* OR tripl*) NEAR/0 (blind* OR mask* OR dummy))) Editions: WOS.SCI	2,354,770

Global Index Medicus *www.globalindexmedicus.net/*

Date searched: 7 November 2022

Databases:

All the Regional Indexes Medici: African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asia Region (IMSEAR), Latin America and the Caribbean Literature on Health Sciences (LILACS), Western Pacific Region Index Medicus (WPRO)

Search screen: Advanced, available at: https://search.bvsalud.org/gim/advanced/?lang=en

Search strategy: (note tw fields are Title, Abstract, Subject)

1.

tw:((tw:(headache* OR ‘head ache’ OR ‘head aches’ OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*))

AND

(tw:((((‘calcitonin gene related peptide’ OR cgrp) AND (antibod* OR antagon* OR inhibit* OR block*)) OR ‘anti-CGRP’ OR ‘anti-calcitonin gene-related peptide’ OR ‘monoclonal antibody’ OR ‘monoclonal antibodies’ OR mab OR mabs OR moab OR moabs OR erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR rimegepant OR ubrogepant OR atogepant OR gepant* OR (botulin* AND toxin*) OR botulinum* OR botox OR onabotulinum* OR antidepress* OR ‘anti depressant’ OR ‘anti depressants’ OR ‘anti depressive’ OR amitriptyline OR venlafaxine OR mirtazapine OR duloxetine OR (serotonin AND (noradrenaline OR norepinephrine) AND reuptake AND inhibit*) OR snri OR snris OR (‘angiotensin converting enzyme’ AND inhibit*) OR ‘ACE inhibitor’ OR ‘ACE inhibitors’ OR acei OR lisinopril OR ((‘angiotensin receptor’ OR ‘angiotensin II receptor’) AND (block* OR antagon*)) OR arb OR arbs OR candesartan OR ‘beta blocker’ OR ‘beta blockers’ OR ‘beta blocking’ OR ‘beta blockade’ OR betablock* OR ((adrenergic OR adrenoreceptor* OR adrenoceptor*) AND beta AND (antagon* OR block*)) OR

propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol OR (calcium AND (block* OR antagon* OR inhibit*)) OR flunarizine OR verapamil OR anticonvuls* OR antiepilep* OR 'anti convulsive' OR 'anti convulsant' OR 'anti convulsives' OR 'anti convulsants' OR 'anti epileptic' OR 'anti epileptics' OR topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin OR pizotifen OR pizotyline OR (alpha AND agonist*) OR clonidine OR guanfacine))

AND

(tw:(random* OR placebo* OR sham OR trial* OR 'double blind' OR 'single blind' OR 'triple blind' OR 'treble blind' OR 'control group' OR 'control groups' OR allocat* OR 'phase 3' OR 'phase III' OR 'open label' OR quasirandom* OR rct)))

204 results

2.

tw:((tw:(headache* OR 'head ache' OR 'head aches' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*))

AND (tw:((('calcitonin gene related peptide' OR cgrp) AND (antibod* OR antagon* OR inhibit* OR block*)) OR 'anti-CGRP' OR 'anti-calcitonin gene-related peptide' OR 'monoclonal antibody' OR 'monoclonal antibodies' OR mab OR mabs OR moab OR moabs OR erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR rimegepant OR ubrogepant OR atogepant OR gepant* OR (botulin* AND toxin*) OR botulinum* OR botox OR onabotulinum* OR antidepress* OR 'anti depressant' OR 'anti depressants' OR 'anti depressive' OR amitriptyline OR venlafaxine OR mirtazapine OR duloxetine OR (serotonin AND (noradrenaline OR norepinephrine) AND reuptake AND inhibit*) OR snri OR snris OR ('angiotensin converting enzyme' AND inhibit*) OR 'ACE inhibitor' OR 'ACE inhibitors' OR acei OR lisinopril OR (('angiotensin receptor' OR 'angiotensin II receptor') AND (block* OR antagon*)) OR arb OR arbs OR candesartan OR 'beta blocker' OR 'beta blockers' OR 'beta blocking' OR 'beta blockade' OR betablock* OR ((adrenergic OR adrenoreceptor* OR adrenoceptor*) AND beta AND (antagon* OR block*)) OR propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol OR (calcium AND (block* OR antagon* OR inhibit*)) OR flunarizine OR verapamil OR anticonvuls* OR antiepilep* OR 'anti convulsive' OR 'anti convulsant' OR 'anti convulsives' OR 'anti convulsants' OR 'anti epileptic' OR 'anti epileptics' OR topiramate OR valproate OR divalproex OR 'valproic acid' OR gabapentin OR pizotifen OR pizotyline OR (alpha AND agonist*) OR clonidine OR guanfacine)))

AND

(type_of_study:('clinical_trials'))

71 results, of which 1 unique (i.e. not found by search 1 – deduplicated in EndNote)

3.

tw:((tw:(headache* OR 'head ache' OR 'head aches' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*))

AND

(tw:(riboflavin OR 'vitamin b2' OR 'vitamin b 2' OR 'coenzyme q' OR 'coenzyme q10' OR 'co enzyme q' OR 'co enzyme q10' OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10' OR magnesium))

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AND

(tw:(random* OR placebo* OR sham OR trial* OR 'double blind' OR 'single blind' OR 'triple blind' OR 'treble blind' OR 'control group' OR 'control groups' OR allocat* OR 'phase 3' OR 'phase III' OR 'open label' OR quasirandom* OR rct)))

26 results, of which 17 unique (i.e. not found by searches 1 or 2 – deduplicated on import into EndNote)

4.

tw:((tw:(headache* OR 'head ache' OR 'head aches' OR migrain* OR cephalgi* OR cephalalgi* OR hemicrani*)) AND (tw:(riboflavin OR 'vitamin b2' OR 'vitamin b 2' OR 'coenzyme q' OR 'coenzyme q10' OR 'co enzyme q' OR 'co enzyme q10' OR ubidecarenone OR ubiquino* OR coq10 OR 'co q10' OR magnesium))) AND (type_of_study:('clinical_trials'))

6 results, of which 0 unique (i.e. not found by searches 1–3 – deduplicated on import into EndNote)

Total unique results: **222**

ClinicalTrials.gov https://clinicaltrials.gov/
Date searched: 8 November 2022

Search screen: basic/home page

Search strategy:

	Condition or disease	Other terms	Filter applied	Hits
1	headache OR migraine	'calcitonin gene related peptide' OR CGRP OR 'monoclonal antibody' OR 'monoclonal antibodies'	Study Type: Interventional	112
2	headache OR migraine	erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR rimegepant OR ubrogepant OR atogepant OR gepant OR gepants	Study Type: Interventional	139
3	headache OR migraine	botox OR 'botulinum toxin' OR onabotulinumtoxin	Study Type: Interventional	57
4	headache OR migraine	antidepressant OR amitriptyline OR venlafaxine OR mirtazapine OR duloxetine	Study Type: Interventional	41
5	headache OR migraine	'serotonin noradrenaline reuptake inhibitor' OR SNRI	Study Type: Interventional	8
6	headache OR migraine	'angiotensin converting enzyme inhibitor' OR lisinopril	Study Type: Interventional	2
7	headache OR migraine	'angiotensin receptor blocker' OR candesartan	Study Type: Interventional	6
8	headache OR migraine	'beta blocker' OR propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol	Study Type: Interventional	30
9	headache OR migraine	calcium AND (blocker OR antagonist)	Study Type: Interventional	33
10	headache OR migraine	flunarizine OR verapamil	Study Type: Interventional	18
11	headache OR migraine	anticonvulsant OR anticonvulsive OR topiramate OR valproate OR divalproex OR valproic acid OR gabapentin	Study Type: Interventional	106

	Condition or disease	Other terms	Filter applied	Hits
12	headache OR migraine	alpha agonist OR clonidine OR guanfacine	Study Type: Interventional	6
13	headache OR migraine	pizotifen OR pizotyline	Study Type: Interventional	0
14	headache OR migraine	riboflavin	Study Type: Interventional	3
15	headache OR migraine	'coenzyme Q10'	Study Type: Interventional	6
16	headache OR migraine	magnesium	Study Type: Interventional	15
	Total number of records retrieved: 582 Total number of unique records (after deduplication using EndNote): **390**			

International Clinical Trials Registry Platform (WHO ICTRP)

https://trialsearch.who.int/

Date searched: 8 November 2022

Search screen: basic/home page

	Search	Number of trials found
1	(migrain* OR headache*) AND (calcitonin gene related peptide OR CGRP OR monocolonal antibod*)	66
2	(migrain* OR headache*) AND (erenumab OR amg334 OR amg-334 OR galcanezumab OR LY2951742 OR fremanezumab OR TEV-48125 OR eptinezumab OR ALD403)	167
3	(migrain* OR headache*) AND (rimegepant OR BHV-3000 OR BHV3000 OR BMS-927711 OR ubrogepant OR MK-1602 OR atogepant OR AGN-241689 OR MK-8031 OR gepant*)	58
4	(migrain* OR headache*) AND (botulin* OR botox OR onabotulinum* OR AGN 191622 OR NT 201)	75
5	(migrain* OR headache*) AND (antidepress* OR anti depress* OR anti-depress* OR serotonin norepinephrine reuptake inhibitor OR serotonin noradrenaline reuptake inhibitor OR SNRI OR SNRIs)	2
6	(migrain* OR headache*) AND (amitriptyline OR venlafaxine OR mirtazapine OR duloxetine OR LY248686)	51
7	(migrain* OR headache*) AND (angiotensin converting enzyme inhibit* OR ACE inhibit* OR lisinopril)	1
8	(migrain* OR headache*) AND (angiotensin OR ARB OR ARBs OR candesartan)	7
9	(migrain* OR headache*) AND (beta block* OR beta-block* OR betablock*)	2
10	(migrain* OR headache*) AND (propranolol OR metoprolol OR timolol OR atenolol OR nadolol OR nebivolol OR pindolol)	67
11	(migrain* OR headache*) AND calcium AND (block* OR antagon* OR inhibit*)	0
12	(migrain* OR headache*) AND (flunarizine OR verapamil)	37
13	(migrain* OR headache*) AND (anticonvuls* OR antiepilep* OR anti convuls* OR anti epilep* OR anti-convuls* OR anti-epilep*)	7
14	(migrain* OR headache*) AND (topiramate OR RWJ-17021 OR USL255 OR valproate OR divalproex OR valproic acid OR gabapentin)	140
15	(migrain* OR headache*) AND (clonidine OR guanfacine OR SPD503 OR pizotifen OR pizotyline)	6
16	(migrain* OR headache*) AND (riboflavin OR vitamin b2 OR vitamin b 2)	8
17	(migrain* OR headache*) AND (coenzyme q OR coenzyme q10 OR co enzyme q OR co enzyme q10 OR ubidecarenone OR ubiquino* OR coq10 OR co q10)	11

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	Search	Number of trials found
18	(migrain* OR headache*) AND magnesium	25
	Total number of records retrieved: 730 Total number of unique records (after deduplication using EndNote): 631	

Reference lists and forward citation searches

Web of Science Core Collection: Science Citation Index Expanded – 1970–present; Social Sciences Citation Index (SSCI) – 1900–present; Arts and Humanities Citation Index (AHCI) – 1975–present; Conference Proceedings Citation Index – Science (CPCI-S) – 1990–present; Conference Proceedings Citation Index – Social Science and Humanities (CPCI-SSH) – 1990–present; Emerging Sources Citation Index (ESCI) – 2015–present.

Dates searched: 22–24 November 2022

Searched for each included study by combinations of author and title keywords

69/72 included study papers had records in Web of Science, yielding **2710** citing paper results and **875** reference list results

Google Scholar https://scholar.google.co.uk/
Date searched: 23 November 2022

The remaining 3 study papers were found via Google Scholar; 2 had 0 citing papers in Google Scholar, 1 had **23** citing papers.

Searches to check for retraction notices, errata and comments relating to included studies

MEDLINE (Ovid) search strategy, date searched: 22 November 2022
Database: Ovid MEDLINE(R) ALL <1946 to 21 November 2022>

Search Strategy:

---------- ---------- ---------- ---------- ---------- ----------

1 ('33069214' or '34407343' or '33549036' or '34246226' or '33231489' or '33400330' or '32075406' or '29984601' or '24107267' or '20647170' or '17445098' or '32985341' or '31816249' or '21070231' or '33338437' or '30446596' or '17988947' or '20647171' or '33314079' or '12047461' or '15316798' or '29471679' or '19393844' or '25127173' or '31234642' or '18052949' or '29800211' or '31112399' or '20487038' or '17018329' or '31427046' or '32930994' or '30594122' or '30982348' or '29171821' or '23406477' or '32747522' or '31291516' or '32209650' or '27288354' or '20974598' or '30996060' or '3180198' or '32949542' or '31721185' or '17428299' or '30360965' or '31559634' or '31104507' or '34324700' or '34323290' or '33023473' or '19719543' or '32958075' or '33026630' or '29171818' or '17300356' or '29255900' or '33250209' or '34374086' or '29813147' or '30942898' or '26879279' or '28460892' or '30996056' or '34171973').ui. (66)

Annotation: MEDLINE accession numbers/PubMed IDs of 66 included studies identified via MEDLINE, exported from EndNote

2 (cin or comment or con or concern or cri or crf or ecf or eci or efr or ein or erratum or expression or republished or retracted or retraction or rin or rof or rpf or rpi or rrf or rri or uin or uof or update).cm. (2,146,340)
3 1 and 2 (22)
4 fazlalizadeh h.au. (4)
5 Erenumab versus topiramate for the prevention of migraine.m_titl. (1)
6 '10.1177/2515816320932573'.do,cm. (0)
7 (Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine).m_titl. (0)
8 Time course of efficacy of atogepant for the preventive treatment of migraine: Results from the randomized, double-blind ADVANCE trial.m_titl. (1)
9 Early onset of efficacy with fremanezumab for the preventive treatment of chronic migraine.m_titl. (1)
10 5 or 8 or 9 (3)

Annotation: 3 additional included studies now available in MEDLINE

11 2 and 10 (1)
12 3 or 11 (23)

EMBASE (Ovid) search strategy, date searched: 22 November 2022

Checking for Sakai *et al.*, 2020 only (as not in MEDLINE):

EMBASE Classic+EMBASE <1947 to 21 November 2022>

1 '2005611510'.rr.0
2 (Efficacy and safety and galcanezumab and 'prevention of migraine' and Japanese).mp.2
3 erratum/ or 'expression of concern'/ or retraction notice/262,282
4 Retracted article/13,012
5 yes.ne.5434
6 (erratum or tombstone).pt.268,823
7 3 or 4 or 5 or 6272,030
8 (retraction or retracted).ti.16,218
9 (comment on or erratum or corrigendum or withdrawn).ti.236,362
10 7 or 8 or 9312,106
11 2 and 10**0**

Retraction Watch Database http://retractiondatabase.org/RetractionSearch.aspx

Date searched: 22 November 2022

Searched for 'migraine' in Title field (as all included studies include this word in the title): 7 results, none of which are in the included studies.

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Appendix 2 Baseline characteristics of the included studies for clinical effectiveness review

TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
Author, year: Silberstein, 2007[28] **Country:** USA	**Purpose**: To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine **Study design:** randomised, double-blind, placebo-controlled, parallel-group, multicentre trial **Date:** September 2003–March 2005	• Adult subjects with at least 15 headache days per 28 days with head pain for at least 30 minutes. On at least half of these days, subjects have experienced migraine with or without aura or migrainous headache	• Previously failed more than 2 adequate trials of migraine preventive medications • Previously failed an adequate trial of topiramate therapy due to lack of efficacy or adverse events	Topiramate resulted in statistically significant improvements compared with placebo in mean monthly migraine and migraine headache days. Topiramate is safe and generally well tolerated
		• At least 11 score of MIDAS at visit 1	• History of cluster headache or basilar, ophthalmoplegic, or hemiplegic migraines • Migraine onset after age 50 • Overuse of acute migraine medication • History of hepatic disorder or nephrolithiasis • Progressive neurological disorder other than migraine • Pregnant or nursing	

continued

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TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
Author, year: Rothrock, 2019[88] **Country:** USA	**Purpose:** To compare effectiveness of onabotulinumtoxinA and topiramate for CM prevention **Study design:** multicentre, randomised, parallel-group, post-authorisation, open label prospective study. After 12 weeks, patients initially randomised to topiramate could cross over to onabotulinumtoxinA treatment **Date:** August 2014–September 2017	• Adult (18–65) had to record ≥ 20 diary days during 28 days baseline screening • Reported ≥ 15 headache days • Patients taking other preventive treatments were eligible for enrolment if the dose had been stable and well tolerated for ≥ 12 weeks before screening and the patient was willing to maintain a stable dose	• Taking opioid-containing products for acute headache treatment more than 8 days during a 28-day period • Previous treatment with onabotulinumtoxin of any serotype for any reason • Previous treatment with topiramate • On a ketogenic diet (high in fat, low in carbohydrates) • History of acute myopia or increased intraocular pressure	In those few patients who were randomised to the oral medication and completed the treatment phase, topiramate was at least as efficacious as onabotulinumtoxin A. However, the high discontinuation rate associated with topiramate [the majority (51%) of patients discontinued treatment because of AEs] appears to diminish its clinical value significantly, compared to only 4% of BTA group. Results also demonstrate that BTA is a safe and often effective alternative for patients with CM who discontinue treatment with topiramate
		• Patients were permitted to take prescription or over the-counter acute headache pain medication, recording use in their daily diary	• Diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function • Acupuncture, TENS, cranial traction, dental splints for headache, or injection of anaesthetics/steroids in the 4 weeks prior to screening	

TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
Author, year: Tepper, 2017[45] **Country:** North America (Canada and the USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, and the UK)	**Purpose:** To assess the safety and efficacy of erenumab 70 and 140 mg in patients with chronic migraine **Study design:** Phase 2, randomised, double-blind, placebo-controlled, multicentre **Date:** 3 April 2014–4 December 2015	• History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine day	• History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • Failed > 3 medication categories due to lack of efficacy for prophylactic treatment of migraine	In patients with chronic migraine, erenumab 70 and 140 mg reduced the number of MMDs with a safety profile similar to placebo, providing evidence that erenumab could be a potential therapy for migraine prevention. Further research is needed to understand long-term efficacy and safety of erenumab, and the applicability of this study to real- world settings
		• ≥ 4 distinct headache episodes, each lasting ≥ 4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the eDiary calculations. • Demonstrated at least 80% compliance with the eDiary	• Received onabotulinum toxin in head or neck region within 4 months prior to screening • Used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase	
Author, year: Dodick, 2019[89] **Country:** 82 in the USA, 4 in Australia, and 3 each in New Zealand and the Republic of Georgia	**Purpose:** To determine the safety, tolerability, and effectiveness of 4 dose levels of eptinezumab and to inform the phase 3 development programme **Study design:** Phase 2b, parallel-group, double-blind, randomised, placebo-controlled, dose-ranging clinical trial **Date:** December 2014–December 2016	• Adult 18–55 years with CM according to ICHD-3b • Established at age ≥ 35 years and history of CM of ≥ 1 year • ≥ 15 headache days, of which ≥ 8 were assessed as migraine days during baseline priod	• Confounding pain syndromes (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome) or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening	The results of this trial demonstrate that eptinezumab appears effective and well tolerated for the preventive treatment of chronic migraine and justifies the conduct of pivotal phase 3 trials for migraine prevention

continued

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TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
		• Use of hormonal therapy and preventive medications for headache except botulinum toxin, was allowed if the dosing has been stable for > 3 months before screening, and was maintained at the same dosing level throughout the trial • The use of barbiturates or opioids for the acute treatment of CM was allowed if the dosing had been stable for 3 months before screening, and dosing did not exceed 4 days/month. • Patients with CM who were diagnosed with medication overuse headache	• History or diagnosis of complicated migraine (ICHD-3b), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine • Unable to differentiate migraine from other headaches • Subject has received botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck within 4 months prior to screening. • Have any clinically significant concurrent medical condition	
Author, year: Detke, 2018[95] **Country:** Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, UK and USA	**Purpose:** To evaluate the efficacy and safety of galcanezumab, a humanised monoclonal antibody that selectively binds to calcitonin gene-related peptide, in the preventive treatment of chronic migraine **Study design:** Phase 3, randomised, double-blind, placebo-controlled study **Date:** January 2016–March 2017	• Adult 18–65 years with CM as defined by ICHD-3 beta with at least 15 headache days • Migraine onset before 50 years of age • Patients could take acute headache medication as needed throughout the trial but could take opioid- or barbiturate containing medications no more than 3 days per month, could not take oral corticosteroids, and could receive no more than 1 steroid injection during the study and only if in an emergency setting	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product • Current use or prior exposure to galcanezumab or another CGRP antibody • Known hypersensitivity to multiple drugs, MAbs or other therapeutic proteins, or to galcanezumab	Both doses of galcanezumab were superior to placebo in reducing the number of monthly MHDs. Galcanezumab appears efficacious, safe and well tolerated for the preventive treatment of chronic migraine
		• Patients had to wash out all migraine preventive medications except topiramate or propranolol • Patients also needed at least 1 headache-free day per month within 3 months before screening period	• History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by ICHD-3b	

TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
Author, year: Aurora, 2010[92] **Country:** 56 North American sites	**Purpose:** To assess efficacy, safety and tolerability of BTA as headache prophylaxis in adults with chronic migraine **Study design:** Phase 3 study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open label phase **Date:** 23 January 2006–16 July 2008	• Adult (18–65 years) with a history of migraine according to ICHD-II • Randomised patients provided diary data on > 20 of 28 days during baseline	• Previous use of botulinum toxin of any serotype or immunisation to any botulinum toxin serotype • Any medical condition that puts the patient at increased risk with exposure to BTA • Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache	There was no between-group difference for the primary endpoint, headache episodes. However, significant reductions from baseline were observed for BTA for headache and migraine days, cumulative hours of headache-on-headache days and frequency of moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling chronic migraine
		• Having > 15 headache days with each day consisting of > 4 hours of continuous headache and with > 50% of days being migraine or probable migraine days and > 4 distinct headache episodes, each lasting > 4 hours	• Use of prophylactic headache medication within 28 days prior to week 4 • Unremitting headache lasting continuously throughout the 4-week baseline period • Known or suspected TMD • Diagnosis of fibromyalgia • Beck depression inventory score > 24 at week 4 • Psychiatric problems that may have interfered with study participation	

continued

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TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
Author, year: Diener, 2010 [93] **Country:** At 66 global sites in North America and 16 in Europe	**Purpose:** To evaluate the efficacy and safety of BTA for prophylaxis of headaches in adults with chronic migraine **Study design:** Phase 3 study, with a 24-week, double-blind, placebo-controlled phase, followed by a 32-week, open label phase **Date:** 7 February 2006–11 August 2008	• Men or women aged 18–65 years with a history of migraine meeting the diagnostic criteria listed in ICHD-II section 1, migraine – with the exception of 'complicated migraine' (i.e. hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, migrainous infarction) – and with headache occurring on > 15 days/4 weeks were eligible	• With any medical condition that might put them at increased risk if exposed to onabotulinumtoxinA (e.g. myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, any other significant disease that could interfere with neuromuscular function) • Diagnosis of other primary or secondary headache disorder, use of any headache prophylactic medication within 28 days of day 1 of baseline • Beck Depression Inventory score of > 24 at day 1 of baseline, temporomandibular disorder, fibromyalgia, psychiatric disorders that could interfere with study participation, or previous exposure at any time to any botulinum toxin serotype • Prior to administration of study treatment, women of childbearing potential were required to have a negative urine pregnancy test and have been using a reliable means of contraception	The results of PREEMPT 2 demonstrate that BTA is effective for prophylaxis of headache in adults with chronic migraine. Repeated BTA treatments were safe and well tolerated
Author, year: Ferrari, 2019 [90] **Country:** Belgium, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, UK and USA	**Purpose:** To investigate the efficacy and tolerability of monthly and fremanezumab quarterly compared with placebo in patients with difficult-to-treat episodic or chronic migraine, who had documented failure to two to four pharmacological classes of migraine preventive medications **Study design:** Phase 3 FOCUS trial, randomised, double-blind, placebo-controlled, parallel-group	• Adult (18–70 years), had a diagnosis of migraine with onset at or before age 50 years • Chronic migraine history at least 12 months before screening	• At the time of screening visit, participant is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications • Participant has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit	Fremanezumab was effective and well tolerated in patients with difficult-to-treat migraine who had previously not responded to up to four classes of migraine preventive medications

TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
		• > 15 headache days per month, with at least 8 migraine days • Participants with and without overuse of acute headache medication • With failure to two to four classes of migraine preventive medications in the past 10 years	• The participant has used an intervention/device (e.g. scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening • The participant uses triptans/ergots as preventive therapies for migraine. • Participant uses NSAIDs as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (e.g. 81 mg) used for cardiovascular disease prevention is allowed	
Author, year: Sakai, 2021[91] **Country:** Japan and Korea	**Purpose**: To determine the efficacy and safety of fremanezumab administration in Japanese and Korean patients with chronic migraine **Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group **Date:** November 2017 and November 2019	• Patient with migraine onset at ≤ 50 years of age • Headache occurring on ≥ 15 days and fulfilling any of the following on ≥ 8 days: (ICHD-3b diagnostic criteria C and D for 1.1 Migraine without aura, criteria B and C for 1.2 Migraine with aura, Probable migraine).	• The lack of efficacy of at least two of four clusters of preventive medications despite an adequate treatment • Unremitting headaches with duration more than 80% of waking hours and with < 4 days without headache per month • Clinically significant major organ disease	Fremanezumab effectively prevents CM in Japanese and Korean patients and was well tolerated. No safety signal was detected
		• Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions if the dose and regimen have been stable for at least 2 months prior to giving informed consent	• Patient has received onabotulinumtoxin A for migraine or for any medical or cosmetic reason requiring injection in the head, face, or neck during the 4 months prior to giving informed consent • Patient is using medications containing opioids or barbiturates on more than 4 days per month for the treatment of migraine or for any other reason • Patient has used an intervention or device for migraine during the 2 months prior to giving informed consent	

continued

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TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
Author, year: Silberstein, 2017[37] **Country:** 132 sites in 9 countries	**Purpose:** To compare two fremanezumab dose regimens with placebo for the prevention of chronic migraine **Study design:** Randomised, double-blind, placebo-controlled, parallel-group trial **Date:** March 2016–January 2017	• Adult (18–70 years), a history of migraine according to ICHD-3b for at least 12 months. • ≥ 15 headache days with ≥ 8 migraine days	• The use of BTA during the 4 months before screening • The use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during the 2 months before screening	Fremanezumab as a preventive treatment for chronic migraine resulted in a lower frequency of headache than placebo in this 12-week trial. Injection-site reactions to the drug were common
		• The protocol allowed inclusion of up to 30% of patients using a stable dose of one migraine preventive medication (hereafter referred to as preventive medication) for at least 2 months before the beginning of the pre-intervention period to continue these medications	• The use of opioid or barbiturate medications on more than 4 days during the pre-intervention period and a lack of efficacy, after an adequate therapeutic trial, of at least two of four clusters of preventive medications	
Author, year: Lipton, 2020[94] **Country:** 13 countries (USA, Spain, Ukraine, Russian Federation, UK, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark and Belgium)	**Purpose:** To evaluate the efficacy and safety of eptinezumab, a humanised CGRP MAb in the preventive treatment of chronic migraine **Study design:** Phase 3, double-blind, randomised, placebo-controlled, parallel-group **Date:** 30 November 2016–20 April 2018	• Adults (18–65 years) of age (inclusive) with a diagnosis of migraine at or before 50 years of age if they had a history of CM for ≥ 12 months before screening, completed the headache electronic diary (eDiary) on ≥ 24 of the 28 days and experienced ≥ 15 to ≤ 26 headache days and ≥ 8 migraine days during the 28-day screening period	• Patients using opioids or barbiturates ≥ 5 days per month • With a confounding pain disorder or clinically significant pain syndromes; uncontrolled or untreated psychiatric conditions; acute or active temporomandibular disorders; history or diagnosis of a headache or migraine disorders that did not meet the ICHD-3 criteria	In patients with CM, eptinezumab 100 and 300 mg was associated with a significant reduction in MMDs from the day after IV administration through to week 12, was well tolerated, and demonstrated an acceptable safety profile

TABLE 23 More details on baseline characteristics of the included studies for clinical effectiveness review (*continued*)

First author, year/country	Purpose/study design and date	Key inclusion criteria	Key exclusion criteria	Conclusion
		• Migraine preventive medication use had to be stable for ≥ 3 months before screening. Hormonal therapy was also permitted if it was stable and ongoing ≥ 3 months before screening • Patients using barbiturates or prescription opioids ≤ 4 days/month were eligible for participation if use was stable for ≥ 2 months before screening • Patients with CM and medication overuse headache with the exception of the overuse of barbiturates or opioids	• Present or previous malignancies, any active, progressive, or unstable cardiovascular, neurological, or autoimmune disorder; newly diagnosed or uncontrolled hypertension • Women who were pregnant, breastfeeding, or planning to become pregnant during the study • Positive for HIV, hepatitis B surface antigen, or hepatitis C • A concurrent medical condition or laboratory abnormality during the screening period or before dosing on day 0 • BMI ≥ 39 kg/m^2 • Or recent or planned surgery requiring general anaesthesia within 8 weeks before screening or during the duration of the study • Botulinum toxin (any type) for migraine or for any other medical cosmetic reasons requiring injections within 4 months before screening or during the screening period • Any monoclonal antibody treatment within 6 months of screening; or eptinezumab or any monoclonal antibody targeting the CGRP pathway	

NSAID, non-steroidal anti-inflammatory drug; TENS, transcutaneous electrical stimulation; TMD, temporomandibular disorders.

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Appendix 3 Further results from the network meta-analysis

Mean change in monthly headache day from baseline

TABLE 24 The model fit result for mean change in MHD from baseline

	Residual deviance (20 data points)	pD[a]	DIC[b]
Fixed model	18.7	17	35.6
Random model	18.7	18.2	36.9

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

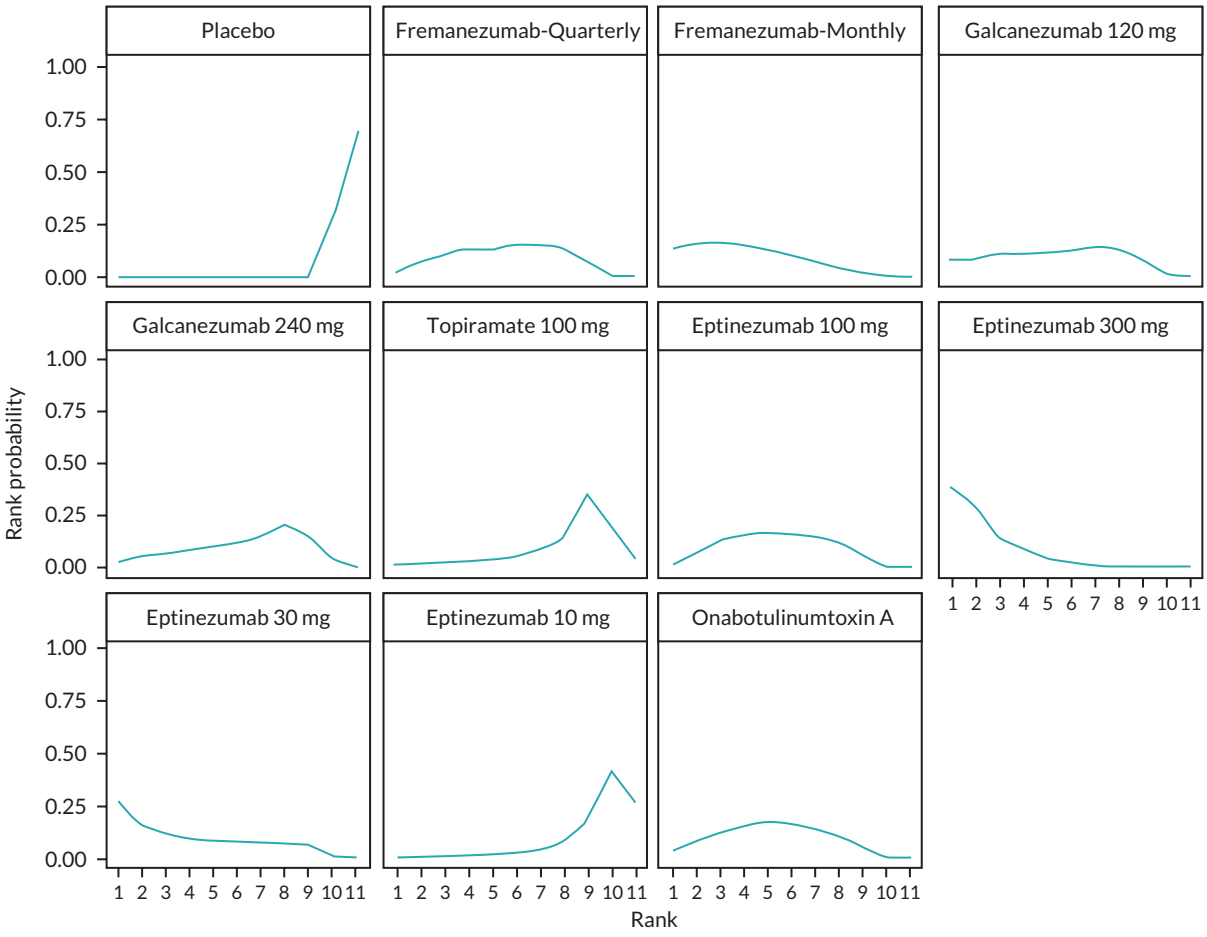

FIGURE 28 Treatment probabilities ranking curves for each treatment (mean change in MHD from baseline). Probabilities ranking graph shows the probability of each intervention to being 1st best, 2nd best, etc.

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TABLE 25 Treatment probabilities ranking for each treatment (mean change in MHD from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9	P. rank 10	P. rank 11
Eptinezumab 300 mg	0.38	0.29	0.16	0.08	0.04	0.03	0.01	0	0	0	0
Fremanezumab monthly	0.14	0.16	0.17	0.15	0.13	0.11	0.08	0.04	0.02	0	0
Eptinezumab 30 mg	0.27	0.16	0.11	0.09	0.08	0.08	0.07	0.07	0.06	0.01	0
OnabotulinumtoxinA	0.04	0.08	0.12	0.15	0.17	0.16	0.13	0.1	0.04	0.01	0
Galcanezumab 120 mg	0.08	0.09	0.11	0.11	0.12	0.12	0.14	0.13	0.08	0.02	0
Eptinezumab 100 mg	0.02	0.07	0.13	0.14	0.17	0.16	0.15	0.11	0.05	0	0
Fremanezumab-quarterly	0.03	0.07	0.1	0.14	0.13	0.16	0.15	0.14	0.07	0.01	0
Galcanezumab 240 mg	0.03	0.06	0.07	0.09	0.1	0.11	0.15	0.2	0.15	0.04	0
Topiramate 100 mg	0.01	0.02	0.02	0.04	0.04	0.06	0.08	0.14	0.35	0.2	0.04
Eptinezumab 10 mg	0	0	0.01	0.01	0.01	0.02	0.03	0.07	0.17	0.41	0.26
Placebo	0	0	0	0	0	0	0	0	0.01	0.29	0.7

Note
The table shows the probability of each intervention to being 1st best, 2nd best, etc.

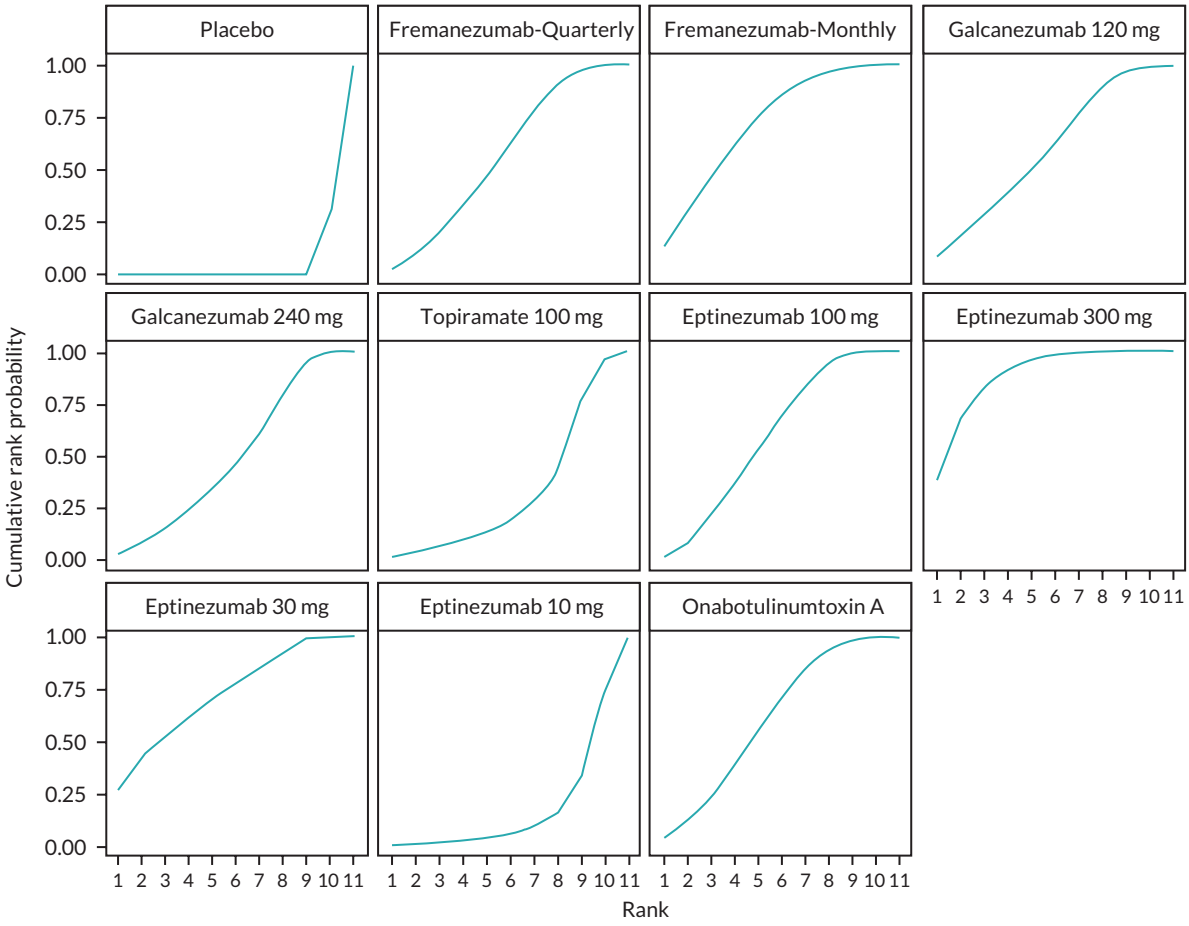

FIGURE 29 Treatment cumulative ranking curves for each treatment (mean change im MHD from baseline). Cumulative rank probabilities graph shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 26 Treatment cumulative ranking for each treatment (mean change in MHD from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9	P. rank 10	P. rank 11
Eptinezumab 300 mg	0.39	0.68	0.83	0.91	0.96	0.98	1	1	1	1	1
Fremanezumab monthly	0.14	0.3	0.47	0.63	0.76	0.86	0.94	0.98	1	1	1
Eptinezumab 30 mg	0.27	0.43	0.54	0.62	0.71	0.78	0.86	0.93	0.99	1	1
OnabotulinumtoxinA	0.04	0.12	0.24	0.39	0.56	0.72	0.85	0.95	0.99	1	1
Galcanezumab 120 mg	0.08	0.17	0.28	0.39	0.51	0.63	0.77	0.9	0.98	1	1
Eptinezumab 100 mg	0.02	0.08	0.22	0.37	0.53	0.69	0.84	0.95	1	1	1
Fremanezumab-quarterly	0.03	0.1	0.2	0.34	0.47	0.63	0.78	0.92	0.99	1	1
Galcanezumab 240 mg	0.03	0.09	0.15	0.24	0.34	0.46	0.61	0.81	0.95	1	1
Topiramate 100 mg	0.01	0.03	0.06	0.09	0.14	0.19	0.28	0.42	0.77	0.96	1
Eptinezumab 10 mg	0	0	0.01	0.02	0.03	0.05	0.09	0.15	0.33	0.74	1
Placebo	0	0	0	0	0	0	0	0	0.01	0.3	1

Note
Cumulative rank probabilities table shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 27 Comparing fit of NMA and UME models for MHD

	Residual deviance (20 data points)	pD[a]	DIC[b]
NMA (Consistency) model	18.7	17	35.6
UMEs (Inconsistency) model	18.9	17.2	36.1

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

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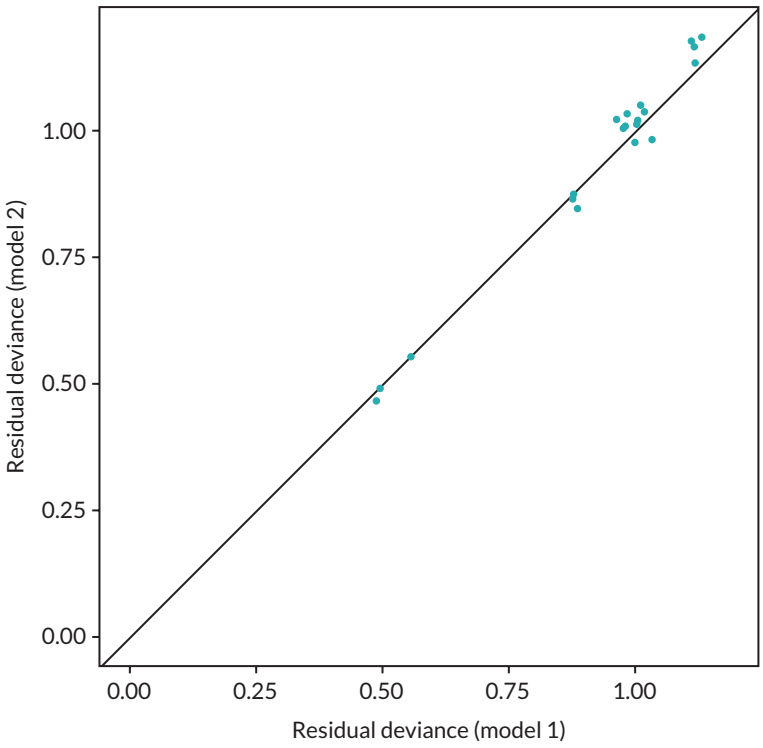

FIGURE 30 Global consistency test for mean change in MHD from baseline [UMEs (Inconsistency) Model and Fixed NMA model]. Dev-Dev plot to identify inconsistent data points, the data points are scattered in a further distance from the bivector from the origin, and these show global inconsistency.

Mean change in monthly migraine day from baseline

TABLE 28 The model fit result for mean change in MMD from baseline

	Residual deviance (29 data points)	pD[a]	DIC[b]
Fixed model	34	21.8	55.8
Random model	28.7	25.8	54.5

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

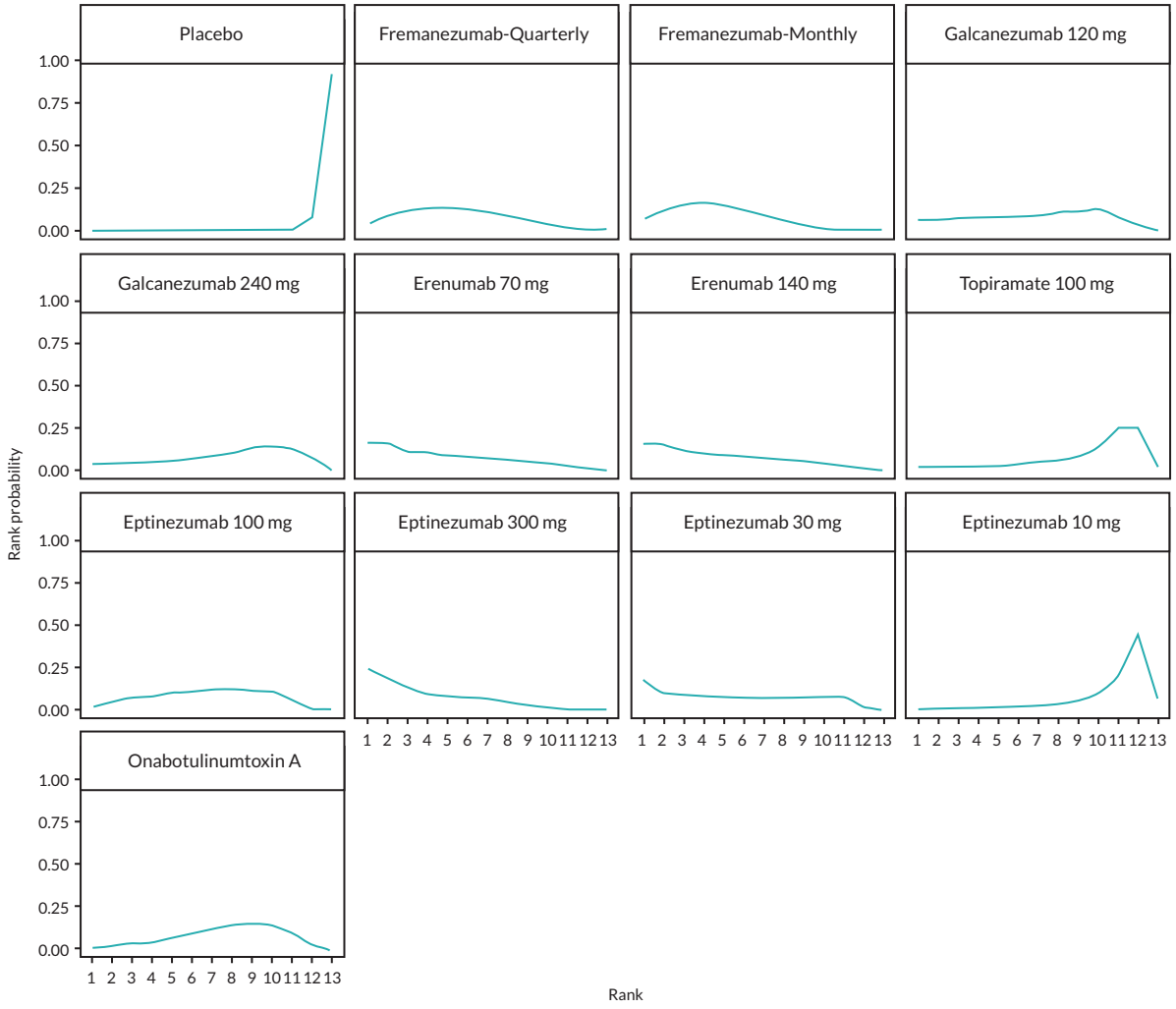

FIGURE 31 Treatment probabilities ranking curves for each treatment (mean change in MMD from baseline). Probabilities ranking graph shows the probability of each intervention to being 1st best, 2nd best, etc.

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TABLE 29 Treatment probabilities ranking for each treatment (mean change in MMD from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9	P. rank 10	P. rank 11	P. rank 12	P. rank 13
Eptinezumab 300 mg	0.24	0.19	0.13	0.1	0.09	0.08	0.07	0.04	0.03	0.02	0.01	0	0
Fremanezumab monthly	0.07	0.12	0.17	0.17	0.16	0.13	0.09	0.05	0.03	0.01	0	0	0
Erenumab 70 mg	0.17	0.16	0.11	0.11	0.08	0.09	0.07	0.07	0.06	0.04	0.03	0.01	0
Erenumab 140 mg	0.15	0.15	0.12	0.1	0.1	0.09	0.07	0.07	0.06	0.05	0.03	0.01	0
Fremanezumab-quarterly	0.04	0.08	0.12	0.14	0.14	0.13	0.12	0.1	0.07	0.04	0.02	0	0
Eptinezumab 30 mg	0.18	0.1	0.09	0.08	0.07	0.07	0.07	0.08	0.08	0.08	0.08	0.02	0
Eptinezumab 100 mg	0.03	0.05	0.07	0.08	0.1	0.11	0.12	0.13	0.12	0.11	0.06	0.02	0
Galcanezumab 120 mg	0.06	0.06	0.08	0.08	0.08	0.08	0.09	0.11	0.11	0.13	0.08	0.04	0
OnabotulinumtoxinA	0.01	0.02	0.04	0.05	0.07	0.09	0.13	0.15	0.16	0.15	0.1	0.03	0
Galcanezumab 240 mg	0.03	0.04	0.04	0.05	0.06	0.07	0.09	0.1	0.14	0.15	0.14	0.09	0
Topiramate 100 mg	0.02	0.02	0.02	0.03	0.03	0.04	0.05	0.06	0.09	0.13	0.24	0.25	0.02
Eptinezumab 10 mg	0	0.01	0.01	0.01	0.02	0.02	0.03	0.04	0.05	0.09	0.21	0.45	0.06
Placebo	0	0	0	0	0	0	0	0	0	0	0	0.08	0.92

Note
The table shows the probability of each intervention to being 1st best, 2nd best, etc.

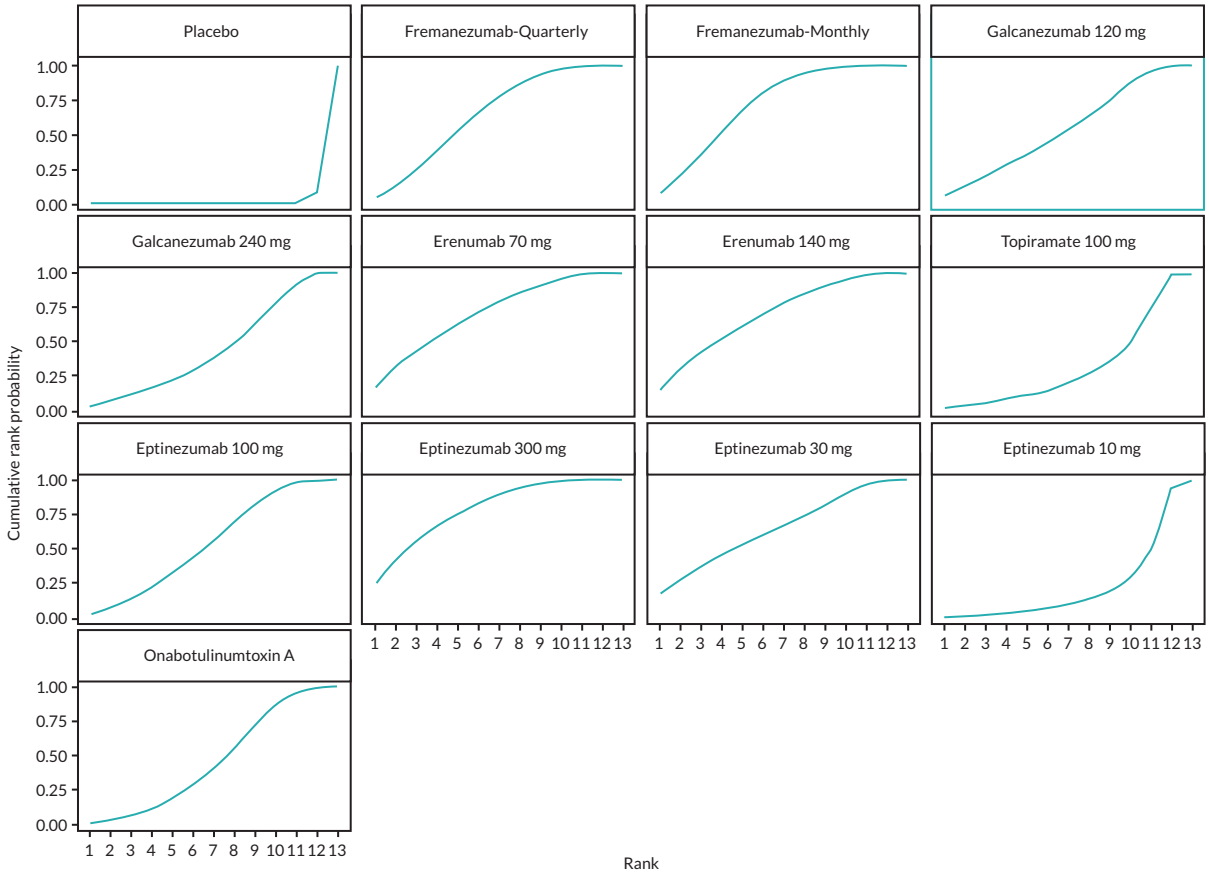

FIGURE 32 Treatment cumulative ranking curves for each treatment (mean change in MMD from baseline). Cumulative rank probabilities graph shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 30 Treatment cumulative ranking for each treatment (mean change in MMD from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9	P. rank 10	P. rank 11	P. rank 12	P. rank 13
Eptinezumab 300 mg	0.24	0.43	0.56	0.66	0.75	0.83	0.89	0.94	0.97	0.99	1	1	1
Fremanezumab monthly	0.07	0.19	0.35	0.52	0.68	0.8	0.89	0.95	0.98	1	1	1	1
Erenumab 70 mg	0.17	0.33	0.44	0.55	0.63	0.72	0.79	0.86	0.91	0.96	0.99	1	1
Erenumab 140 mg	0.15	0.3	0.43	0.53	0.62	0.71	0.78	0.85	0.91	0.96	0.99	1	1
Fremanezumab-quarterly	0.04	0.12	0.24	0.39	0.52	0.65	0.77	0.87	0.94	0.98	1	1	1
Eptinezumab 30 mg	0.18	0.28	0.37	0.45	0.52	0.59	0.66	0.74	0.81	0.89	0.98	1	1
Eptinezumab 100 mg	0.02	0.07	0.14	0.23	0.33	0.44	0.57	0.7	0.82	0.93	0.99	1	1
Galcanezumab 120 mg	0.06	0.12	0.2	0.28	0.36	0.44	0.54	0.64	0.75	0.88	0.96	1	1
OnabotulinumtoxinA	0.01	0.03	0.07	0.12	0.19	0.29	0.42	0.56	0.72	0.87	0.97	1	1
Galcanezumab 240 mg	0.03	0.07	0.11	0.16	0.23	0.3	0.39	0.49	0.63	0.78	0.92	1	1
Topiramate 100 mg	0.02	0.04	0.06	0.09	0.12	0.15	0.21	0.27	0.36	0.49	0.73	0.99	1
Eptinezumab 10 mg	0	0.01	0.02	0.03	0.05	0.07	0.1	0.14	0.19	0.29	0.49	0.94	1
Placebo	0	0	0	0	0	0	0	0	0	0	0	0.08	1

Note
Cumulative rank probabilities table shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 31 Comparing fit of NMA and UME models for MMD

	Residual deviance (20 data points)	pD[a]	DIC[b]
NMA (Consistency) Model	41.1	22	63.1
UMEs (Inconsistency) Model	41.1	22	63

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

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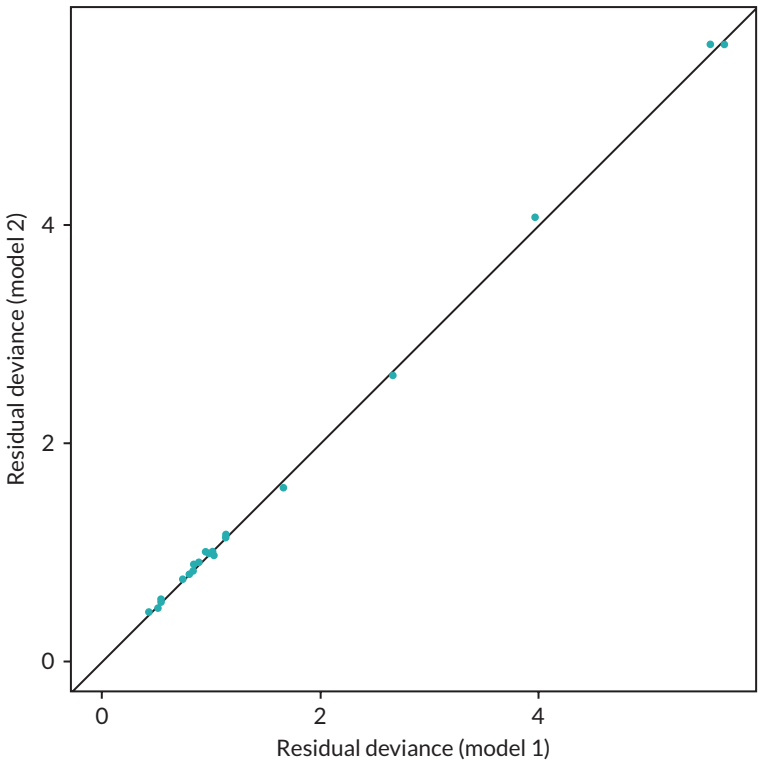

FIGURE 33 Global consistency test for mean change in MMD from baseline [UMEs (Inconsistency) Model and Fixed NMA model]. Dev-Dev plot to identify inconsistent data points, the data points are scattered in a further distance from the bivector from the origin, and these show global inconsistency.

Mean change in migraine-specific quality of life – restrictive role from baseline

TABLE 32 The model fit result for mean change in MSQ-RR from baseline

	Residual deviance (13 data points)	pD[a]	DIC[b]
Fixed model	12.9	12.9	25.8
Random model	13.1	13.1	26.3

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

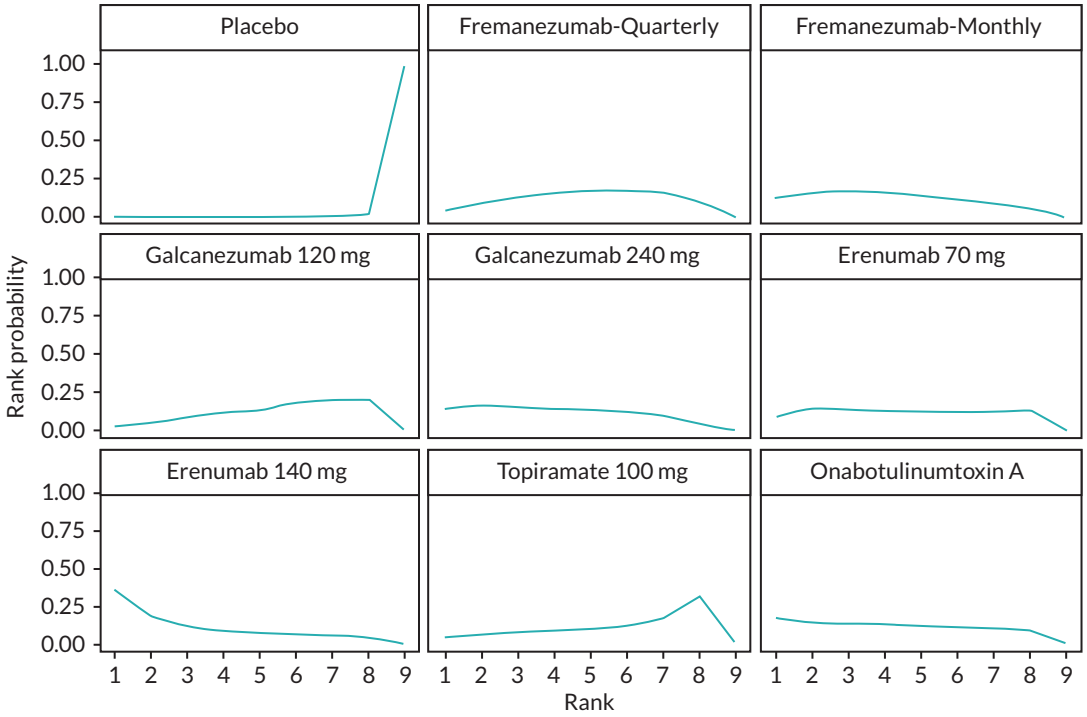

FIGURE 34 Treatment probabilities ranking curves for each treatment (mean change in MSQ-RR from baseline). Probabilities ranking graph shows the probability of each intervention to being 1st best, 2nd best, etc.

TABLE 33 Treatment probabilities ranking curves for each treatment (mean change in MSQ-RR from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9
Erenumab 140 mg	0.36	0.18	0.12	0.09	0.08	0.07	0.06	0.04	0
Galcanezumab 240 mg	0.15	0.16	0.15	0.14	0.14	0.12	0.1	0.04	0
Fremanezumab monthly	0.12	0.16	0.17	0.15	0.14	0.11	0.09	0.06	0
OnabotulinumtoxinA	0.17	0.15	0.13	0.12	0.12	0.11	0.1	0.1	0
Erenumab 70 mg	0.09	0.14	0.14	0.13	0.13	0.12	0.12	0.13	0
Fremanezumab-quarterly	0.04	0.09	0.13	0.16	0.16	0.16	0.16	0.1	0
Galcanezumab 120 mg	0.03	0.05	0.08	0.12	0.13	0.18	0.2	0.21	0
Topiramate 100 mg	0.04	0.07	0.08	0.09	0.1	0.13	0.17	0.31	0.01
Placebo	0	0	0	0	0	0	0	0.01	0.99

Note
The table shows the probability of each intervention to being 1st best, 2nd best, etc.

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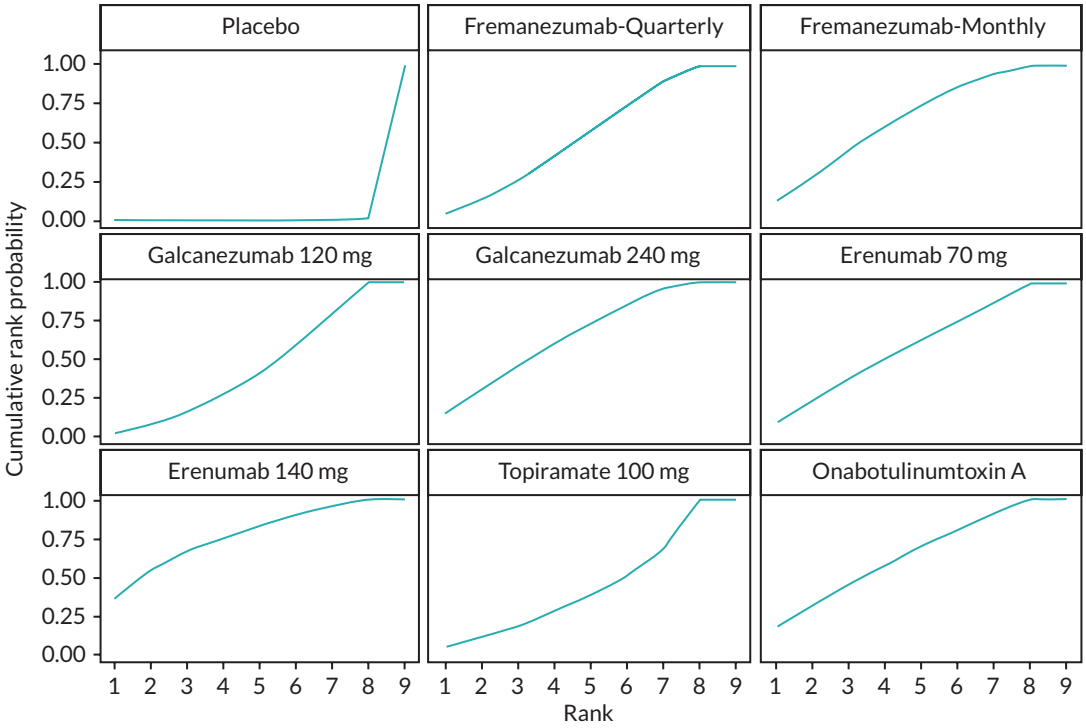

FIGURE 35 Treatment cumulative ranking curves for each treatment (mean change in MSQ-RR from baseline). Cumulative rank probabilities graph shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 34 Treatment cumulative ranking for each treatment (mean change in MSQ-RR from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9
Erenumab 140 mg	0.36	0.54	0.66	0.75	0.83	0.9	0.96	1	1
Galcanezumab 240 mg	0.15	0.31	0.46	0.6	0.74	0.86	0.96	1	1
Fremanezumab monthly	0.12	0.28	0.45	0.61	0.75	0.86	0.95	1	1
OnabotulinumtoxinA	0.17	0.32	0.45	0.57	0.7	0.8	0.91	1	1
Erenumab 70 mg	0.09	0.24	0.38	0.5	0.63	0.75	0.87	1	1
Fremanezumab-quarterly	0.04	0.13	0.26	0.41	0.57	0.74	0.9	1	1
Galcanezumab 120 mg	0.03	0.08	0.16	0.28	0.41	0.59	0.79	1	1
Topiramate 100 mg	0.04	0.11	0.18	0.28	0.38	0.5	0.68	0.99	1
Placebo	0	0	0	0	0	0	0	0.01	1

Note
Cumulative rank probabilities table shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 35 Comparing fit of NMA and UME models for MSQ-RR

	Residual deviance (13 data points)	pD[a]	DIC[b]
NMA (Consistency) model	12.9	12.9	25.8
UMEs (Inconsistency) model	13	13	26

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

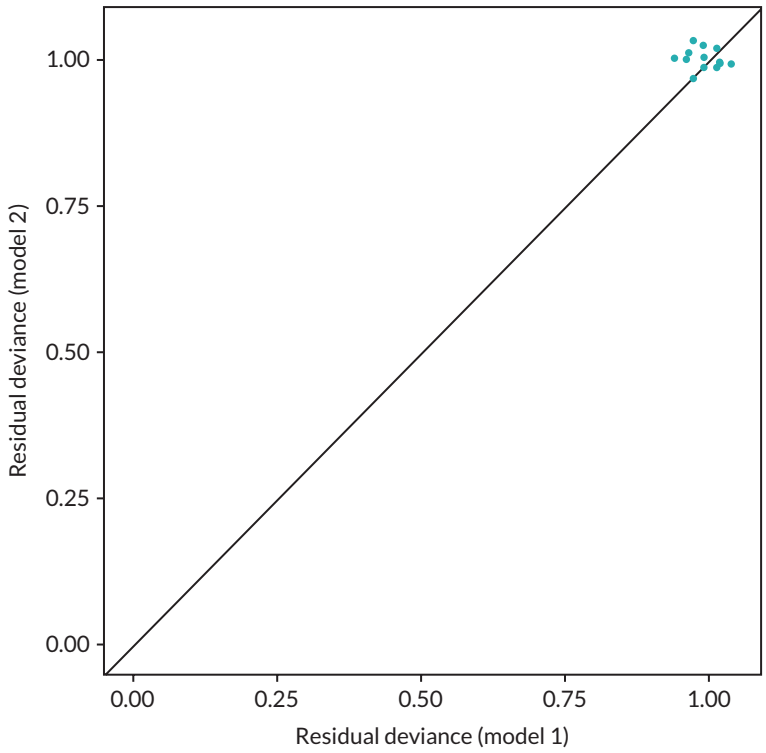

FIGURE 36 Global consistency test for mean change in MSQ-RR from baseline [UMEs (Inconsistency) model and fixed NMA model]. Dev-Dev plot to identify inconsistent data points, the data points are scattered in a further distance from the bivector from the origin, and these show global inconsistency.

Mean change in migraine-specific quality of life – preventative role from baseline

TABLE 36 The model fit result for mean change in MSQ-PR from baseline

	Residual deviance (13 data points)	pD[a]	DIC[b]
Fixed model	13.1	13.1	26.2
Random model	12.8	12.8	25.7

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

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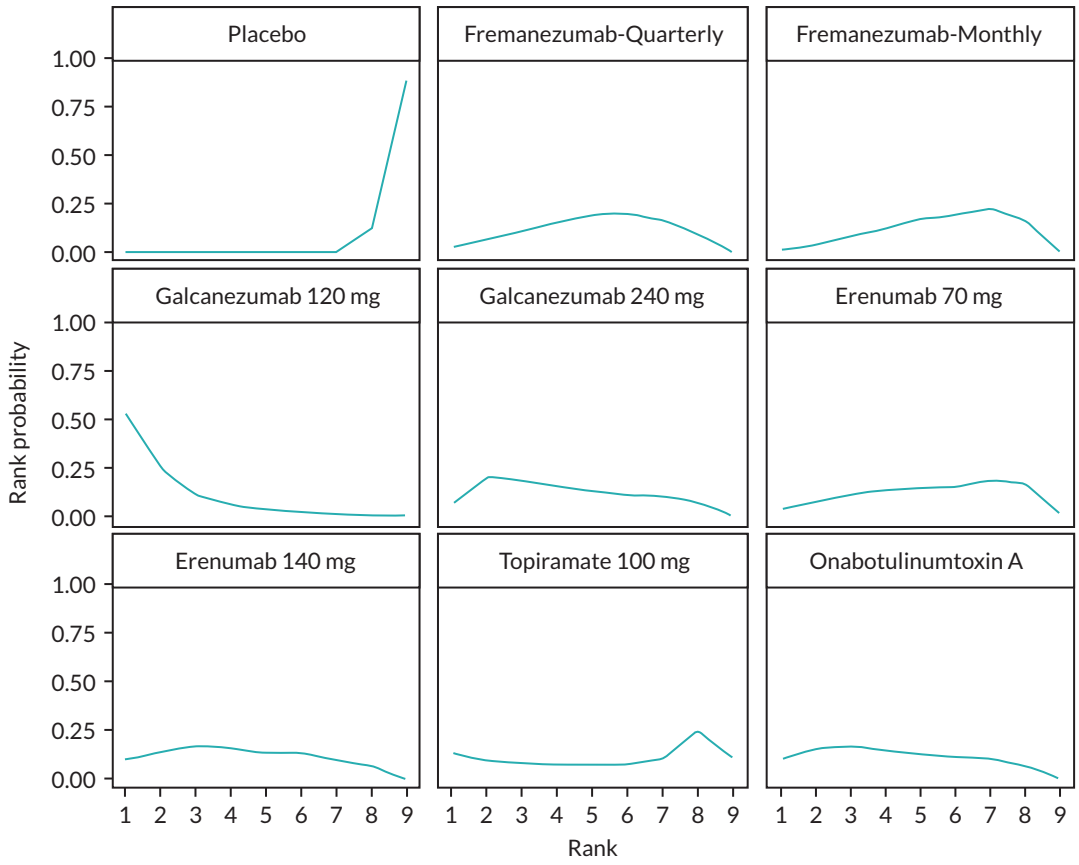

FIGURE 37 Treatment probabilities ranking curves for each treatment (mean change in MSQ-PR from baseline). Probabilities ranking graph shows the probability of each intervention to being 1st best, 2nd best, etc.

TABLE 37 Treatment probabilities ranking curves for each treatment (mean change in MSQ-PR from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9
Galcanezumab 120 mg	0.53	0.24	0.11	0.06	0.03	0.02	0.01	0	0
OnabotulinumtoxinA	0.11	0.15	0.17	0.15	0.13	0.12	0.1	0.07	0
Galcanezumab 240 mg	0.06	0.2	0.18	0.15	0.13	0.11	0.1	0.07	0
Erenumab 140 mg	0.1	0.14	0.17	0.16	0.13	0.13	0.1	0.07	0
Fremanezumab-quarterly	0.03	0.07	0.11	0.15	0.19	0.2	0.16	0.09	0
Erenumab 70 mg	0.03	0.07	0.11	0.14	0.14	0.15	0.19	0.16	0.01
Topiramate 100 mg	0.13	0.09	0.08	0.07	0.08	0.08	0.11	0.25	0.11
Fremanezumab monthly	0.01	0.04	0.07	0.12	0.17	0.19	0.23	0.17	0
Placebo	0	0	0	0	0	0	0	0.12	0.88

Note
The table shows the probability of each intervention to being 1st best, 2nd best, etc.

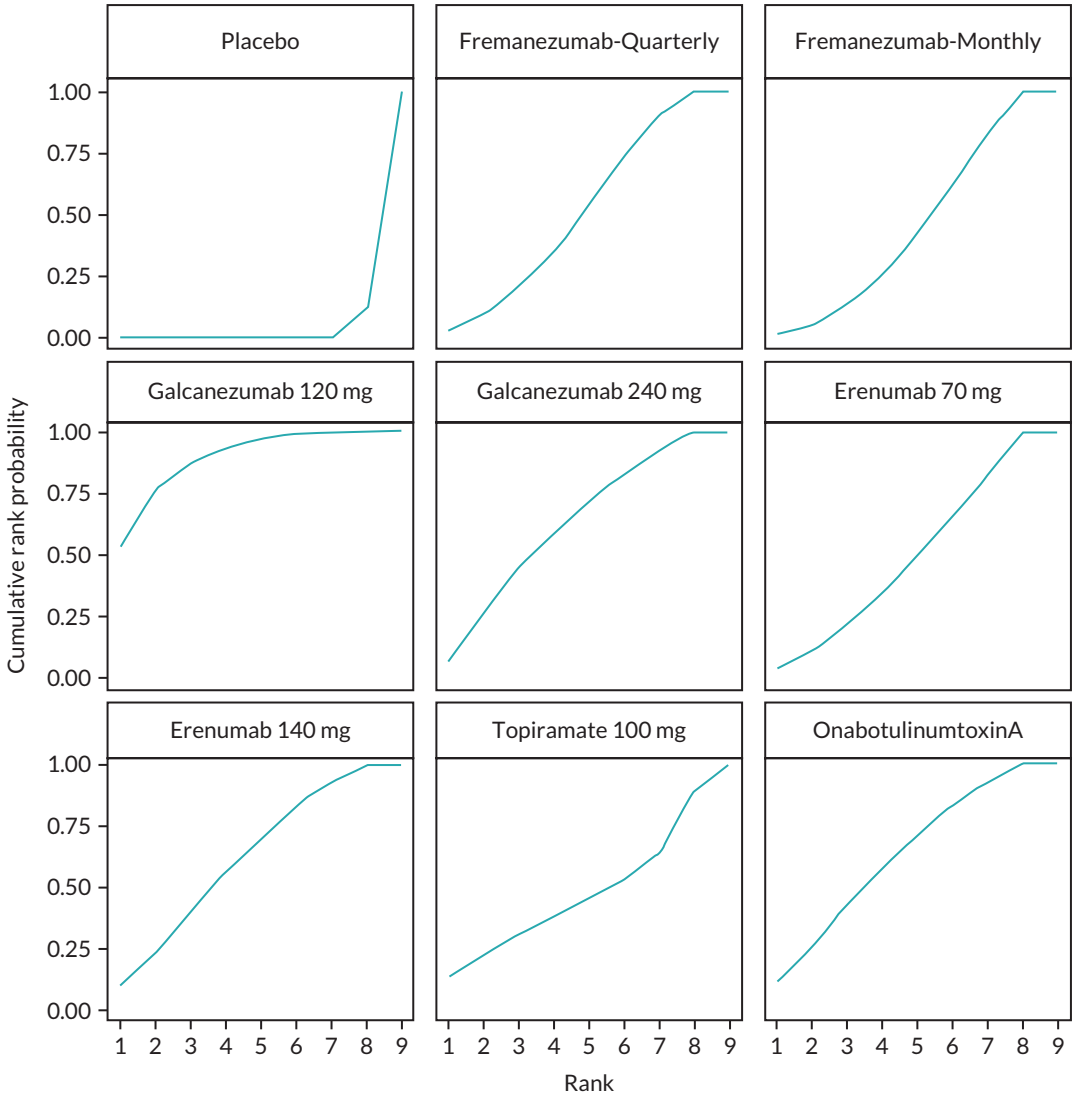

FIGURE 38 Treatment cumulative ranking curves for each treatment (mean change in MSQ-PR from baseline). Cumulative rank probabilities graph shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 38 Treatment cumulative ranking for each treatment (mean change in MSQ-PR from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9
Galcanezumab 120 mg	0.53	0.77	0.87	0.93	0.96	0.98	1	1	1
OnabotulinumtoxinA	0.11	0.26	0.43	0.58	0.71	0.83	0.93	1	1
Galcanezumab 240 mg	0.06	0.26	0.44	0.59	0.72	0.83	0.93	1	1
Erenumab 140 mg	0.1	0.24	0.41	0.57	0.7	0.83	0.93	1	1
Fremanezumab-quarterly	0.03	0.09	0.2	0.36	0.55	0.74	0.91	1	1
Erenumab 70 mg	0.03	0.1	0.21	0.34	0.49	0.64	0.83	0.93	1
Topiramate 100 mg	0.13	0.22	0.31	0.38	0.45	0.53	0.64	0.89	1
Fremanezumab monthly	0.01	0.05	0.13	0.25	0.42	0.61	0.84	1	1
Placebo	0	0	0	0	0	0	0	0.12	1

Note
Cumulative rank probabilities table shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

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TABLE 39 Comparing fit of NMA and UME models for MSQ-PR

	Residual deviance (13 data points)	pD[a]	DIC[b]
NMA (Consistency) model	13.1	13.1	26.2
UMEs (Inconsistency) model	12.9	12.9	25.8

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

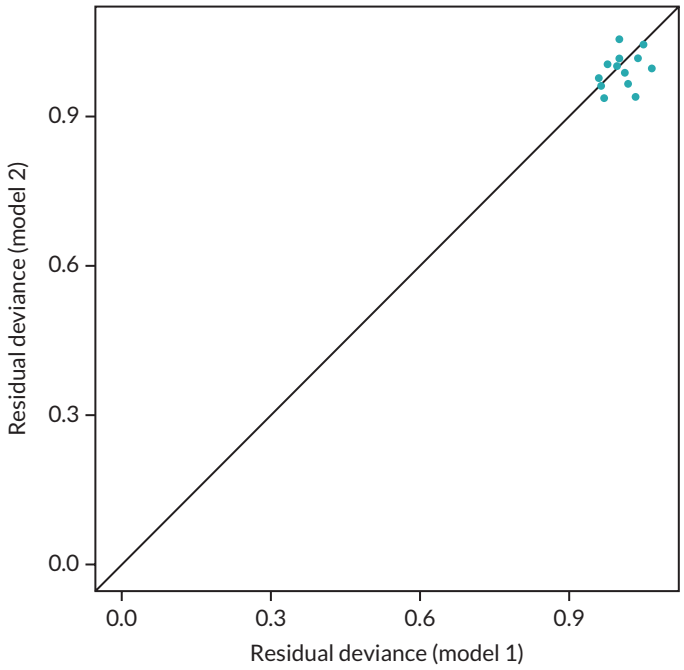

FIGURE 39 Global consistency test for mean change in MSQ-PR from baseline [UMEs (Inconsistency) Model and fixed NMA model]. Dev-Dev plot to identify inconsistent data points, the data points are scattered in a further distance from the bivector from the origin, and these show global inconsistency.

Mean change in migraine-specific quality of life – emotional function from baseline

TABLE 40 The model fit result for mean change in MSQ-EF from baseline

	Residual deviance (13 data points)	pD[a]	DIC[b]
Fixed model	13	13	26
Random model	12.8	12.8	25.6

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

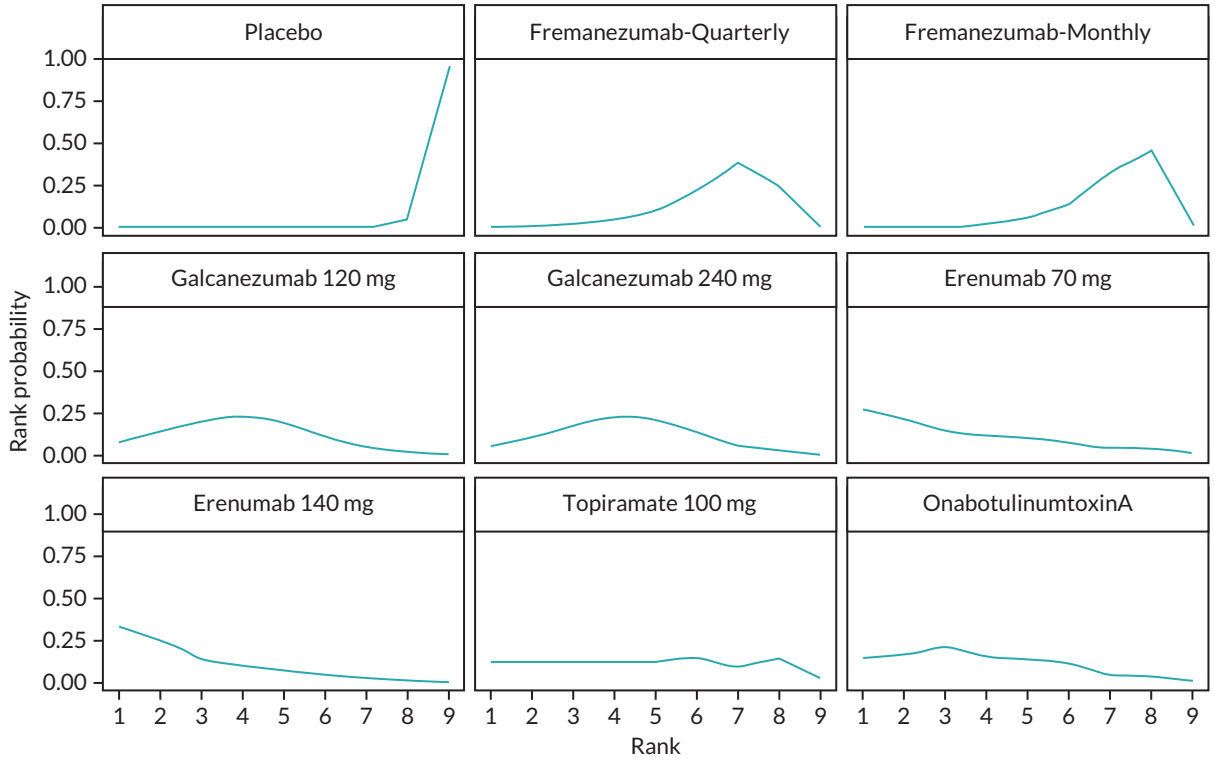

FIGURE 40 Treatment probabilities ranking curves for each treatment (mean change in MSQ-EF from baseline). Probabilities ranking graph shows the probability of each intervention to being 1st best, 2nd best, etc.

TABLE 41 Treatment probabilities ranking curves for each treatment (mean change in MSQ-EF from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9
Erenumab 140 mg	0.34	0.25	0.14	0.1	0.07	0.05	0.03	0.02	0
Erenumab 70 mg	0.27	0.22	0.14	0.11	0.1	0.07	0.04	0.04	0.01
OnabotulinumtoxinA	0.14	0.17	0.21	0.16	0.14	0.11	0.04	0.03	0
Galcanezumab 120 mg	0.07	0.13	0.2	0.23	0.2	0.11	0.04	0.02	0
Galcanezumab 240 mg	0.06	0.1	0.17	0.23	0.21	0.15	0.05	0.03	0
Topiramate 100 mg	0.12	0.12	0.12	0.12	0.13	0.15	0.09	0.13	0.02
Fremanezumab-quarterly	0	0.01	0.02	0.04	0.1	0.22	0.38	0.23	0
Fremanezumab monthly	0	0	0	0.01	0.05	0.14	0.33	0.46	0.01
Placebo	0	0	0	0	0	0	0	0.04	0.96

Note
The table shows the probability of each intervention to being 1st best, 2nd best, etc.

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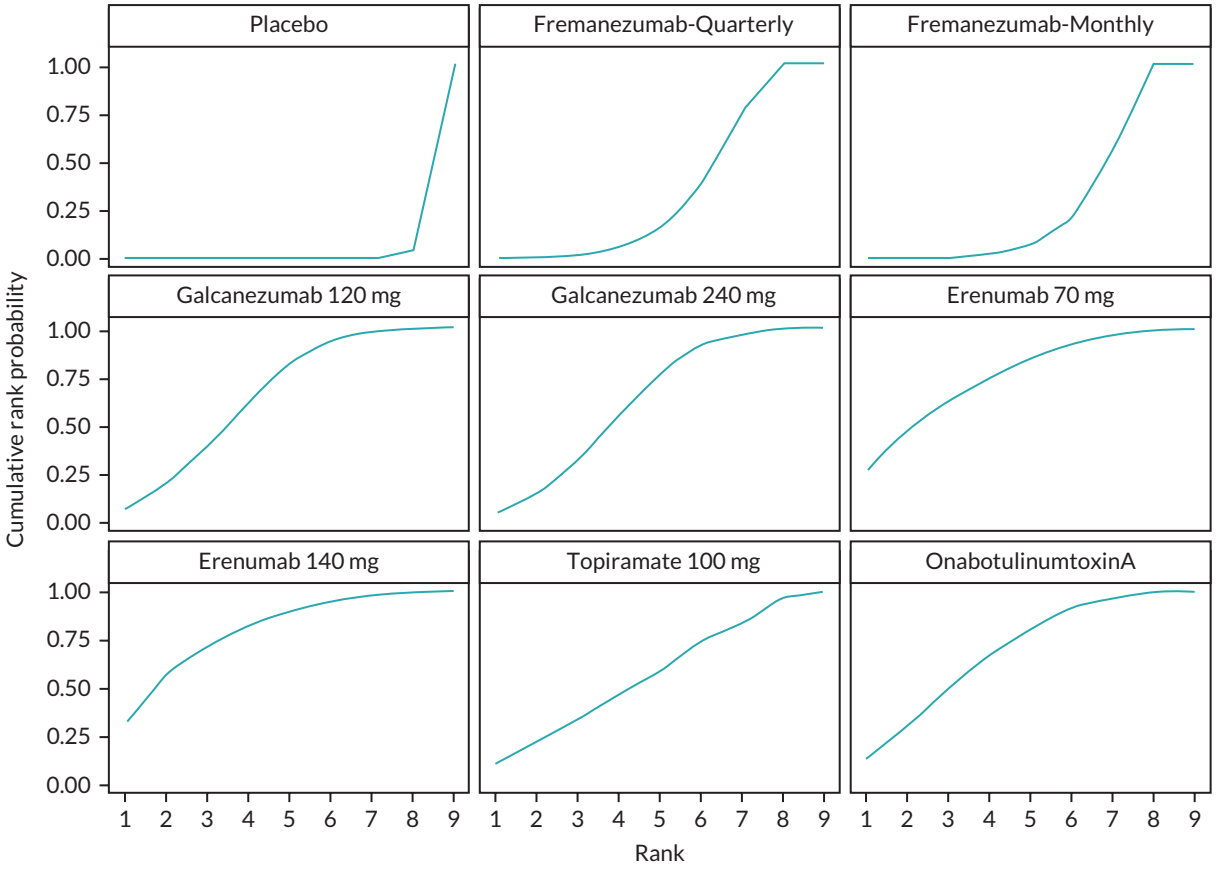

FIGURE 41 Treatment cumulative ranking curves for each treatment (mean change in MSQ-EF from baseline). Cumulative rank probabilities graph shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 42 Treatment cumulative ranking for each treatment (mean change in MSQ-EF from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9
Erenumab 140 mg	0.34	0.59	0.73	0.83	0.91	0.96	0.98	1	1
Erenumab 70 mg	0.27	0.49	0.63	0.74	0.84	0.92	0.95	0.99	1
OnabotulinumtoxinA	0.14	0.31	0.52	0.68	0.81	0.92	0.97	1	1
Galcanezumab 120 mg	0.07	0.21	0.4	0.63	0.83	0.94	0.98	1	1
Galcanezumab 240 mg	0.05	0.16	0.33	0.56	0.77	0.92	0.97	1	1
Topiramate 100 mg	0.12	0.24	0.36	0.48	0.6	0.75	0.84	0.98	1
Fremanezumab-quarterly	0	0.01	0.02	0.06	0.16	0.38	0.76	1	1
Fremanezumab monthly	0	0	0.01	0.02	0.07	0.21	0.54	0.99	1
Placebo	0	0	0	0	0	0	0	0.04	1

Note
Cumulative rank probabilities table shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 43 Comparing fit of NMA and UME models for MSQ-EF

	Residual deviance (13 data points)	pD[a]	DIC[b]
NMA (Consistency) Model	13	13	26
UMEs (Inconsistency) Model	13	13	26

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

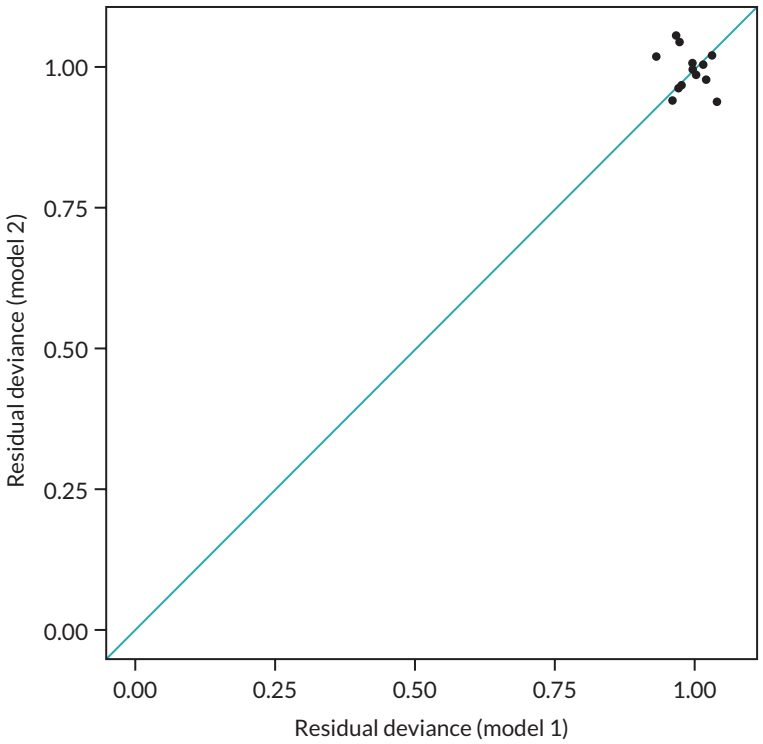

FIGURE 42 Global consistency test for mean change in MSQ-EF from baseline [UMEs (Inconsistency) Model and Fixed NMA model]. Dev-Dev plot to identify inconsistent data points, the data points are scattered in a further distance from the bivector from the origin, and these show global inconsistency.

Mean change in headache impact test-6 from baseline

TABLE 44 The model fit result for mean change in HIT-6 from baseline

	Residual deviance (19 data points)	pD[a]	DIC[b]
Fixed model	18.3	15.1	33.4
Random model	18.1	16.6	34.7

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

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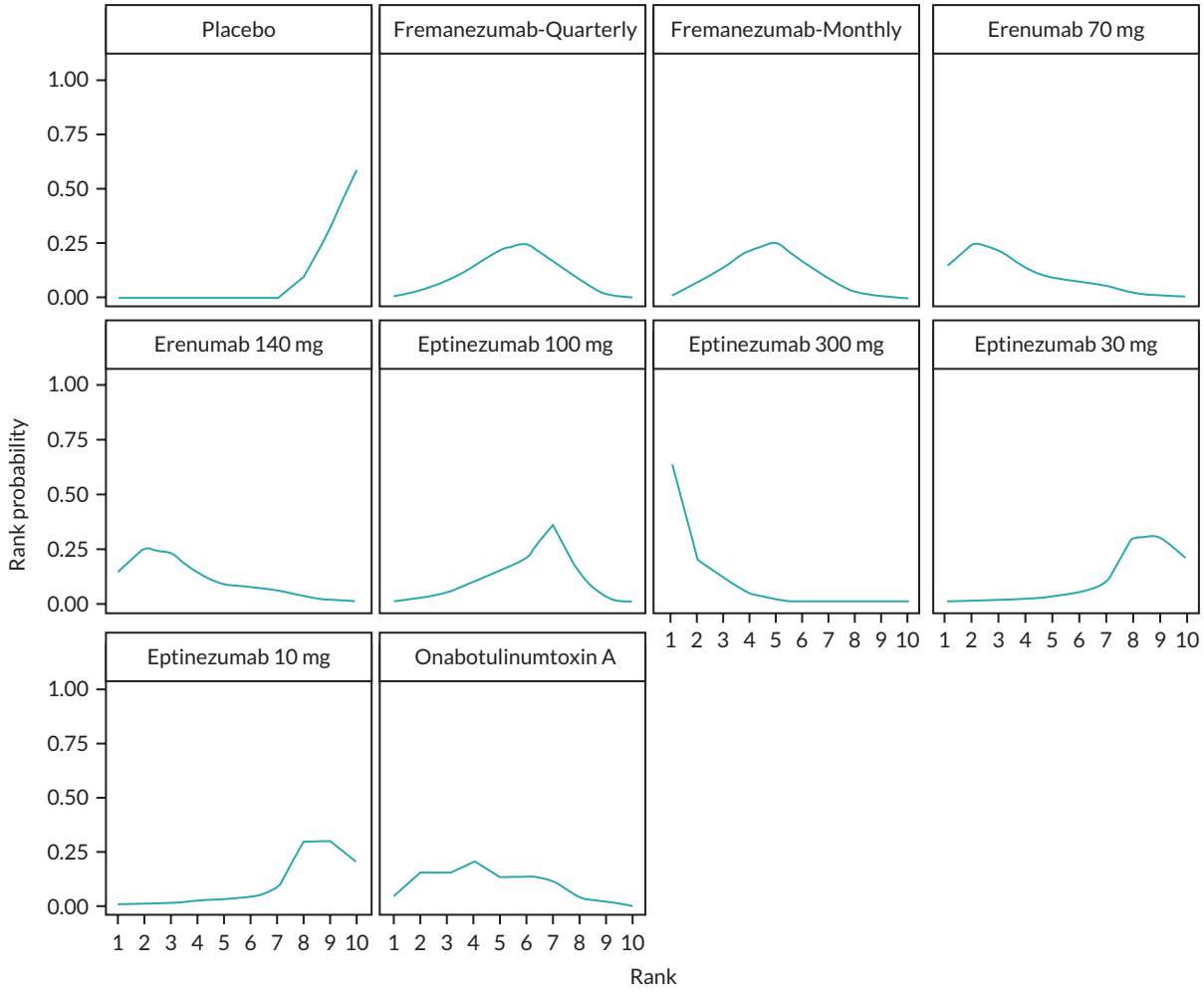

FIGURE 43 Treatment probabilities ranking curves for each treatment (mean change in HIT-6 from baseline). Probabilities ranking graph shows the probability of each interventions to being 1st best, 2nd best, etc.

TABLE 45 Treatment probabilities ranking curves for each treatment (mean change in HIT-6 from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9	P. rank 10
Eptinezumab 300 mg	0.63	0.2	0.11	0.04	0.01	0	0	0	0	0
Erenumab 140 mg	0.15	0.25	0.23	0.13	0.09	0.07	0.05	0.02	0.01	0
Erenumab 70 mg	0.15	0.26	0.22	0.13	0.09	0.07	0.05	0.03	0.01	0
BTA	0.05	0.15	0.15	0.2	0.13	0.14	0.11	0.04	0.02	0
Fremanezumab monthly	0.01	0.07	0.14	0.23	0.26	0.17	0.09	0.02	0.01	0
Fremanezumab-quarterly	0.01	0.04	0.08	0.15	0.22	0.25	0.17	0.07	0.02	0
Eptinezumab 100 mg	0	0.02	0.04	0.1	0.15	0.21	0.36	0.12	0.02	0
Eptinezumab 10 mg	0	0.01	0.01	0.03	0.03	0.04	0.08	0.3	0.29	0.21
Eptinezumab 30 mg	0	0.01	0.01	0.02	0.03	0.04	0.09	0.29	0.31	0.2
Placebo	0	0	0	0	0	0	0	0.1	0.31	0.59

Note
The table shows the probability of each interventions to being 1st best, 2nd best, etc.

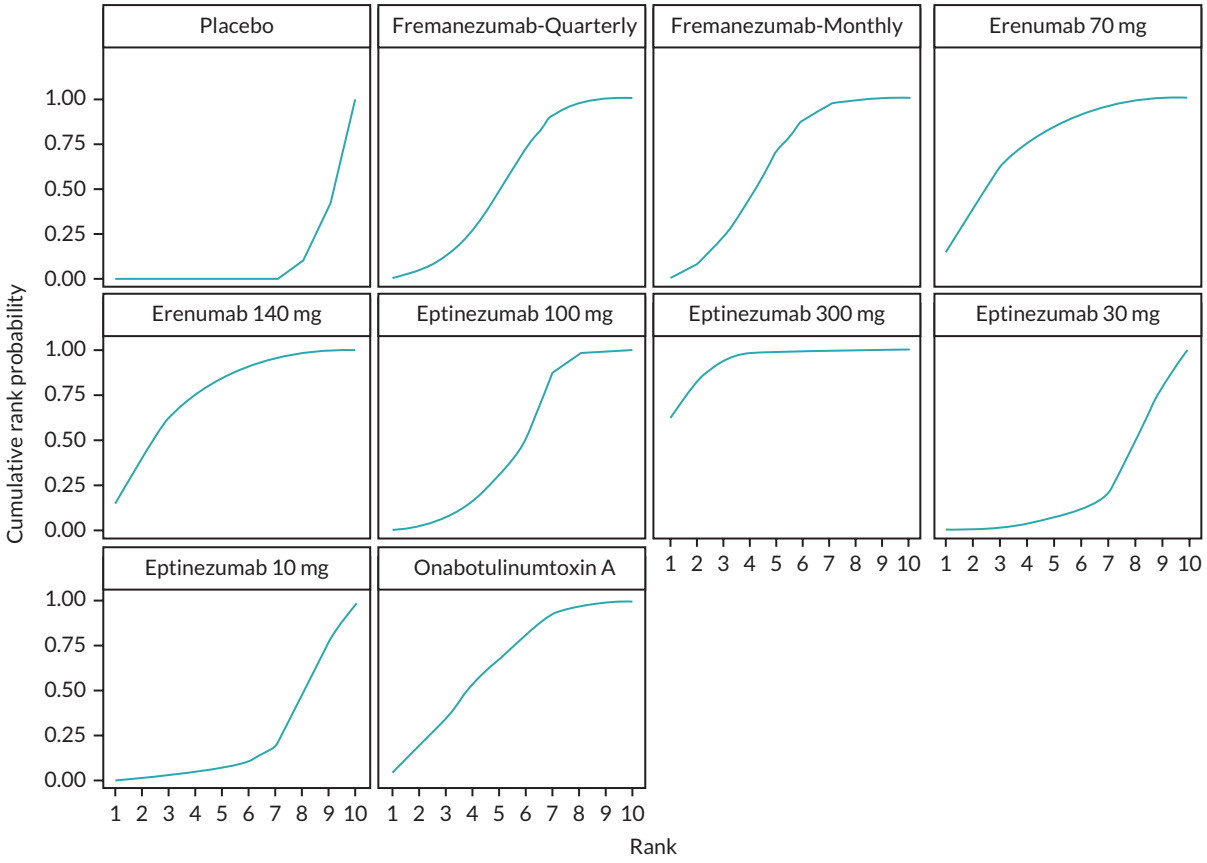

FIGURE 44 Treatment cumulative ranking curves for each treatment (mean change in HIT-6 from baseline). Cumulative rank probabilities graph shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

TABLE 46 Treatment cumulative ranking for each treatment (mean change in HIT-6 from baseline)

Interventions	P. rank 1	P. rank 2	P. rank 3	P. rank 4	P. rank 5	P. rank 6	P. rank 7	P. rank 8	P. rank 9	P. rank 10
Eptinezumab 300 mg	0.63	0.83	0.94	0.98	0.99	1	1	1	1	1
Erenumab 140 mg	0.16	0.44	0.69	0.81	0.89	0.95	0.99	1	1	1
Erenumab 70 mg	0.16	0.46	0.68	0.81	0.88	0.95	0.99	0.99	1	1
BTA	0.01	0.1	0.26	0.56	0.77	0.93	0.98	1	1	1
Fremanezumab monthly	0.02	0.09	0.21	0.41	0.65	0.85	0.96	0.99	1	1
Fremanezumab-quarterly	0.01	0.04	0.11	0.23	0.42	0.67	0.89	0.98	1	1
Eptinezumab 100 mg	0	0.01	0.04	0.12	0.28	0.48	0.88	0.98	1	1
Eptinezumab 10 mg	0	0.01	0.02	0.03	0.06	0.09	0.16	0.48	0.8	1
Eptinezumab 30 mg	0	0.01	0.01	0.03	0.05	0.09	0.15	0.48	0.8	1
Placebo	0	0	0	0	0	0	0	0.1	0.4	1

Note
Cumulative rank probabilities table shows likelihood of therapy to be at the top rank and presented by the SUCRA values (ranges 0–1).

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TABLE 47 Comparing fit of NMA and UME models for HIT-6

	Residual deviance (19 data points)	pD[a]	DIC[b]
NMA (Consistency) Model	18.3	15.1	33.4
UMEs (Inconsistency) Model	18	16.5	34.5

a pD: sum of leverage, also known as the effective number of parameters and shows the model complexity.
b DIC: Deviance Information Criteria provides a measure of goodness of model fit that penalises model complexity, the lower is more fitted. More than three difference is meaningful.

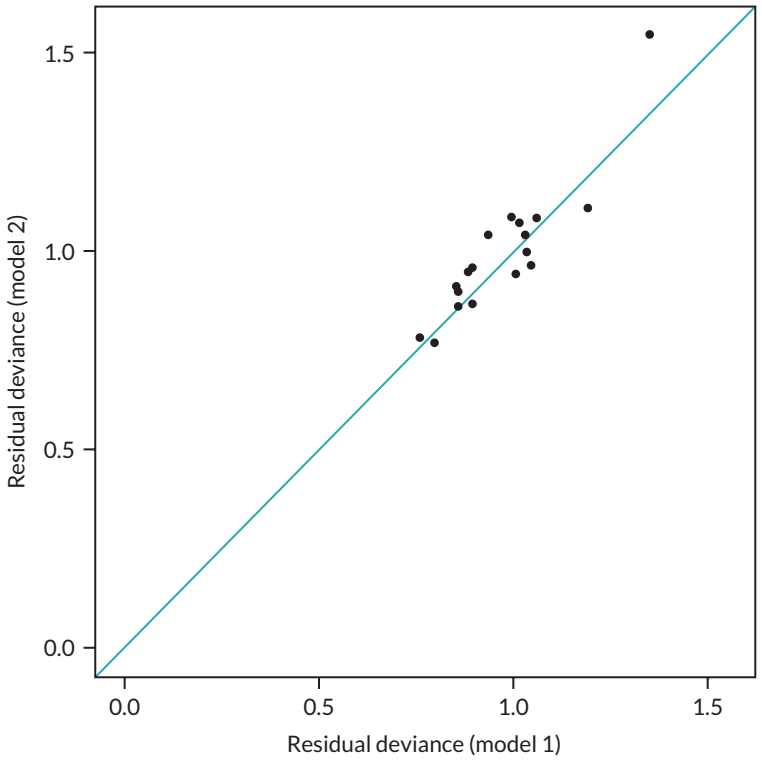

FIGURE 45 Global Consistency Test for mean change in HIT-6 from baseline [UMEs (Inconsistency) Model and Fixed NMA model]. Dev-Dev plot to identify inconsistent data points, the data points are scattered in a further distance from the bivector from the origin, and these show global inconsistency.

Sensitivity analysis results

Mean change in monthly headache day from baseline

The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs were lower than zero indicating favourable results for the intervention (*Figure 46*).

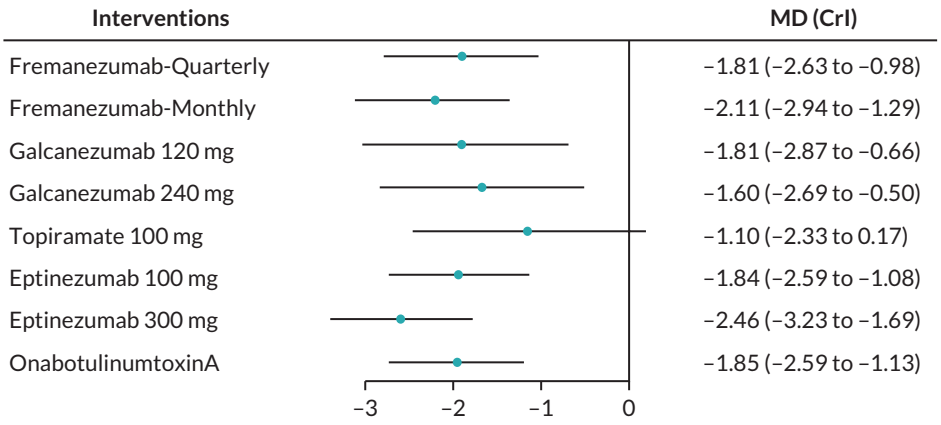

FIGURE 46 Forest plot for mean change in MHD from baseline (MDs, 95% CrI).

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TABLE 48 Head-to-head comparisons of treatments for mean change in MHD from baseline (MDs, 95% CrI)

Eptinezumab 300 mg							
−0.36 (−1.47 to 0.78)	Fremanezumab-M						
−0.62 (−1.38 to 0.16)	0.27 (−0.89 to 1.37)	Eptinezumab 100 mg					
0.61 (−0.48 to 1.65)	0.25 (−0.82 to 1.35)	−0.01 (−1.06 to 1.02)	OnabotulinumtoxinA				
−0.66 (−1.97 to 0.67)	0.30 (−1.02 to 1.72)	−0.04 (−1.31 to 1.28)	−0.05 (−1.41 to 1.26)	Galcanezumab 120 mg			
−0.65 (−1.77 to 0.49)	−0.30 (−1.11 to 0.50)	−0.03 (−1.15 to 1.10)	−0.04 (−1.11 to 1.06)	0.01 (−1.33 to 1.42)	Fremanezumab-Q		
−0.86 (−2.16 to 0.46)	0.51 (−0.88 to 1.85)	−0.24 (−1.52 to 1.06)	−0.25 (−1.56 to 1.06)	0.21 (−0.87 to 1.32)	0.21 (−1.18 to 1.58)	Galcanezumab 240 mg	
−1.36 (−2.84 to 0.06)	1.01 (−0.53 to 2.52)	−0.74 (−2.20 to 0.67)	−0.75 (−2.18 to 0.68)	0.71 (−0.93 to 2.37)	0.71 (−0.76 to 2.22)	0.50 (−1.12 to 2.18)	Topiramate 100 mg
−2.46 (−3.23 to −1.69)	**−2.11 (−2.94 to −1.29)**	**−1.84 (−2.59 to −1.08)**	**−1.85 (−2.59 to −1.13)**	**−1.81 (−2.87 to −0.66)**	**−1.81 (−2.63 to −0.98)**	**−1.60 (−2.69 to −0.50)**	−1.10 (−2.33 to 0.17)	Placebo

Fremanezumab-Q, fremanezumab- quarterly; fremanezumab-M, Fremanezumab monthly.

Note
Mean differences lower than zero favour the column-defining treatment. CrIs not including 0 are highlighted in bold.

The SUCRA values range from 0 to 1; presents the likelihood of drug being at the top rank (*Figure 47*).

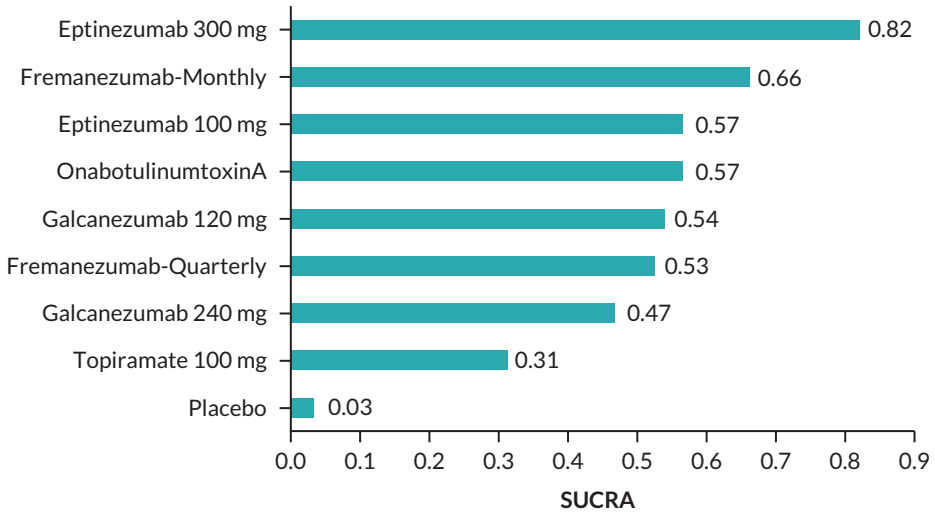

FIGURE 47 The surface under the cumulative ranking curve (SUCRA) for mean change in MHD from baseline.

Mean change in monthly migraine day from baseline

The forest plot shows the MDs and 95% CrI compared with placebo as reference treatment. MDs lower than 0 indicate favoured results for the intervention (*Figure 48*).

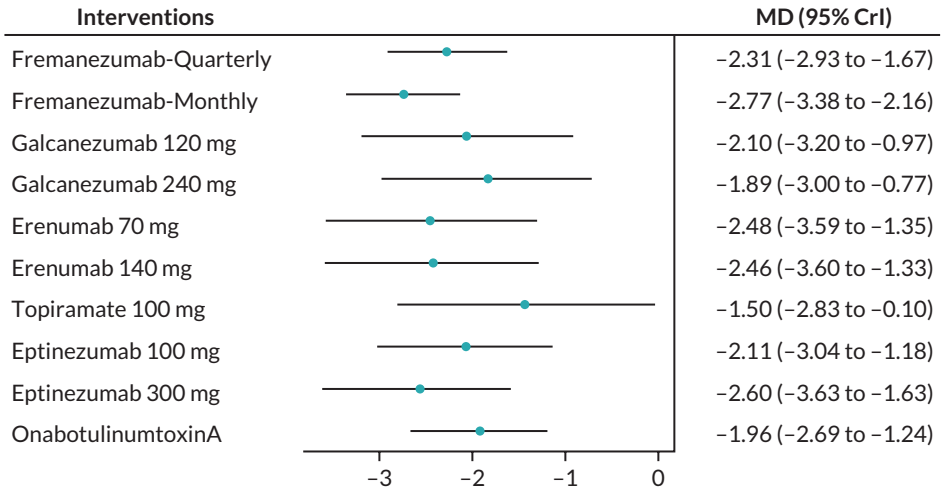

FIGURE 48 Forest plot for mean change in MMD from baseline (MDs, 95% CrI).

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TABLE 49 Head-to-head comparisons of treatments for mean change in MMD from baseline (MDs, 95% CrI)

Fremanezumab-M									
0.17 (−0.98 to 1.33)	Eptinezumab 300 mg								
0.29 (−0.96 to 1.54)	−0.12 (−1.72 to 1.42)	Erenumab 70 mg							
0.31 (−0.96 to 1.61)	−0.14 (−1.71 to 1.36)	0.v02 (−1.11 to 1.17)	Erenumab 140 mg						
−0.46 (−1.06 to 0.17)	−0.29 (−1.51 to 0.09)	−0.17 (−1.47 to 1.10)	−0.15 (−1.48 to 1.16)	Fremanezumab-Q					
0.67 (−0.0.60 to 1.94)	−0.01 (−2.03 to 0.98)	−0.39 (−1.93 to 1.23)	−0.36 (−1.93 to 1.25)	0.22 (−1.05 to 1.46)	Galcanezumab120 mg				
0.66 (−0.44 to 1.80)	−0.49 (−1.49 to 0.48)	0.38 (−1.15 to 1.80)	0.35 (−1.16 to 1.88)	0.20 (−0.91 to 1.33)	−0.01 (−1.47 to 1.45)	Eptinezumab100 mg			
0.81 (−0.14 to 1.74)	0.64 (−0.59 to 1.87)	0.52 (−0.81 to 1.87)	0.50 (−0.86 to 1.83)	0.35 (−0.64 to 1.28)	0.14 (−1.18 to 1.49)	0.15 (−1.02 to 1.31)	OnabotulinumtoxinA		
0.88 (−0.35 to 2.17)	−0.71 (−2.24 to 0.77)	−0.59 (−2.20 to 0.96)	−0.57 (−2.14 to 1.03)	0.42 (−0.84 to 1.73)	0.21 (−0.91 to 1.31)	−0.22 (−1.69 to 1.20)	−0.07 (−1.39 to 1.23)	Galcanezumab 240 mg	
1.27 (−0.21 to 2.76)	−1.10 (−2.83 to 0.57)	0.99 (−0.76 to 2.73)	0.96 (−0.82 to 2.74)	0.81 (−0.69 to 2.34)	0.60 (−1.12 to 2.36)	−0.61 (−2.25 to 1.07)	−0.46 (−1.98 to 1.02)	0.39 (−1.34 to 2.19)	Topiramate 100 mg
−2.77 (−3.38 to −2.16)	**−2.60 (−3.63 to −1.63)**	**−2.48 (−3.59 to −1.35)**	**−2.46 (−3.60 to −1.33)**	**−2.31 (−2.93 to −1.67)**	**−2.10 (−3.20 to −0.97)**	**−2.11 (−3.04 to −1.18)**	**−1.96 (−2.69 to −1.24)**	**−1.89 (−3.00 to −0.77)**	**−1.50 (−2.83 to −0.10)**	Placebo

Fremanezumab-Q, fremanezumab- quarterly; fremanezumab-M, Fremanezumab monthly.

Note
Mean differences lower than zero favour the column-defining treatment. CrIs not including 0 are highlighted in bold.

The SUCRA values ranges from 0 to 1; presents the likelihood of therapy to be at the top rank (*Figure 49*).

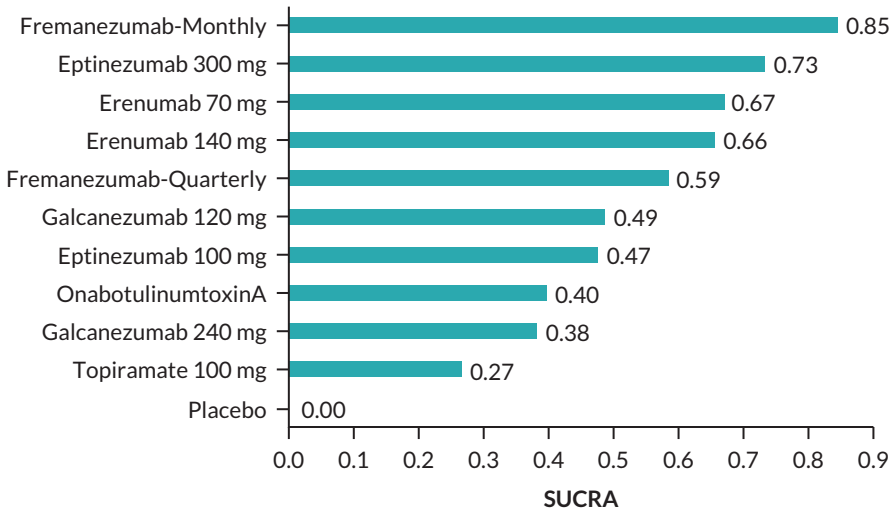

FIGURE 49 The SUCRA for mean change in MMD from baseline.

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Appendix 4 Baseline characteristics of the included studies for adverse events review

TABLE 50 More details on baseline characteristics of the included studies for AEs review

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Silberstein SD, 2007[28] **Country:** USA	**Study design:** Randomised, double-blind, placebo-controlled, parallel-group, multicentre trial **Date:** September 2003–March 2005	• Adult subjects with at least 15 headache days per 28 days with head pain for at least 30 minutes, on at least half of these days, subjects have experienced migraine with or without aura or migrainous headache • At least 11 score of MIDAS at visit 1	• Previously failed more than 2 adequate trials of migraine preventive medications • Previously failed an adequate trial of topiramate therapy due to lack of efficacy or AEs • History of cluster headache or basilar, ophthal-moplegic or hemiplegic migraines • Migraine onset after age 50
			• Overuse of acute migraine medication • History of hepatic disorder or nephrolithiasis • Progressive neurologic disorder other than migraine • Pregnant or nursing
Author, year: Rothrock, 2019[88] **Country:** USA	**Study design:** Multicentre, randomised, parallel-group, post-authorisation, open label prospective study. After 12 weeks, patients initially randomised to topiramate could cross over to BTA treatment **Date:** August 2014–September 2017	• Adults (18–65) had to record ≥ 20 diary days during 28 days baseline screening • Reported ≥ 15 headache days. • Patients taking other preventive treatments were eligible for enrolment if the dose had been stable and well tolerated for ≥ 12 weeks before screening and the patient was willing to maintain a stable dose	• Taking opioid-containing products for acute headache treatment more than 8 days during a 28-day period • Previous treatment with botulinum toxin of any serotype for any reason • Previous treatment with topiramate • On a ketogenic diet (high in fat, low in carbohydrates) • History of acute myopia or increased intraocular pressure
		• Patients were permitted to take prescription or over the counter acute headache pain medication, recording use in their daily diary	• Diagnosis of myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function • Acupuncture, TENS, cranial traction, dental splints for headache, or injection of anaesthetics/steroids in the 4 weeks prior to screening

continued

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Tepper, 2017[45] **Country:** North America (Canada and USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden and UK)	**Study design:** Phase 2, randomised, double-blind, placebo-controlled, multicentre **Date:** April 2014–December 2016	• History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine day	• History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • Failed > 3 medication categories due to lack of efficacy for prophylactic treatment of migraine
		• ≥ 4 distinct headache episodes, each lasting ≥ 4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the eDiary calculations • Demonstrated at least 80% compliance with the eDiary	• Received botulinum toxin in head or neck region within 4 months prior to screening • Used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase
Author, year: Dodick, 2019[89] **Country:** 82 in USA, 4 in Australia, and 3 each in New Zealand and the Republic of Georgia	**Study design:** Phase 2b, parallel-group, double-blind, randomised, placebo-controlled, dose-ranging clinical trial **Date:** December 2014–December 2016	• Adults 18–55 years with CM according to ICHD-3b • Established at age ≥ 35 years and history of CM of ≥ 1 year • ≥ 15 headache days, of which ≥ 8 were assessed as migraine days during baseline priod • Use of hormonal therapy and preventive medications for headache, except botulinum toxin, was allowed if the dosing has been stable for > 3 months before screening, and was maintained at the same dosing level throughout the trial	• Confounding pain syndromes (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome) or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening • History or diagnosis of complicated migraine (ICHD-3b), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine
		• The use of barbiturates or opioids for the acute treatment of CM was allowed if the dosing had been stable for 3 months before screening, and dosing did not exceed 4 days/month. • Patients with CM who were diagnosed with medication overuse headache	• Unable to differentiate migraine from other headaches • Subject has received botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face or neck within 4 months prior to screening • Have any clinically significant concurrent medical condition

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Detke, 2018[95] **Country:** Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, UK and USA	**Study design:** Phase 3, randomised, double-blind, placebo-controlled study **Date:** January 2016–March 2017	• Adults 18–65 years with CM as defined by ICHD-3 beta with at least 15 headache days • Migraine onset before 50 years of age	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product
		• Patients could take acute headache medication as needed throughout the trial but could take opioid or barbiturate containing medications no more than 3 days per month, could not take oral corticosteroids, and could receive no more than 1 steroid injection during the study and only if in an emergency setting	• Current use or prior exposure to galcanezumab or another CGRP antibody • Known hypersensitivity to multiple drugs, MAbs or other therapeutic proteins, or to galcanezumab
		• Patients had to wash out all migraine preventive medications except topiramate or propranolol • Patients also needed at least 1 headache-free day per month within 3 months before screening period	• History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta
Author, year: Dodick 2010;[97] (pooled Aurora 2010,[92] Diener 2010[93]) **Country:** 56 North American sites	**Study design:** Phase 3 study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open label phase **Date:** 23 January 2006–16 July 2008 and 7 February 2006–11 August 2008	• Adults (18–65 years) with a history of migraine according to ICHD-II • Randomised patients provided diary data on > 20 of 28 days during baseline • Having > 15 headache days with each day consisting of > 4 hours of continuous headache and with > 50% of days being migraine or probable migraine days and > 4 distinct headache episodes, each lasting > 4 hours	• Previous use of botulinum toxin of any serotype or immunisation to any botulinum toxin serotype • Any medical condition that puts the patient at increased risk with exposure to BTA • Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache • Use of prophylactic headache medication within 28 days prior to week 4

continued

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
			• Unremitting headache lasting continuously throughout the 4-week baseline period • Known or suspected TMD • Diagnosis of fibromyalgia • Beck depression inventory score > 24 at week 4 • Psychiatric problems that may have interfered with study participation
Author, year: Ferrari, 2019[90] **Country:** Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK and USA	**Study design:** Phase 3 FOCUS trial, randomised, double-blind, placebo-controlled, parallel-group **Date:** October 2017–May 2019	• Adults (18–70 years), had a diagnosis of migraine with onset at or before age 50 years • Chronic migraine history at least 12 months before screening • > 15 headache days per month, with at least 8 migraine days • Participants with and without overuse of acute headache medication • With failure to 2 to 4 classes of migraine preventive medications in the past 10 years	• At the time of screening visit, participant is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications • Participant has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face or neck during the 3 months before screening visit
			• Participant has used an intervention/device (e.g. scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening • Participant uses triptans/ergots as preventive therapies for migraine • Participant uses NSAIDs as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (e.g. 81 mg) used for cardiovascular disease prevention is allowed
Author, year: Sakai F, 2021[91] **Country:** Japan and Korea	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group **Date:** November 2017 and November 2019	• Patient with migraine onset at ≤ 50 years of age • Headache occurring on ≥ 15 days and fulfilling any of the following on ≥ 8 days: ICHD-3 beta diagnostic criteria C and D for 1.1 Migraine without aura, criteria B and C for 1.2 Migraine with aura, probable migraine	• The lack of efficacy of at least 2 of 4 clusters of preventive medications despite an adequate treatment • Unremitting headaches with duration more than 80% of waking hours and with < 4 days without headache per month • Clinically significant major organ disease
		• Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions if the dose and regimen have been stable for at least 2 months prior to giving informed consent	• Patient has received onabotulinumtoxin A for migraine or for any medical or cosmetic reason requiring injection in the head, face or neck during the 4 months prior to giving informed consent • Patient is using medications containing opioids or barbiturates on more than 4 days per month for the treatment of migraine or for any other reason • Patient has used an intervention or device for migraine during the 2 months prior to giving informed consent

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Silberstein SD, 2017[37] **Country:** 132 sites in 9 countries	**Study design:** Randomised, double-blind, placebo-controlled, parallel-group trial **Date:** March 2016 to January 2017	• Adults (18–70 years), a history of migraine according to ICHD-3 beta for at least 12 months • ≥ 15 headache days with ≥ 8 migraine days • The protocol allowed inclusion of up to 30% of patients using a stable dose of one migraine preventive medication (hereafter referred to as preventive medication) for at least 2 months before the beginning of the pre-intervention period to continue these medications	• The use of BTA during the 4 months before screening • The use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during the 2 months before screening • The use of opioid or barbiturate medications on more than 4 days during the pre-intervention period and a lack of efficacy, after an adequate therapeutic trial, of at least 2 of 4 clusters of preventive medications
Author, year: Lipton, 2020[94] **Country:** 13 countries (USA, Spain, Ukraine, Russian Federation, UK, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark and Belgium)	**Study design:** Phase 3, double-blind, randomised, placebo-controlled, parallel-group **Date:** November 2016–April 2018	• Adults (18–65 years) of age (inclusive) with a diagnosis of migraine at or before 50 years of age if they had a history of CM for ≥ 12 months before screening • Completed the headache electronic diary (eDiary) on ≥ 24 of the 28 days and experienced ≥ 15 to ≤ 26 headache days and ≥ 8 migraine days during the 28-day screening period • Migraine preventive medication use had to be stable for ≥ 3 months before screening. Hormonal therapy was also permitted if it was stable and ongoing ≥ 3 months before screening • Patients using barbiturates or prescription opioids ≤ 4 days/month were eligible for participation if use was stable for ≥ 2 months before screening • Patients with CM and medication overuse headache with the exception of the overuse of barbiturates or opioids	• Patients using opioids or barbiturates ≥ 5 days/month • With a confounding pain disorder or clinically significant pain syndromes; uncontrolled or untreated psychiatric conditions; acute or active temporomandibular disorders; history or diagnosis of a headache or migraine disorders that did not meet the ICHD-3 criteria • Present or previous malignancies, any active, progressive or unstable cardiovascular, neurological or autoimmune disorder; newly diagnosed or uncontrolled hypertension • Women who were pregnant, breastfeeding, or planning to become pregnant during the study • Positive for HIV, hepatitis B surface antigen or hepatitis C • A concurrent medical condition or laboratory abnormality during the screening period or before dosing on day 0 • BMI ≥ 39 kg/m^2 • Or recent or planned surgery requiring general anaesthesia within 8 weeks before screening or during the duration of the study • Botulinum toxin (any type) for migraine or for any other medical cosmetic reasons requiring injections within 4 months before screening or during the screening period • Any monoclonal antibody treatment within 6 months of screening; or eptinezumab or any monoclonal antibody targeting the CGRP pathway

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Silberstein, 2007[28] **Country:** USA	**Study design:** Randomised, double-blind, placebo-controlled, parallel-group, multicentre trial **Date:** September 2003–March 2005	• Adult subjects with at least 15 headache days per 28 days with head pain for at least 30 minutes, on at least half of these days, subjects have experienced migraine with or without aura or migrainous headache • At least 11 score of MIDAS at visit 1	• Previously failed more than 2 adequate trials of migraine preventive medications • Previously failed an adequate trial of topiramate therapy due to lack of efficacy • History of cluster headache or basilar, ophthal-moplegic or hemiplegic migraines • Migraine onset after age 50 • Overuse of acute migraine medication • History of hepatic disorder or nephrolithiasis • Progressive neurological disorder other than migraine • Pregnant or nursing
Author, year: Lucking, 1988[128] **Country:** Germany	**Study design:** Double-blind	• Adults who during the preceding 6 months had suffered from at least 2 attacks a month or single attacks lasting several days • A wash-out period of 2 weeks preceded the treatment in all cases	• Concomitant prophylactic treatment with serotonin antagonists, calcium antagonists, clonidin or beta-receptor blockers
Author, year: Ailani, 2021[129] **Country:** USA	**Study design:** Multicentre, double-blind, parallel-group, randomised, placebo-controlled trial **Date:** December 2018–June 2020	• Adults 18–80 years of age with 4–14 migraine days per month in the 3 months before visit 1 and 4–14 migraine days during the 28-day baseline period according to an electronic diary • Participants had to have at least a 1-year history of migraine with or without aura, diagnosed as specified in the ICHD-3, and with migraine onset before 50 years of age	• Diagnosis of chronic migraine, new daily persistent headache, trigeminal autonomic cephalalgia or painful cranial neuropathy as defined by the ICHD-3 or if they averaged 15 or more headache days per month across the 3 months before visit 1 or during the 28-day baseline period • An inadequate response to more than 4 oral medications prescribed for the preventive treatment of migraine, 2 of which needed to have different mechanisms of action • Participants who used opioids or barbiturates on more than 2 days per month, triptans or ergots on 10 or more days per month, or simple analgesic agents on 15 or more days per month in the 3 months before visit 1 or during the 28-day baseline period • Use of barbiturates 30 days before screening • Pregnant, planning to become pregnant, or lactating
Author, year: Sun, 2016[130] **Country:** North America (Canada, USA) and Europe (Denmark, Finland, Germany, Norway, Sweden and Portugal)	**Study design:** Multicentre, randomised, double-blind, placebo-controlled trial **Date:** August 2013–November 2019	• Adults, 18–60 years • History of migraine for more than 12 months prior to screening	• Older than 50 years of age at migraine onset • History of cluster headache or basilar or hemiplegic migraine headache

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• Migraine frequency: ≥ 4 and ≤ 14 migraine days per month in each of the 3 months prior to screening and during baseline phase • Headache frequency: < 15 headache days per month (with > 50% of the headache days being migraine days) in each of the 3 months prior to screening and during baseline phase • Demonstrated at least 80% compliance with the eDiary during baseline phase	• Unable to differentiate migraine from other headaches • No therapeutic response with > 2 of the following e8 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. Medication categories are: Category 1: Divalproex Sodium, Sodium Valproate; Category 2: Topiramate; Category 3: Beta-blockers (e.g. Atenolol, Bisoprolol, Metoprolol, Nadolol, Nebivolol, Pindolol, Propranolol, Timolol); Category 4: Tricyclic antidepressants (e.g. Amitriptyline, Nortriptyline, Protriptyline); Category 5: Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran; Category 6: Flunarizine, Verapamil; Category 7: Lisinopril, Candesartan; Category 8: Butterbur, Feverfew, Magnesium (≥ 600 mg/day), Riboflavin (≥ 100 mg/day) • Overuse of acute migraine medications in any month during the 3 months prior to screening or during screening
Author, year: Ashina, 2020[131] **Country:** USA and Republic of Georgia	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group study **Date:** September 2015–December 2017	• Adults, 18–75 years • Diagnosis of migraine at ≤ 50 years of age • History of migraine ≥ 12 months with ◦ ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) in each 28-day period in the 3 months prior to screening ◦ During the 28 days following the screening visit, the subject experiences ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) as recorded in the eDiary	• Confounding pain syndromes, for example fibromyalgia, complex regional pain syndrome or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening • History or diagnosis of complicated migraine (ICHD-II), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine
		• No use of any botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face or neck 4 months prior to screening and during the 28-day period prior to randomisation • Headache eDiary was completed on at least 25 of the 28 days prior to randomisation	• Unable to differentiate migraine from other headaches • Have any clinically significant concurrent medical condition • Receipt of any monoclonal antibody treatment within 6 months of screening (within or outside a clinical trial) • Previously dosed with ALD403 or any monoclonal antibody targeting the CGRP pathway

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Aurora, 2007[132] **Country:** North America	**Study design:** Randomised, double-blind, placebo-controlled, parallel-group, multicentre clinical study	• Adults 18–65 years (least 4 migraine episodes to 15 headache days per month). • Migraine episodes at least 1 year prior to enrolment and first diagnosed before age 50 years	• Any medical condition or used any agent that may have put them at risk with exposure to this formulation of BTA or if they had an infection or skin problem at any of the injection sites or a known allergy or sensitivity to the study medication or its components
		• Patients' chronic medication regimens, if any, had to be stable – including migraine prophylactic medications – for at least 3 months immediately prior to the initiation of the baseline period	• A history of 'complicated' migraine (e.g. hemiplegic migraine, ophthalmoplegic migraine or basilar migraine), or an inadequate response to 2 or more prophylactic treatments after an adequate trial • Patients with psychiatric problems that were severe enough to interfere with study implementation. • Concurrent chronic use or chronic use in the 3 months prior to the screening period of muscle relaxants
Author, year: Couch, 2011[22] **Country:** USA	**Study design:** Double-blind, placebo-controlled study **Date:** 1976 and 1979	• Adults between 18 and 70 years of age with at least 2 moderate or worse migraine headaches per month (diagnosis of migraine by ICHD published in 1988)	• Absence of migraine headache • Secondary headache • Pregnant females or nursing mother • Known allergy to amitriptyline
			• Urinary retention, glaucoma, any cardiac disease, sustained hypertension, subjects taking guanethidine or monoamine oxidase inhibitors, prostatic hypertrophy, thyroid disease or taking thyroid medication, seizure disorder • Patients taking any known (at that time) preventative anti-migraine agent including methysergide, propranolol, cyproheptadine, anti-anxiety agents, or other tricyclic antidepressants
Author, year: Dodick, 2014[133] **Country:** USA	**Study design:** Randomised, double-blind, placebo-controlled, phase 2 proof-of-concept study, parallel assignment **Date:** July 2012–September 2013	• Adults 18–65 years with 4–14 migraine headache days per month • Have a history of migraine as defined by ICHD-II, of at least 1 year prior to enrolment, migraine onset prior to age 50, and a moderate frequency of migraine headaches • Women of childbearing potential (not surgically sterile or at least 1 year post-menopause) must test negative for pregnancy at the time of screening based on a serum pregnancy test and must agree to use a reliable method of birth control during the study and for 3 months following completion of participation in the study	• Current enrolment in, or discontinuation within the last 30 days from, a clinical trial involving any investigational drug or device, or concurrent enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study • Previous completion or withdrawal from this study or any other study investigating LY2951742 or other therapeutic antibodies that target CGRP • History of chronic migraine or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine and basilar-type migraine

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• Have clinical laboratory test results within normal reference ranges or, if outside the normal range, judged not clinically significant by the investigator • Must not be on any migraine prevention therapy, including botulinum toxin • Agree not to post any personal medical data related to the study or information related to the study on any website or social media site	• Evidence of significant active psychiatric disease including, but not limited to, manic depressive illness, schizophrenia, generalised anxiety disorder, obsessive compulsive disorder, personality disorders, or other serious mood, anxiety, depression or substance use disorders • Have a history or presence of any other medical illness • Women who are pregnant or nursing • Confirmed corrected QT (QTc) interval > 470 ms for women and > 450 for men
Author, year: Dodick, 2018[134] **Country:** 69 sites across North America and Europe (including Russia)	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial **Date:** July 2015–March 2017	• Adults 18–65 years • Migraine onset prior to age 50 • History of migraines (with or without aura) for ≥ 12 months • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening	• History of cluster headache or hemiplegic migraine headache • No therapeutic response with > 2 categories for prophylactic treatment of migraine after an adequate therapeutic trial • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase
		• Headache (i.e. migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening • Demonstrated compliance with the eDiary	• Used a prohibited medication, device or procedure within 2 months prior to the start of the baseline phase or during the baseline phase • Received botulinum toxin • Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain) • History of major psychiatric disorder, seizure, HIV • MI, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularisation procedure within 12 months prior to screening
Author, year: Dodick, 2009[135] **Country:** USA	**Study design:** Multicentre, randomised, double-blind, double-dummy, parallel-group noninferiority study **Date:** February 2004–October 2005	• Adults (age ≥ 18 years) with a history of migraine without or with aura (International Headache Society class 1.1 and 1.2, respectively) for at least 6 months before the screening • Wash-out period, along with ~3 to 12 migraines per month in the 3 months before the screening • Wash-out period, from 3 to 12 migraine episodes during the 28-day prospective baseline period, and no more than 15 headache days (migraine and non-migraine) during the prospective baseline period, based on headache records • Onset of migraine prior the age of 50 years	• With previously failed > 2 adequate trials of migraine preventive medications or had failed an adequate trial of topiramate or amitriptyline because of lack of efficacy or AEs • Acute abortive medication uses on > 15 treatment days per month • Migraine aura only (without headache) • History of cluster headache, a progressive neurological disorder other than migraine, or a condition more painful than headache • History of a medical condition in which use of amitriptyline is contra-indicated • History of an unstable medical condition within the past 2 years or of a major psychiatric disorder within the past 6 months that could impair reliable participation in the study or necessitate the use of medications not permitted in the study

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
			• History of drug or alcohol abuse within the past 2 years • History of nephrolithiasis, active liver disease or liver function tests ≥ 2 times the upper limit of normal • Pregnant or nursing women and those who were not practising a medically accepted method of birth control
Author, year: Diener, 2002[136] **Country:** 8 countries: Belgium, Denmark, Spain, France, Germany, Italy, Portugal, Switzerland	**Study design:** A phase-IV double-blind equivalence trial **Date:** April 1992–March 1996	• Adults aged 18–65 years • Having 2–6 migraine attacks every month • Migraine present for at least 1 year • Migraine with aura (classic) or without aura (common) as defined by the International Headache Society	• Use of prophylactic migraine therapy in the two preceding months (reference period) • Previous adequate (i.e. 160 mg propranolol or 10 mg flunarizine per day for at least 2 months) prophylactic use of Propranolol or flunarizine without success. • History of depressive illness
		• Occurrence of interval headaches: permitted only if these attacks were well recognised by the subject and if they did not occur more frequently than 6 days per month	• Extrapyramidal disorders • Chronic obstruction airways disease, bronchospasm or asthma • Serious diseases (diabetes, serious hepatic, renal, cardiovascular, respiratory or malignant illness) • Alcohol or drug dependence (documented or suspected) • Pregnancy, lactation, or childbearing potential without adequate contraception • Absence of 2–6 migraine attacks during the run-in phase
Author, year: Dodick, 2018[35] **Country:** Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain, USA	**Study design:** Randomised, double-blind, placebo-controlled, parallel group **Date:** March 2016–April 2017	• Males or females aged 18–70 years inclusive, with migraine onset at ≤ 50 years of age (ICHD-3 beta) • Patient signs and dates the informed consent document • Patient has history of migraine according to ICHD, or clinical judgment suggests a migraine diagnosis • 85% eDiary compliance • Total body weight between 99 and 265 lb inclusive	• Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurological, hepatic, or ocular disease, at the discretion of the investigator • History of clinically significant psychiatric issues • History of cardiovascular disease or vascular ischaemia or thromboembolic events, such as cerebrovascular accident, deep vein thrombosis or pulmonary embolism • History of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection
		• A subset of patients was allowed to use 1 concomitant preventive migraine medication if the dosing was stable for at least 2 months prior to the beginning of the pre-treatment period and without any change in dose during the study • Acute headache medications were permitted	• Pregnant or nursing females • Using onabotulinumtoxinA during the 4 months before screening • Using opioids or barbiturates on more than 4 days during the pre-treatment baseline period • Having previous failure of 2 or more of the following medication clusters after at least 3 months of treatment for episodic or chronic migraine: divalproex sodium and sodium valproate; flunarizine and pizotifen; amitriptyline, nortriptyline, venlafaxine and duloxetine; and atenolol, nadolol, metoprolol, propranolol and timolol

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Goadsby, 2017[36] **Country:** 121 sites across North America, Europe, and Turkey	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial **Date:** July 2015–September 2016	• Adults 18–65 years • History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS ICHD-3 classification • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening and during baseline	• Older than 50 years of age at migraine onset • History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headache • No therapeutic response with > 2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial
		• Headache frequency: < 15 headache days per month on average across the 3 months prior to screening and baseline • Demonstrated at least 80% compliance with the eDiary	• Used a prohibited medication, device or procedure within 2 months prior to the start of the baseline phase or during the baseline phase • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. If only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study
Author, year: Kalita, 2013[137] **Country:** India	**Study design:** Single-centre prospective study with randomised controlled open labelled design **Date:**-	• Migraine patients between 15 and 60 years of age having more than 4 moderate to severe attacks • The diagnosis of migraine was based on International Headache Society Criteria	• The patients with history of drug allergy, severe hypertension, coronary artery disease, pregnancy, menstrual irregularity, liver or kidney dysfunction, polycystic ovary, systemic or psychiatric disease, malignancy, glaucoma, dysautonomia
Author, year: Relja, 2007[138] **Country:** 37 study centres in 9 countries (1 centre in Belgium, 6 in Croatia, 1 in Denmark, 3 in Finland, 6 in France, 5 in Germany, 2 in Norway, 1 in Switzerland and 12 in UK)	**Study design:** Randomised, double-blind, placebo-controlled, parallel-group, multicentre clinical study of multiple treatments of BTA **Date:** -	• Adults aged 18–65 years who suffered from an average of at least 3 moderate to severe untreated migraine episodes per month (defined by IHS 1988 ICHD-I) or at least 3 treated migraine episodes of any severity per month • ≤ 15 headache days per month as confirmed by a headache diary during the baseline period • Occurred for at least 1 year prior to enrolment and be first diagnosed before age 50 years	• Having any medical condition or used any agent that may have put them at risk with exposure to BTA, or having an infection or skin problem at any of the injection sites or a known allergy or sensitivity to the study medication or its components • Having an inadequate response to 3 or more prophylactic treatments after an adequate trial as determined by the investigator, a Beck Depression Inventory score of > 24, or psychiatric problems that, in the investigator's opinion, were severe enough to interfere with study participation or results

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• Patients had to have a stable medical condition and acceptable blood haematology and chemistry results • Patients were required to discontinue headache prophylactic medications for at least 3 months immediately prior to the initiation of the baseline period and had to be willing and able to stay on current medications (other than headache prophylaxis) during the course of the study, as well as comply with study instructions including the use of a daily electronic telephone diary capture system	• Having previous therapy with botulinum toxin of any serotype, having been injected with anaesthetics or steroids into the study-targeted muscles during the 30 days immediately prior to initiation of the baseline period • If they were overusing or abusing symptomatic medication, alcohol or drugs • Concurrent chronic use or chronic use in the 3 months prior to the screening period of muscle relaxants was prohibited • Having uncontrolled systemic disease • Females who were pregnant, nursing, or planning a pregnancy during the study
Author, year: Lipton, 2011[139] **Country:** 81 sites in the USA	**Study design:** Multicentre, randomised, double blind, placebo-controlled, parallel-group study **Date:** September 2005 and August 2007	• Adults 18–65 years of age with an established history of migraine headache (ICHD-II) for at least 12 months before entering the screening period • Having at least 9 but < 15 migraine headache days and < 15 total headache days over the 28 days before the screening visit and during the 28-day baseline period • Having generally good health, as confirmed by medical history, baseline physical examination, baseline neurological exam, vital signs and clinical laboratory evaluations, and to be capable of taking oral medication	• Previously failed more than 2 adequate trials of medications from different drug classes used for migraine prophylaxis because of a lack of efficacy, or used a medication generally considered to be effective for migraine prevention in the 6 weeks before visit 2 (initiation of baseline period) • Previously discontinued topiramate therapy because of a lack of efficacy or discontinued topiramate therapy because of an AE • Having onset of migraine after age 50, had exclusively migraine aura without headache or, at the time of screening, had an equally painful or more painful condition than their headache pain or had cluster headache or basilar or hemiplegic migraine
		• Females had to be postmenopausal for at least 1 year, surgically sterile or otherwise incapable of pregnancy, or using an acceptable method of birth control • Female subjects of childbearing potential had to have a negative result on a urine pregnancy test before beginning study medication	• Using a combination of acute headache medications for any reason for > 4 days/week on a regular basis during the 3 months before visit 2 • Having a progressive neurological disorder other than migraine; a malignancy or a history of malignancy within the past 5 years, except for a basal cell carcinoma that was treated with local excision and was no longer present; a significant medical history or medical condition of neurological, cardiovascular, hepatic or renal disease; nephrolithiasis or any unstable medical condition • Renal or liver function tests at least two times the ULN range or abnormal screening laboratory tests exceeding any of the following limits: alanine transaminase or aspartate transaminase > 2 × ULN; total white blood cell count 2 × ULN; platelet count 2 × ULN transaminase or aspartate transaminase > 2 × ULN; total white blood cell count 2 × ULN; platelet count 2 × ULN • Any history of suicide attempt or suicidal ideation or of a major psychiatric disorder • A history of drug or alcohol abuse

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Sakai, 2020[127] **Country:** Japan from 40 sites	**Study design:** Phase 2, randomised, double-blind, placebo-controlled parallel-design study **Date:** December 2016–January 2019	• Adults 18–65 years • Have a diagnosis of migraine as defined by IHS ICHD-3 beta guidelines • History of migraine headaches of at least 1 year prior to screening, and migraine onset prior to age 50	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product • Current use or prior exposure to galcanezumab or other antibodies to CGRP or its receptor
		• Patients had to demonstrate ≥ 80% compliance (completion of daily entries) with the ePRO diary, and all patients agreed to use reliable methods of contraception during the study and for 5 months after the last dose	• Known hypersensitivity to multiple drugs, MAbs or other therapeutic proteins, or to galcanezumab and the excipients in the investigational product • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta
Author, year: Sakai, 2021[126] **Country:** Japan and Korea	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase 2b/3 trial **Date:** November 2017 and November 2019	• Adults 18–70 years • Patient with migraine onset at ≤ 50 years of age • Patient has a history of migraine, based on (ICHD-3 beta) criteria or clinical judgment suggests a migraine diagnosis for ≥ 12 months prior to giving informed consent • Patient fulfils the criteria for episodic migraine in baseline information collected during the 28-day screening period	• Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the medications for treatment of migraine after use for at least 3 months at accepted migraine therapeutic doses • Haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurological, hepatic or ocular disease considered clinically significant in the judgment of the investigator
		• Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions (e.g. propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent	• Female patient who is nursing at the time informed consent is obtained or who tests positive in pregnancy test at screening or baseline • History of hypersensitivity reactions to injected proteins, including MAbs
Author, year: Stauffer, 2018[140] **Country:** 90 sites in North America	**Study design:** Phase 3, randomised, double-blind, placebo-controlled study, parallel design **Date:** November 2015–August 2018	• Adults 18–65 years • Have a diagnosis of episodic migraine as defined by IHS ICHD-3 beta guidelines • History of migraine headaches of at least 1 year prior to screening,	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product • Current use or prior exposure to galcanezumab or another CGRP antibody

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• Migraine onset prior to age 50 • Monthly frequency of 4–14 MHDs	• Known hypersensitivity to multiple drugs, MAbs or other therapeutic proteins, or to galcanezumab • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta
Author, year: Skljarevski, 2018[141] **Country:** 109 study sites in USA, UK, Netherlands, Spain, Czech Republic, Germany, Argentina, Israel, Korea, Taiwan and Mexico	**Study design:** Phase 3, multicentre, placebo-controlled, double-blind, randomised **Date:** January 2016 and March 2017	• Adults 18–65 years • Have a diagnosis of episodic migraine as defined by IHS ICHD-3 beta guidelines • History of migraine headaches of at least 1 year prior to screening,	• Having failed treatment with 3 or more migraine prevention drugs from different classes (level A or B evidence per American Academy of Neurology guidelines for episodic migraine prevention)
		• Migraine onset prior to age 50 • Monthly frequency of 4–14 MHDs • 80% compliance rate in using the electronic diary • Patients had to agree to use an acceptable method of birth control during the study and for at least 5 months afterwards	• Using opioids or barbiturates more than twice per month. • If participation were in another clinical trial within the past 30 days, prior exposure to galcanezumab or any another CGRP antibody, taking any therapeutic antibody in the past 12 months, known hypersensitivity to multiple drugs • Presence of any medical or psychiatric illness that would preclude study participation
Author, year: Reuter, 2018[143] **Country:** 59 sites in 16 countries across Europe and Australia	**Study design:** Randomised, double-blind, placebo-controlled, phase 3b study **Date:** March 2017–January 2021	• Adults 18–65 years • Documented history of migraine in the 12 months prior to screen • 4–14 days per month of migraine symptoms • ≥ 80% diary compliance during the baseline period • Failure of previous migraine prophylactic treatments	• > 50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or psychiatric disorder • Score of over 19 on Beck Depression Inventory-2 • Active chronic pain syndrome • Cardiac or hepatic disease
Author, year: Reuter, 2022[142] **Country:** 82 study sites in Germany	**Study design:** Randomised, double-blind, double dummy, active-controlled, parallel-group phase 4 **Date:** February 2019–July 2020	• Adults • Documented history of migraine in the 12 months prior to screen according to ICHD-3 episodic and chronic migraine • At least 4 days per month of migraine symptoms	• Older than 50 years of age at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache, or if they were unable to differentiate migraine from other headaches

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• ≥ 80% diary compliance during the baseline period • If patients had not received prior prophylactic migraine treatment (naive) or, due to lack of efficacy or tolerability, had failed or had not been suitable for up to 3 previous prophylactic treatments from the following: metoprolol/propranolol, amitriptyline, and flunarizine	• History or evidence of major psychiatric disorder • Score of 19 or higher on BDI • Having previously received valproate or, in the event of chronic migraine, onabotulinumtoxin A, in line with recommendations of the German HTA body
Author, year: Wang, 2021[144] **Country:** 83 sites across 11 countries in Asia, the Middle East and Latin America	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 study **Date:** February 2018–January 2020	• Adults 16–65 years old with migraine diagnosis according with ICHD-3 beta • ≥ 4 and < 15 migraine days per month and < 15 headache days in the 12 months prior to screening • 4–14 days per month of migraine symptoms	• > 50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or major psychiatric disorder • Score of 19 or higher on the BDI • Active chronic pain syndrome • Cardiac or hepatic disease
		• ≥ 80% diary compliance during the baseline period	• No therapeutic response to > 2 of the 7 categories of migraine preventive treatments after an adequate therapeutic trial • Use of a prohibited medication, device or procedure prior to the start of the study • Use of botulinum toxin within 4 months, ergotamines or triptans on ≥ 10 days per month, simple analgesics on ≥ 15 days per month, or opioid or butalbital-containing analgesics on ≥ 4 days per month
Author, year: Diene, 2007[152] **Country:** 88 neurology clinics in 21 countries in Europe and the Middle East	**Study design:** Randomised, double-blind, placebo-controlled trial **Date:** December 2003–February 2005	• Adults 18–80 years of age and fulfilled International Headache Society criteria for migraine with or without aura • Having history of migraine for at least 1 year, with a mean of at least 4 migraine days per month during the 3 months before trial entry • All patients needed to be able to keep trial records	• Using migraine prophylactic medication in the month before trial entry (or flunarizine in the 3 months before entry) or had experienced poor or no efficacy with more than 2 regimens of migraine prophylactic medication • Patients were excluded if they overused acute medication (defined as ≥ 10 days in every 4 weeks for opioids, ergots, triptans, or combination analgesics, and ≥ 15 days in every 4 weeks for other analgesics) or had used topiramate regularly for more than 2 weeks before study entry • Women who were pregnant or breastfeeding were excluded, and all women of childbearing age were required to have a negative pregnancy test before enrolment and to confirm that they would use adequate contraception throughout the study

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
Author, year: Elkind, 2006[145] **Country:** USA	**Study design:** A series of 3 sequential, randomised, controlled studies **Date:** -	• Adults 18–65 years, with International Headache Society–defined migraines with or without aura • Having an average of 4–8 moderate to severe migraines per month that occurred with a stable frequency and severity and had begun at least 1 year prior to the study	• Patients with more than 15 headache days per month • History of complicated migraine or typical migraine pain localised predominantly to the occipital or suboccipital region • Patients were ineligible if they were consistently refractory to multiple acute therapies or had never tried any acute therapies
		• Patients were first diagnosed with migraine before age 50 years and could distinguish between migraine and non-migraine headaches • Eligible patients were in a stable medical condition and, if taking chronic medications (including prophylactic migraine medications), were on stable doses and regimens for at least 3 months prior to enrolment, which they agreed to continue throughout the study	• Patients who overused symptomatic medications, as were those who used caffeine excessively or abused alcohol/drugs • Any medical condition or use of any agent that might have put the patient at increased risk with exposure to BTA or interfered with study participation or the results • Women who were pregnant, breastfeeding, or planning a pregnancy • Those with infection or skin problems at the injection site
Author, year: Mulleners, 2020[146] **Country:** 64 sites (hospitals, clinics or research centres) in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, UK and USA)	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, phase 3b trial **Date:** September 2018–21 March 2019	• Adults 18–75 years with a diagnosis of migraine with aura or without aura, or chronic migraine defined by ICHD-3, with a history of migraine headaches of at least 1 year before screening, and migraine onset before the age of 50 years • History of at least 4 migraine headache days and at least 1 headache-free day per month on average within the past 3 months	• History of cluster headache or migraine subtypes including hemiplegic migraine, ophthalmoplegic migraine and migraine with brainstem aura, history of head or neck injury within 6 months before the screening visit, or history of traumatic head injury associated with significant change in the quality or frequency of headaches • Current use or prior exposure to galcanezumab or another CGRP antibody • Pregnant or nursing

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• History of documented treatment failure of 2–4 standard-of-care migraine preventive medication categories in the past 10 years owing to inadequate efficacy, or safety or tolerability reasons, or both, were eligible • Treatment failure did not include contraindications; patients had to have taken the medications • The medication categories were: propranolol or metoprolol, topiramate, valproate or divalproex, amitriptyline, flunarizine, candesartan, botulinum toxin A or B, and medications locally approved for prevention of migraine	• Having acute cardiovascular events or a serious cardiovascular risk, or both, based on ECG results during the screening visit, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 6 months before screening, hepatic disease based on liver tests, or serious or unstable medical or psychiatric condition
Author, year: Fazlalizadeh, 2008[147] **Country:** Iran	**Study design:** Double-blind randomised clinical trial **Date:** 2006–7	• Having at least a 6-month history of migraines with a diagnosis according to ICHD-3 • Having at least 3 migraine attacks per month and lasting for at least 30 minutes	• Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the medications for treatment of migraine • Current use or prior exposure to CGRP antibody
Author, year: Croop, 2021[148] **Country:** 92 sites in USA	**Study design:** Multicentre, randomised, double-blind, placebo-controlled trial **Date:** November 2018–August 2019	• Adults 18 years and older • Subject has at least a 1-year history of migraine (with or without aura) consistent with a diagnosis according to the ICHD-3, including the following: ◦ Age of onset of migraines prior to 50 years of age ◦ Migraine attacks, on average, lasting 4–72 hours if untreated	• History of HIV disease • Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischaemic heart disease, coronary artery vasospasm and cerebral ischaemia. Subjects with MI, ACS, PCI, cardiac surgery, stroke or TIA during the 6 months prior to screening • Uncontrolled hypertension (high blood pressure) or uncontrolled diabetes (however, subjects can be included who have stable hypertension and/or diabetes for at least 3 months prior to screening)
		◦ Per subject report, 4–18 migraine attacks of moderate to severe intensity per month within the last 3 months prior to the screening visit ◦ 6 or more migraine days during the observation period ◦ Not more than 18 headache days during the observation period	• Subjects with major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the screening visit • Subjects with other pain syndromes, psychiatric conditions, dementia or significant neurological disorders (other than migraine) that, in the investigator's opinion, might interfere with study assessments

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		◦ Ability to distinguish migraine attacks from tension/cluster headaches ◦ Subjects on prophylactic migraine medication are permitted to remain on 1 medication with possible migraine prophylactic effects if the dose has been stable for at least 3 months prior to the screening visit, and the dose is not expected to change during the course of the study	• Subject has a history of gastric or small intestinal surgery (including gastric bypass, gastric banding, gastric sleeve, gastric balloon, etc.), or has a disease that causes malabsorption • Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder or borderline personality disorder • History of gallstones or cholecystectomy • The subject has a history or current evidence of any unstable medical conditions (e.g. history of congenital heart disease or arrhythmia, known or suspected infection, hepatitis B or C, or cancer) that, in the investigator's opinion, would expose them to undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial
Author, year: Winner, 2021[149] **Country:** 47 sites in USA and Republic of Georgia	**Study design:** Phase 3, multicentre, parallel-group, double-blind, randomised, placebo-controlled trial **Date:** November 2019–July 2020	• > 1-year history of migraine, with or without aura, with onset of first migraine before age 50 • Migraine on 4–15 days per month in the 3 months prior to screening • Headache-free for at least 24 hours prior to onset of a qualifying migraine • Adults 18–75 years • Diagnosis of migraine based on ICHD-3 criteria for migraine with or without aura	• Use of the following medication, for any indication, within the 24-hour period prior to dosing with study drug: ◦ Triptans, ergotamines and ergot-derivatives, analgesics and other acute migraine medication(s), antiemetic medications, antihistamines, devices, neuromodulation, neurostimulation, or injectable therapy
			• Use of the following medication, for any indication, in each of the 3 months prior to screening: ◦ Opioids/narcotics or butalbital containing products (including combinations) on more than 4 days per month ◦ Triptans, ergotamines or combination analgesics for 10 or more days per month ◦ Acetaminophen, aspirin or NSAIDs for 15 or more days per month (except if participant is taking 81 mg dose of aspirin for cardiac prophylaxis) • History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache or unusual migraine subtypes that are not typical of migraine aura • Any use of approved devices, neuromodulation, neurostimulation, or injectable therapy within the 24-hour period prior to treatment with study drug (Day 0) • Any use of botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections within 7 days prior to treatment with study drug (Day 0)

TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
			• Any use of systemic corticosteroid for migraine or any other reason within 3 months prior to treatment with study drug (Day 0) • History of clinically significant psychiatric diseases • Receipt of any monoclonal antibody treatment, for migraine or any other indication, within 6 months prior to screening
Author, year: Hu, 2022[150] **Country:** 40 centres in China (*n* = 26), India (*n* = 10) and Russia (*n* = 4)	**Study design:** Phase 3, randomised, double-blind, placebo-controlled study **Date:** July 2019–March 2022	• Participants must have a diagnosis of migraine as defined by ICHD-3 with a history of migraine of at least 1 year prior to screening and migraine onset prior to age 50 • Prior to screening, participants must have a history of 4–14 migraine headache days and at least 2 migraine attacks per month on average within the past 3 months	• Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study • Current use or prior exposure to galcanezumab or another CGRP antibody, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antibody
		• Adults 18–65 years	• Participants who are taking, or are expected to take, therapeutic antibodies during the course of the study (e.g. adalimumab, infliximab, trastuzumab, bevacizumab, etc.) • Known hypersensitivity to multiple drugs, MAbs or other therapeutic proteins, or to galcanezumab • Women who are pregnant or nursing • History of chronic migraine, daily persistent headache, cluster headache, medication overuse headache, migraine with brainstem aura or hemiplegic migraine
Author, year: Ashina, 2022[151] **Country:** 96 study locations across Europe (*n* = 93) and USA (*n* = 3)	**Study design:** Multicentre, multi-arm, double-blind, placebo-controlled **Date:** June 2020–October 2021	• Diagnosis of migraine, with a history of chronic or episodic migraines of at least 12 months prior to the screening visit • History of migraine onset of ≤ 50 years of age • The participant has ≥ 4 migraine days per month for each month within the past 3 months prior to the screening visit • The participant has demonstrated compliance with the headache eDiary by entry of data for at least 24 of the 28 days following the screening visit	• History of failure on a previous treatment targeting the CGRP pathway • Participant has a treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion. The medication is regarded as the latest if the medication start date is after the start date of the other preventive medications and the medication stop date is after the stop date of the other preventive medications • Participant has confounding and clinically significant pain syndromes • History of acute or active temporomandibular disorder

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TABLE 50 More details on baseline characteristics of the included studies for AEs review (*continued*)

First author, year/country	Study design and date	Key inclusion criteria	Key exclusion criteria
		• The participant fulfils the following criteria for CM or EM in prospectively collected information in the eDiary during the screening period: • For CM participants: Migraine occurring on ≥ 8 days and headache occurring on > 14 days	• History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache or unusual migraine subtypes such as hemiplegic migraine, ophthalmoplegic migraine and migraine with neurological accompaniments that are not typical of migraine aura
		• For EM participants: Migraine occurring on ≥ 4 days and headache occurring on ≤ 14 days • Participant has documented evidence of treatment failure (must be supported by medical record or by physician's confirmation specific to each treatment) in the past 10 years of 2–4 different migraine preventive medications • Participant has a history of either previous or active use of triptans for migraine	• Participant has a psychiatric condition • Participants with a lifetime history of psychosis and/or mania in the last 5 years prior to the screening visit are excluded • History of clinically significant cardiovascular disease or vascular ischaemia or thromboembolic events

ACS, acute coronary syndrome; BDI, Beck Depression Inventory; ECG, electrocardiogram; IHS, International Headache Society; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; TENS, transcutaneous electrical stimulation; TIA, transient ischaemic attack; TMD, temporomandibular disorder; ULN, upper limit of the normal.

Appendix 5 Further results for adverse events

TABLE 51 Classification of AEs by SOC

SOC	AEs
Cardiac disorders	Acute myocardial infarction, atrial fibrillation, syncope
Ear and labyrinth disorders	Labyrinthitis, sudden hearing loss, vertigo, vestibular neuronitis
Eye disorders	Angle closure glaucoma, diplopia, optic neuritis, retinal detachment, rhegmatogenous retinal detachment
Gastrointestinal disorders	Abdominal pain, alcoholic pancreatitis, appendicitis, diverticulitis, oesophagitis, gastric ulcer haemorrhage, gastritis, haemorrhoids, intestinal haemorrhage, irritable bowel syndrome, mechanical ileus, obstructive defaecation, pancreatitis, pancreatitis acute, parotitis, small intestinal obstruction, vomiting
General disorders and administration site conditions	Abdominal adhesions, asthenia, chest pain, oedema peripheral, malaise, nasal septum deviation, non-cardiac chest pain, tooth impacted, vocal cord thickening
Hepatobiliary disorders	Cholecystitis, cholecystitis acute, cholelithiasis, common bile duct stone
Immune system disorders	Anaphylactic reaction, anaphylactic shock, hypersensitivity
Infections and infestations	Acute pyelonephritis, bacterial pharyngitis, bacteriuria, clostridium difficile colitis, COVID-19 pneumonia, gastroenteritis, gastrointestinal infection, infected dermal cyst, influenza, kidney infection, nasopharyngitis, papilloma viral infection, parasitic gastroenteritis, pyelonephritis, pyrexia, sepsis, tonsillitis, urinary tract infection, viral gastroenteritis, viral infection
Injury	Accident, ankle fracture, brain contusion, cartilage injury, clavicle fracture, concussion, contusion, fall, foot fracture, hand fracture, humerus fracture, injury, ligament rupture, limb injury, lower limb fracture, meniscus injury, radius fracture, respiratory fume inhalation, rib fracture, road traffic accident, skin laceration, sternal fracture, tendon injury, thoracic vertebral fracture, traumatic orbital fracture, ulna fracture, wrist fracture
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatraemia
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, Behçet syndrome, costochondritis, flank pain, intervertebral disc protrusion, osteoarthritis, periarthritis, post-traumatic neck syndrome
Neoplasms: benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of the cervix, brain neoplasm, breast cancer, colon cancer, fibroma, gall bladder polyp, ovarian cyst, polycystic ovaries, rectal polyp, ruptured ovarian cyst, uterine leiomyoma, breast neoplasm, fibroadenoma of breast, malignant melanoma, neoplasm malignant, vulval cancer
Nervous system disorders	Cerebellar syndrome, cerebral venous thrombosis, cervical radiculopathy, hypoaesthesia, lumbar spinal stenosis, migraine, migraine aggravated, migraine with aura, nervous system disorders, neuropathy, seizure, speech disorder, transient ischaemic attack
Neurological	Spinal pain
Poisoning and procedural complications	Overdose, intentional overdose
Pregnancy, puerperium and perinatal conditions	Pregnancy
Psychiatric disorders	Confusional state, depression, disorientation, major depression, psychogenic seizure, suicidal ideation, suicide attempt

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TABLE 51 Classification of AEs by SOC (*continued*)

SOC	AEs
Psychiatry	Panic attack
Renal and urinary disorders	Bladder dysfunction, calculus urinary, nephrolithiasis, renal calculus, renal colic, urinary incontinence
Reproductive system and breast disorders	Cervical dysplasia, dysmenorrhoea, endometriosis, menorrhagia, menstrual disorder and vaginal haemorrhage, metrorrhagia, ovarian disorder, spontaneous abortion, threatened abortion
Respiratory, thoracic and mediastinal	Asthma, chronic obstructive pulmonary disease, COPD and apnoea related to COPD, dyspnoea, epistaxis, pneumonia, post-surgical laryngospasm with hypoxic brain injury
Skin and subcutaneous tissue disorders	Erythema nodosum
Vascular disorders	Hypertensive crisis, orthostatic hypotension, peripheral vascular disease, pulmonary embolism

COPD, chronic obstructive pulmonary disease.

Note
Adverse events in bold font were not found in the CTCAE Version 5.0; thus the best respective categories were chosen by clinical consensus.

TABLE 52 Arm level data on AEs and treatment-related AEs (%)

Study ID	Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs	AEs definition
666	Hu	2022	Galcanezumab 120 mg	261	49.8		Standard
666	Hu	2022	Placebo	259	43.2		Standard
555	Ashina	2022	Eptinezumab 100 mg	299	42	3	Standard
555	Ashina	2022	Eptinezumab 300 mg	294	41	1	Standard
555	Ashina	2022	Placebo	298	40	3	Standard
158	Sakai	2021	Fremanezumab-M	188	61.7	29.3	Standard
158	Sakai	2021	Fremanezumab-Q	190	61.1	32.1	Standard
158	Sakai	2021	Placebo	191	61.8	28.3	Standard
8	Ailani	2021	Atogepant 10 mg	221	52.9	23.1	Standard
8	Ailani	2021	Atogepant 30 mg	228	52.2	14.9	Standard
8	Ailani	2021	Atogepant 60 mg	231	53.7	19.5	Standard
8	Ailani	2021	Placebo	222	56.8	9	Standard
157	Sakai	2021	Fremanezumab-M	121	57	26.4	Standard
157	Sakai	2021	Fremanezumab-Q	118	62.7	31.4	Standard
157	Sakai	2021	Placebo	117	65.8	23.9	Standard
197	Reuter	2021	Erenumab 140 mg	388		55.4	Standard
197	Reuter	2021	Topiramate 100 mg	388		81.2	Standard
203	Wang	2021	Erenumab 70 mg	335	34.9	11.3	Standard
203	Wang	2021	Erenumab 140 mg	224	34.4	10.7	Standard

TABLE 52 Arm level data on AEs and treatment-related AEs (%) (*continued*)

Study ID	Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs	AEs definition
203	Wang	2021	Placebo	335	36.7	9.6	Standard
777	Winner	2021	Eptinezumab 100 mg	238	10.9		Standard
777	Winner	2021	Placebo	242	10.3		Standard
105	Lipton	2020	Eptinezumab 100 mg	356	43.5		Standard
105	Lipton	2020	Eptinezumab 300 mg	350	52		Standard
105	Lipton	2020	Placebo	366	46.7		Standard
19	Ashina	2020	Eptinezumab 30 mg	219	58.4		Standard
19	Ashina	2020	Eptinezumab 100 mg	223	63.2		Standard
19	Ashina	2020	Eptinezumab 300 mg	224	57.6		Standard
19	Ashina	2020	Placebo	222	59.5		Standard
156	Sakai	2020	Galcanezumab 120 mg	115	85.2		Standard
156	Sakai	2020	Galcanezumab 240 mg	114	81.6		Standard
156	Sakai	2020	Placebo	230	64.8		Standard
221	Mulleners	2020	Galcanezumab 120 mg	232	51	15	Standard
221	Mulleners	2020	Placebo	230	53	16	Standard
888	Croop	2020	Rimegepant 75 mg	370	36	11	Standard
888	Croop	2020	Placebo	371	36	9	Standard
61	Dodick	2019	Eptinezumab 100 mg	122	57.5	19.8	Standard
61	Dodick	2019	Eptinezumab 300 mg	121	63.6	17.4	Standard
61	Dodick	2019	Eptinezumab 30 mg	122	45.9	14.8	Standard
61	Dodick	2019	Eptinezumab 10 mg	130	56.9	16.2	Standard
61	Dodick	2019	Placebo	121	56.2	14	Standard
217	Ferrari	2019	Fremanezumab-Q	276	55	21	Standard
217	Ferrari	2019	Fremanezumab-M	285	45	19	Standard
217	Ferrari	2019	Placebo	277	48	20	Standard
148	Rothrock	2019	BTA 150U	220	48	17	Standard
148	Rothrock	2019	Topiramate 100 mg	142	79	70	Standard
49	Detke	2018	Galcanezumab 120 mg	273	58		Standard
49	Detke	2018	Galcanezumab 240 mg	282	57		Standard
49	Detke	2018	Placebo	558	50		Standard
45	Dodick	2018	Erenumab 70 mg	283	48.1		Standard
45	Dodick	2018	Placebo	289	54.7		Standard
60	Dodick	2018	Fremanezumab-M	290	66.2	47.6	Standard
60	Dodick	2018	Fremanezumab-Q	291	66.3	47.1	Standard
60	Dodick	2018	Placebo	293	58.4	37.2	Standard

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TABLE 52 Arm level data on AEs and treatment-related AEs (%) (*continued*)

Study ID	Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs	AEs definition
181	Stauffer	2018	Galcanezumab 120 mg	206	65.5		Standard
181	Stauffer	2018	Galcanezumab 240 mg	220	67.7		Standard
181	Stauffer	2018	Placebo	432	60.4		Standard
201	Vladimir	2018	Galcanezumab 120 mg	226	65		Standard
201	Vladimir	2018	Galcanezumab 240 mg	228	71.5		Standard
201	Vladimir	2018	Placebo	461	62.3		Standard
196	Reuter	2018	Erenumab 140 mg	119	55		Standard
196	Reuter	2018	Placebo	124	54		Standard
173	Silberstein	2017	Fremanezumab-Q	376	70	49	Standard
173	Silberstein	2017	Fremanezumab-M	379	71	51	Standard
173	Silberstein	2017	Placebo	375	64	42	Standard
185	Tepper	2017	Erenumab 70 mg	190	44		Standard
185	Tepper	2017	Erenumab 140 mg	188	47		Standard
185	Tepper	2017	Placebo	282	39		Standard
77	Goadsby	2017	Erenumab 70 mg	314	57.3		Standard
77	Goadsby	2017	Erenumab 140 mg	319	55.5		Standard
77	Goadsby	2017	Placebo	319	63		Standard
88	Hong Sun	2016	Erenumab 7 mg	108	50		Standard
88	Hong Sun	2016	Erenumab 21 mg	105	51		Standard
88	Hong Sun	2016	Erenumab 70 mg	106	54		Standard
88	Hong Sun	2016	Placebo	153	54		Standard
44	Dodick	2014	Galcanezumab 150 mg	107	72		Standard
44	Dodick	2014	Placebo	110	67		Standard
94	Kalita	2013	Divalproate 250–1000 mg	143	47.6		No definition
94	Kalita	2013	Amitriptyline 50 mg	144	56.3		No definition
41	Couch	2011	Amitriptyline 100 mg	194	57.2		No definition
41	Couch	2011	Placebo	197	26.9		No definition
143	Lipton	2011	Topiramate 100 mg	176	82.4		No definition
143	Lipton	2011	Placebo	185	73.5		No definition
59	Dodick	2010	BTA 150U	687	62.4	29.4	Standard
59	Dodick	2010	Placebo	692	51.7	12.7	Standard
47	Dodick	2009	Topiramate 100 mg	177	85.9	68.4	Standard

TABLE 52 Arm level data on AEs and treatment-related AEs (%) (*continued*)

Study ID	Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs	AEs definition
47	Dodick	2009	Amitriptyline 100 mg	169	88.8	75.7	Standard
999	Fazlalizadeh	2008	Topiramate 100 mg	284	14.4		No definition
999	Fazlalizadeh	2008	Sodium valproate 200 mg	285	14		No definition
170	Silberstein	2007	Topiramate 100 mg	160	82.5		Standard
170	Silberstein	2007	Placebo	161	70.2		Standard
111	M Relja	2007	BTA 225U	129	76.7	67.4	No definition
111	M Relja	2007	BTA 150U	125	77.6	63.2	No definition
111	M Relja	2007	BTA 75U	123	77.2	62.6	No definition
111	M Relja	2007	Placebo	118	54.2	31.4	No definition
215	Diener	2007	Topiramate 200 mg	254	68		No definition
215	Diener	2007	Placebo	258	59		No definition
21	Aurora	2006	BTA 105 to 260U	187	81.3	60.4	No definition
21	Aurora	2006	Placebo	182	59.9	21.4	No definition
216	Elkind (study1)	2006	BTA 7U	105	49.5	6.7	No definition
216	Elkind (study1)	2006	BTA 25U	101	46.5	21.8	No definition
216	Elkind (study1)	2006	BTA 50U	106	56.6	30.2	No definition
216	Elkind (study1)	2006	Placebo	106	47.2	6.6	No definition
216	Elkind (study2)	2006	BTA 25U	173	77.2	29.4	No definition
216	Elkind (study2)	2006	BTA 50U	180	78	24.9	No definition
216	Elkind (study3)	2006	BTA 25U	50	70		No definition
216	Elkind (study3)	2006	BTA 50U	51	68.8		No definition
216	Elkind (study3)	2006	Placebo	100	60		No definition
53	Diener	2002	Flunarizine 5 mg	263	33.5		No definition

continued

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TABLE 52 Arm level data on AEs and treatment-related AEs (%) (*continued*)

Study ID	Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs	AEs definition
53	Diener	2002	Flunarizine 10 mg	275	32		No definition
53	Diener	2002	Propranolol 160 mg	270	32.6		No definition
109	Lucking	1988	Flunarizine 10 mg	160	24.6		No definition
109	Lucking	1988	Propranolol 40 mg	170	29.6		No definition

TABLE 53 Details for investigations of SOC (%)

Study ID	Author(s)	Year of publication	Intervention	Participants	Weight increase	Weight decrease	Increased blood creatine kinase level	Blood creatinine phosphokinase increased	INR increased	Alanine aminotransferase > 3 × ULN	Aspartate aminotransferase ≥ 3× ULN	Total bilirubin ≥ 2× ULN
666	Hu	2022	Galcanezumab 120 mg	261				1.5			1.9	
666	Hu	2022	Placebo	259				0			0	
555	Ashina	2022	Eptinezumab 100 mg	299				1.5				
555	Ashina	2022	Eptinezumab 300 mg	294				0				
555	Ashina	2022	Placebo	298								
8	Ailani	2021	Atogepant 10 mg	221			2.3			1.4		
8	Ailani	2021	Atogepant 30 mg	228			0.9			0.9		
8	Ailani	2021	Atogepant 60 mg	231			3			0.9		
8	Ailani	2021	Placebo	222			0.9			2.7		
197	Reuter	2021	Erenumab 140 mg	388		0.8						
197	Reuter	2021	Topiramate 100 mg	388		5.7						
217	Ferrari	2019	Fremanezumab-Q	276					1			
217	Ferrari	2019	Fremanezumab-M	285					0.5			
217	Ferrari	2019	Placebo	277					0.5			
181	Stauffer	2018	Galcanezumab 120 mg	206	1.9							
181	Stauffer	2018	Galcanezumab 240 mg	220	0.9							
181	Stauffer	2018	Placebo	432	1.4							

continued

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TABLE 53 Details for investigations of SOC (%) (*continued*)

Study ID	Author(s)	Year of publication	Intervention	Participants	Weight increase	Weight decrease	Increased blood creatine kinase level	Blood creatinine phosphokinase increased	INR increased	Alanine aminotransferase > 3 × ULN	Aspartate aminotransferase ≥ 3× ULN	Total bilirubin ≥ 2× ULN
173	Silberstein	2017	Fremanezumab-Q	376						0.26	0.26	0.6
173	Silberstein	2017	Fremanezumab-M	379						0.26	0.26	0
173	Silberstein	2017	Placebo	375						0	0	0
94	Kalita	2013	Divalproate 250–1000 mg	143	61.7							
94	Kalita	2013	Amitriptyline 50 mg	144	58.7							
41	Couch	2011	Amitriptyline 100 mg	194	1.5							
41	Couch	2011	Placebo	197	1.01							
47	Dodick	2009	Topiramate 100 mg	177	0							
47	Dodick	2009	Amitriptyline 100 mg	169	13.6							
215	Diener	2007	Topiramate 200 mg	254		9						
215	Diener	2007	Placebo	258		7						
53	Diener	2002	Flunarizine 5 mg	263	9.9							
53	Diener	2002	Flunarizine 10 mg	275	5.6							
53	Diener	2002	Propranolol 160 mg	270	2.6							

Fremanezumab-Q, fremanezumab quarterly; Fremanezumab-M, fremanezumab monthly.

TABLE 54 Details for injury, poisoning and procedural complications of SOC (%)

Study ID	First author	Year of publication	Intervention	Participants	Ecchymosis	Injury	Contusion
181	Stauffer	2018	Galcanezumab 120 mg	206			2.4
181	Stauffer	2018	Galcanezumab 240 mg	220			0
181	Stauffer	2018	Placebo	432			1.2
143	Lipton	2011	Topiramate 100 mg	176		1.7	
143	Lipton	2011	Placebo	185		9.2	
170	Silberstein	2007	Topiramate 100 mg	160		5	
170	Silberstein	2007	Placebo	161		1.2	
21	Aurora	2006	BTA 105–260U	187	1.1		
21	Aurora	2006	Placebo	182	1.6		
53	Diener	2002	Flunarizine 5 mg	263		1.9	
53	Diener	2002	Flunarizine 10 mg	275		1.5	
53	Diener	2002	Propranolol 160 mg	270		2.6	

TABLE 55 Details for metabolism and nutrition disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Anorexia	Decreased appetite
197	Reuter	2021	Erenumab 140 mg	388		2.1
197	Reuter	2021	Topiramate 100 mg	388		9
148	Rothrock	2019	BTA 150U	220		0
148	Rothrock	2019	Topiramate 100 mg	142		11
143	Lipton	2011	Topiramate 100 mg	176	8.5	
143	Lipton	2011	Placebo	185	2.7	
47	Dodick	2009	Topiramate 100 mg	177	6.8	
47	Dodick	2009	Amitriptyline 100 mg	169	4.7	
170	Silberstein	2007	Topiramate 100 mg	160	5	
170	Silberstein	2007	Placebo	161	5.6	
215	Diener	2007	Topiramate 200 mg	254		5
215	Diener	2007	Placebo	258		3

TABLE 56 Details for reproductive system and breast disorders of SOC (%)

Study ID	Author(s)	Year of publication	Intervention	Participants	Menstrual irregularity	Dysmenorrhoea
181	Stauffer	2018	Galcanezumab 120 mg	206		0.6
181	Stauffer	2018	Galcanezumab 240 mg	220		2.2
181	Stauffer	2018	Placebo	432		0.6
94	Kalita	2013	Divalproate 250–1000 mg	143	4.8	
94	Kalita	2013	Amitriptyline 50 mg	144	0	

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TABLE 57 Details for skin and subcutaneous of SOC (%)

Study ID	Author(s)	Year of publication	Intervention	Participants	Eczema	Urticaria	Pruritus	Hair fall	Skin tightness	Rash	Alopecia	Sweat discoloration
666	Hu	2022	Galcanezumab 120 mg	261			1.5					
666	Hu	2022	Placebo	259			0.8					
157	Sakai	2021	Fremanezumab-M	121	2.5							
157	Sakai	2021	Fremanezumab-Q	118	0.8							
157	Sakai	2021	Placebo	117	0							
156	Sakai	2020	Galcanezumab 120 mg	115		1.7						
156	Sakai	2020	Galcanezumab 240 mg	114		6.1						
156	Sakai	2020	Placebo	230		0						
217	Ferrari	2019	Fremanezumab-Q	276						0.5	0.5	
217	Ferrari	2019	Fremanezumab-M	285						1	0.5	
217	Ferrari	2019	Placebo	277						0.5	0.5	
181	Stauffer	2018	Galcanezumab 120 mg	206			1					
181	Stauffer	2018	Galcanezumab 240 mg	220			2.7					
181	Stauffer	2018	Placebo	432			0.2					
44	Dodick	2014	Galcanezumab 150 mg	107						5		
44	Dodick	2014	Placebo	110						0		
94	Kalita	2013	Divalproate 250–1000 mg	143				38.5				
94	Kalita	2013	Amitriptyline 50 mg	144				1.4				
41	Couch	2011	Amitriptyline 100 mg	194						0.5		3.1
41	Couch	2011	Placebo	197						1.5		2.5
21	Aurora	2006	BTA 105–260U	187					7.5			
21	Aurora	2006	Placebo	182					0.5			

Fremanezumab-Q, fremanezumab quarterly; Fremanezumab-M, fremanezumab monthly.

TABLE 58 Details for eye disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Belpharotosis	Abnormal vision	Visual disturbance	Vision blurred	Eyelid oedema
148	Rothrock	2019	BTA 150U	220				3	
148	Rothrock	2019	Topiramate 100 mg	142				8	
44	Dodick	2014	Galcanezumab 150 mg	107			3		
44	Dodick	2014	Placebo	110			2		
41	Couch	2011	Amitriptyline 100 mg	194			2.1		
41	Couch	2011	Placebo	197			2.5		
59	Dodick	2010	BTA 150U	687					3.3
59	Dodick	2010	Placebo	692					0.3
47	Dodick	2009	Topiramate 100 mg	177		5.1			
47	Dodick	2009	Amitriptyline 100 mg	169		5.3			
21	Aurora	2006	BTA 105–260U	187	15.5				6.4
21	Aurora	2006	Placebo	182	1.6				0
216	Elkind (study1)	2006	BTA 7U	105	1.9				1
216	Elkind (study1)	2006	BTA 25U	101	5				0
216	Elkind (study1)	2006	BTA 50U	106	7.6				6.6
216	Elkind (study1)	2006	Placebo	106	0				0
216	Elkind (study2)	2006	BTA 25U	173	4				
216	Elkind (study2)	2006	BTA 50U	180	8.9				
216	Elkind (study3)	2006	BTA 25U	50	0				
216	Elkind (study3)	2006	BTA 50U	51	5.9				
216	Elkind (study3)	2006	Placebo	100	0				

TABLE 59 Details for renal and urinary disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Urinary retention	Protein urine present
666	Hu	2022	Galcanezumab 120 mg	261		2.3
666	Hu	2022	Placebo	259		1.5
41	Couch	2011	Amitriptyline 100 mg	194	3.1	
41	Couch	2011	Placebo	197	0	

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TABLE 60 Details for vascular disorders and cardiac disorders of SOC (%)

				Vascular disorders			Cardiac disorders
ID	Author	Year	Intervention	Participants	Hypotension	Hypertension	Tachycardia
217	Ferrari	2019	Fremanezumab quarterly	276		1	
217	Ferrari	2019	Fremanezumab monthly	285		0.5	
217	Ferrari	2019	Placebo	277		0.5	
77	Goadsby	2017	Erenumab 70 mg	314		1.6	
77	Goadsby	2017	Erenumab 140 mg	319		0	
77	Goadsby	2017	Placebo	319		2.5	
44	Dodick	2014	Galcanezumab 150 mg	107		5	
44	Dodick	2014	Placebo	110		0	
216	Elkind (study 3)	2006	BTA 25U	50		2	
216	Elkind (study 3)	2006	BTA 50U	51		2	
216	Elkind (study 3)	2006	Placebo	100		5	
53	Diener	2002	Flunarizine 5 mg	263	1.1		
53	Diener	2002	Flunarizine 10 mg	275	1.1		
53	Diener	2002	Propranolol 160 mg	270	1.5		
41	Couch	2011	Amitriptyline 100 mg	194			3.6
41	Couch	2011	Placebo	197			3

TABLE 61 Details for respiratory, thoracic and mediastinal disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Nasal congestion	Bronchitis	Rhinitis	Sinus congestion	Cough	Asthma
158	Sakai	2021	Fremanezumab-M	188						1.1
158	Sakai	2021	Fremanezumab-Q	190						2.1
158	Sakai	2021	Placebo	191						0
8	Ailani	2021	Atogepant 10 mg	221				0.5		
8	Ailani	2021	Atogepant 30 mg	228				0.9		
8	Ailani	2021	Atogepant 60 mg	231				1.7		
8	Ailani	2021	Placebo	222				2.3		
19	Ashina	2020	Eptinezumab 30 mg	219		2.3			<1	
19	Ashina	2020	Eptinezumab 100 mg	223		2.7			3.6	
19	Ashina	2020	Eptinezumab 300 mg	224		3.1			2.7	
19	Ashina	2020	Placebo	222		3.6			3.2	
221	Mulleners	2020	Galcanezumab 120 mg	232		1				

TABLE 61 Details for respiratory, thoracic and mediastinal disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Nasal congestion	Bronchitis	Rhinitis	Sinus congestion	Cough	Asthma
221	Mulleners	2020	Placebo	230		2				
61	Dodick	2019	Eptinezumab 100 mg	122		3.3				
61	Dodick	2019	Eptinezumab 300 mg	121		3.3				
61	Dodick	2019	Eptinezumab 30 mg	122		3.3				
61	Dodick	2019	Eptinezumab 10 mg	130		3.1				
61	Dodick	2019	Placebo	121		7.4				
60	Dodick	2018	Fremanezumab-M	290		21				
60	Dodick	2018	Fremanezumab-Q	291		1.4				
60	Dodick	2018	Placebo	293		1				
181	Stauffer	2018	Galcanezumab 120 mg	206	0.5	1.5			1.9	
181	Stauffer	2018	Galcanezumab 240 mg	220	2.3	3.2			2.7	
181	Stauffer	2018	Placebo	432	0.9	1.4			1.6	
88	Hong Sun	2016	Erenumab 7 mg	108					2	
88	Hong Sun	2016	Erenumab 21 mg	105					1	
88	Hong Sun	2016	Erenumab 70 mg	106					0	
88	Hong Sun	2016	Placebo	153					2	
47	Dodick	2009	Topiramate 100 mg	177					5.1	
47	Dodick	2009	Amitriptyline 100 mg	169					4.1	
216	Elkind (study2)	2006	BTA 25U	173		3.5				
216	Elkind (study2)	2006	BTA 50U	180		5.6				
216	Elkind (study3)	2006	BTA 25U	50		2				
216	Elkind (study3)	2006	BTA 50U	51		3.9				
216	Elkind (study3)	2006	Placebo	100		7				
53	Diener	2002	Flunarizine 5 mg	263			1.5			
53	Diener	2002	Flunarizine 10 mg	275			2.2			
53	Diener	2002	Propranolol 160 mg	270			2.2			

Fremanezumab-Q, fremanezumab quarterly; Fremanezumab-M, fremanezumab monthly.

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TABLE 62 Details for gastrointestinal disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
666	Hu	2022	Galcanezumab 120 mg	261			1.9	1.5													
666	Hu	2022	Placebo	259			0.8	2.3													
555	Ashina	2022	Eptinezumab 100 mg	299				0					2		1						
555	Ashina	2022	Eptinezumab 300 mg	294				2					1		2						
555	Ashina	2022	Placebo	298				2					1		1						
158	Sakai	2021	Fremanezumab-M	188				1.6							1.1						
158	Sakai	2021	Fremanezumab-Q	190				2.1							2.6						
158	Sakai	2021	Placebo	191				0							1						
8	Ailani	2021	Atogepant 10 mg	221											5		7.7				
8	Ailani	2021	Atogepant 30 mg	228											4.4		7				
8	Ailani	2021	Atogepant 60 mg	231											6.1		6.9				
8	Ailani	2021	Placebo	222											1.8		0.5				
157	Sakai	2021	Fremanezumab-M	121				0					0.8		0.8						
157	Sakai	2021	Fremanezumab-Q	118				2.5					2.5		0						
157	Sakai	2021	Placebo	117				0					0		2.6						
197	Reuter	2021	Erenumab 140 mg	388				1.8		2.1			2.8	1.5	6.7		11.3			4.4	
197	Reuter	2021	Topiramate 100 mg	388				4.1		4.6			2.6	2.3	6.7		3.1			5.9	
203	Wang	2021	Erenumab 70 mg	335													5.7				
203	Wang	2021	Erenumab 140 mg	224													5.4				
203	Wang	2021	Placebo	335													1.5				
777	Winner	2021	Eptinezumab 100 mg	238											0						

TABLE 62 Details for gastrointestinal disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
777	Winner	2021	Placebo	242											0.8						
105	Lipton	2020	Eptinezumab 100 mg	356											1.7						
105	Lipton	2020	Eptinezumab 300 mg	350											3.4						
105	Lipton	2020	Placebo	366											1.9						
19	Ashina	2020	Eptinezumab 30 mg	219				1.8							4.1						
19	Ashina	2020	Eptinezumab 100 mg	223				1.3							2.2						
19	Ashina	2020	Eptinezumab 300 mg	224				3.6							2.2						
19	Ashina	2020	Placebo	222				1.4							3.6						
221	Mulleners	2020	Galcanezumab 120 mg	232		1					1				2		2			2	
221	Mulleners	2020	Placebo	230		2					2				2		2			0.004	
888	Croop	2020	Rimegepant 75 mg	370											3						
888	Croop	2020	Placebo	371											1						
61	Dodick	2019	Eptinezumab 100 mg	122											7.4						
61	Dodick	2019	Eptinezumab 300 mg	121											6.6						
61	Dodick	2019	Eptinezumab 30 mg	122											3.3						
61	Dodick	2019	Eptinezumab 10 mg	130											4.6						

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TABLE 62 Details for gastrointestinal disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
61	Dodick	2019	Placebo	121											7.4						
217	Ferrari	2019	Fremanezumab-Q	276				3					1		1		3				
217	Ferrari	2019	Fremanezumab-M	285				0.5					0.5		0.5		0.5				
217	Ferrari	2019	Placebo	277				1					0		2		0.5				
148	Rothrock	2019	BTA 150U	220											0.5						
148	Rothrock	2019	Topiramate 100 mg	142											13						
49	Detke	2018	Galcanezumab 120 mg	273	2	1		1			1										
49	Detke	2018	Galcanezumab 240 mg	282	1	2		2			2										
49	Detke	2018	Placebo	558	2	1		1			1										
45	Dodick	2018	Erenumab 70 mg	283											2.5		1.4				
45	Dodick	2018	Placebo	289											4.5		2.1				
60	Dodick	2018	Fremanezumab-M	290											1.4						
60	Dodick	2018	Fremanezumab-Q	291											2.4						
60	Dodick	2018	Placebo	293											1.7						
181	Stauffer	2018	Galcanezumab 120 mg	206		1.9					1.9				2.4					1	
181	Stauffer	2018	Galcanezumab 240 mg	220		1.4					1.4				3.6					1.8	
181	Stauffer	2018	Placebo	432		0.7					0.7				3.5					0.5	
201	Vladimir	2018	Galcanezumab 120 mg	226				3.1													

TABLE 62 Details for gastrointestinal disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
201	Vladimir	2018	Galcanezumab 240 mg	228				1.3													
201	Vladimir	2018	Placebo	461				2.4													
173	Silberstein	2017	Fremanezumab-Q	376											1						
173	Silberstein	2017	Fremanezumab-M	379											2						
173	Silberstein	2017	Placebo	375											3						
185	Tepper	2017	Erenumab 70 mg	190											2		0				
185	Tepper	2017	Erenumab 140 mg	188											3		4				
185	Tepper	2017	Placebo	282											2		0.5				
77	Goadsby	2017	Erenumab 70 mg	314											2.2		1.6				
77	Goadsby	2017	Erenumab 140 mg	319											1.9		3.4				
77	Goadsby	2017	Placebo	319											1.9		1.3				
88	Hong Sun	2016	Erenumab 7 mg	108				0							3						
88	Hong Sun	2016	Erenumab 21 mg	105				1							1						
88	Hong Sun	2016	Erenumab 70 mg	106				1							3						
88	Hong Sun	2016	Placebo	153				3							1						
44	Dodick	2014	Galcanezumab 150 mg	107	6							4			4						
44	Dodick	2014	Placebo	110	3							1			9						
94	Kalita	2013	Divalproate 250–1000 mg	143						9.1					1.8			0	12.6		2.1

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TABLE 62 Details for gastrointestinal disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
94	Kalita	2013	Amitriptyline 50 mg	144						56.5					1.1			0.7	8.3		3.6
41	Couch	2011	Amitriptyline 100 mg	194											2.1	35	11.8				
41	Couch	2011	Placebo	197											1.5	7.2	4.1				
143	Lipton	2011	Topiramate 100 mg	176				6.3		6.8					10.8						
143	Lipton	2011	Placebo	185				3.2		2.7					9.2						
47	Dodick	2009	Topiramate 100 mg	177						6.8				5.1	10.2		3.4				
47	Dodick	2009	Amitriptyline 100 mg	169						35.5				8.3	7.1		8.3				
170	Silberstein	2007	Topiramate 100 mg	160						9.4					8.8						
170	Silberstein	2007	Placebo	161						3.1					8.1						
215	Diener	2007	Topiramate 200 mg	254	2										4						
215	Diener	2007	Placebo	258	2										4						
53	Diener	2002	Flunarizine 5 mg	263	1.1										13						
53	Diener	2002	Flunarizine 10 mg	275	1.5										17						
53	Diener	2002	Propranolol 160 mg	270	1.9										8						
109	Lucking	1988	Flunarizine 10 mg	160															7.1	5.2	
109	Lucking	1988	Propranolol 40 mg	170															9.8	7.2	

TABLE 63 Details for psychiatric disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Anxiety	Agitation	Sleep disorder	Nervousness	Insomnia	Mood swings	Irritability	Confusion	Depressed mood	Depression
197	Reuter	2021	Erenumab 140 mg	388			4.1		1.5	2.1	1.3		0.3	1.5
197	Reuter	2021	Topiramate 100 mg	388			1.5		2.6	4.1	4.6		3.6	4.1
221	Mulleners	2020	Galcanezumab 120 mg	232					2					
221	Mulleners	2020	Placebo	230					0					
217	Ferrari	2019	Fremanezumab-Q	276	1				2					
217	Ferrari	2019	Fremanezumab-M	285	0.5				2					
217	Ferrari	2019	Placebo	277	0				0.5					
148	Rothrock	2019	BTA 150U	220										2
148	Rothrock	2019	Topiramate 100 mg	142										6
41	Couch	2011	Amitriptyline 100 mg	194		7.2		5.2	3.6					2.1
41	Couch	2011	Placebo	197		4.1		8.12	7.1					1
143	Lipton	2011	Topiramate 100 mg	176								5.7		
143	Lipton	2011	Placebo	185								1.6		
215	Diener	2007	Topiramate 200 mg	254										5
215	Diener	2007	Placebo	258										5
53	Diener	2002	Flunarizine 5 mg	263										2.7
53	Diener	2002	Flunarizine 10 mg	275										0.7
53	Diener	2002	Propranolol 160 mg	270										1.9

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TABLE 64 Details for musculoskeletal and connective tissue disorders of SOC (%)

Study ID	Author	Year of publication	Intervention	Participants	Muscular weakness	Muscle spasms	Muscle tightness	Myalgia	Musculoskeletal stiffness	Back pain	Musculoskeletal pain	Arthralgia	Neck pain	Arm pain
555	Ashina	2022	Eptinezumab 100 mg	299						2		2		
555	Ashina	2022	Eptinezumab 300 mg	294						1		1		
555	Ashina	2022	Placebo	298						1		0		
158	Sakai	2021	Fremanezumab-M	188						2.7				
158	Sakai	2021	Fremanezumab-Q	190						0.5				
158	Sakai	2021	Placebo	191						0.5				
157	Sakai	2021	Fremanezumab-M	121							0			
157	Sakai	2021	Fremanezumab-Q	118							2.5			
157	Sakai	2021	Placebo	117							0			
777	Winner	2021	Eptinezumab 100 mg	238						0				
777	Winner	2021	Placebo	242						0.8				
19	Ashina	2020	Eptinezumab 30 mg	219						1.8				
19	Ashina	2020	Eptinezumab 100 mg	223						3.1				
19	Ashina	2020	Eptinezumab 300 mg	224						1.3				
19	Ashina	2020	Placebo	222						3.2				
221	Mulleners	2020	Galcanezumab 120 mg	232						3				
221	Mulleners	2020	Placebo	230						2				
217	Ferrari	2019	Fremanezumab-Q	276						2		0.5	0.5	

TABLE 64 Details for musculoskeletal and connective tissue disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Muscular weakness	Muscle spasms	Muscle tightness	Myalgia	Musculoskeletal stiffness	Back pain	Musculoskeletal pain	Arthralgia	Neck pain	Arm pain
217	Ferrari	2019	Fremanezumab-M	285						0.5		0.5	1	
217	Ferrari	2019	Placebo	277						2		1	0	
148	Rothrock	2019	BTA 150U	220									4	
148	Rothrock	2019	Topiramate 100 mg	142									2	
49	Detke	2018	Galcanezumab 120 mg	273						3		0	3	
49	Detke	2018	Galcanezumab 240 mg	282						1		2	0	
49	Detke	2018	Placebo	558						3		1	1	
181	Stauffer	2018	Galcanezumab 120 mg	206						2.4			1.5	
181	Stauffer	2018	Galcanezumab 240 mg	220						3.2			1.8	
181	Stauffer	2018	Placebo	432						1.4			0.9	
196	Reuter	2018	Erenumab 140 mg	119						4			3	
196	Reuter	2018	Placebo	124						2			0	
185	Tepper	2017	Erenumab 70 mg	190		< 1								
185	Tepper	2017	Erenumab 140 mg	188		4								
185	Tepper	2017	Placebo	282		1								
77	Goadsby	2017	Erenumab 70 mg	314						1.9		2.2		
77	Goadsby	2017	Erenumab 140 mg	319						1.9		2.2		
77	Goadsby	2017	Placebo	319						2.2		1.9		
88	Hong Sun	2016	Erenumab 7 mg	108			0			3		1		
88	Hong Sun	2016	Erenumab 21 mg	105			0					0		

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TABLE 64 Details for musculoskeletal and connective tissue disorders of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Participants	Muscular weakness	Muscle spasms	Muscle tightness	Myalgia	Musculoskeletal stiffness	Back pain	Musculoskeletal pain	Arthralgia	Neck pain	Arm pain
88	Hong Sun	2016	Erenumab 70 mg	106			0					1		
88	Hong Sun	2016	Placebo	153			2					3		
44	Dodick	2014	Galcanezumab 150 mg	107						7		6	4	
44	Dodick	2014	Placebo	110						7		6	2	
143	Lipton	2011	Topiramate 100 mg	176						5.7				
143	Lipton	2011	Placebo	185						5.4				
59	Dodick	2010	BTA 150U	687	5.5			2.6	2.3		2.2		6.7	
59	Dodick	2010	Placebo	692	0.3			0.3	0.7		0.7		2.2	
21	Aurora	2006	BTA 105–260U	187	26.2					1.6			17.1	7.5
21	Aurora	2006	Placebo	182	1.1					0.5			4.4	1.1

Fremanezumab-Q, fremanezumab quarterly; Fremanezumab-M, fremanezumab monthly.

TABLE 65 Details for nervous system disorders of SOC (%)

ID	Author	Year	Intervention	Partici-pants	Neck rigidity	Dyses-thesia	Paraes-thesia	Hyper-tonia	Hypoe-sthesia	Difficulty with memory	Difficulty with conce-ntration	Taste perversion	Mig-raine	Diz-ziness	Aphasia	Dys-geusia	Cognitive disorder	Head-ache	Somn-olence	Drows-iness	Facial paralysis
666	Hu	2022	Galcanezumab 120 mg	261										3.4							
666	Hu	2022	Placebo	259										2.3							
555	Ashina	2022	Eptinezumab 100 mg	299										1							
555	Ashina	2022	Eptinezumab 300 mg	294										1							
555	Ashina	2022	Placebo	298										2							
8	Ailani	2021	Atogepant 10 mg	221															3.2		
8	Ailani	2021	Atogepant 30 mg	228															1.8		
8	Ailani	2021	Atogepant 60 mg	231															1.7		
8	Ailani	2021	Placebo	222															0.9		
157	Sakai	2021	Fremanezumab-M	121									0	0				1.7			
157	Sakai	2021	Fremanezumab-Q	118									0	0.8				1.7			
157	Sakai	2021	Placebo	117									2.6	2.6				3.4			
197	Reuter	2021	Erenumab 140 mg	388		0.5	4.4		0.5	0.3	4.6	0		5.2	0.5	0.8		0.5			
197	Reuter	2021	Topiramate 100 mg	388		2.1	39.9		3.4	2.6	16.2	6.2		13.1	2.8	5.7		2.1			
203	Wang	2021	Erenumab 70 mg	335										0.9							
203	Wang	2021	Erenumab 140 mg	224										3.1							
203	Wang	2021	Placebo	335										1.8							
105	Lipton	2020	Eptinezumab 100 mg	356									1.7								
105	Lipton	2020	Eptinezumab 300 mg	350									2.3								

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TABLE 65 Details for nervous system disorders of SOC (%) (*continued*)

ID	Author	Year	Intervention	Partici-pants	Neck rigidity	Dyses-thesia	Paraes-thesia	Hyper-tonia	Hypoe-sthesia	Difficulty with memory	Difficulty with conce-ntration	Taste perversion	Mig-raine	Diz-ziness	Aphasia	Dys-geusia	Cognitive disorder	Head-ache	Somn-olence	Drows-iness	Facial paralysis
105	Lipton	2020	Placebo	366									4.4								
19	Ashina	2020	Eptinezumab 30 mg	219										3.7							
19	Ashina	2020	Eptinezumab 100 mg	223										4.5							
19	Ashina	2020	Eptinezumab 300 mg	224										1.8							
19	Ashina	2020	Placebo	222										3.6							
221	Mulleners	2020	Galcanezumab 120 mg	232									2								
221	Mulleners	2020	Placebo	230									0								
61	Dodick	2019	Eptinezumab 100 mg	122									5.7	9.8							
61	Dodick	2019	Eptinezumab 300 mg	121									0.8	1.7							
61	Dodick	2019	Eptinezumab 30 mg	122									2.5	2.5							
61	Dodick	2019	Eptinezumab 10 mg	130									1.5	8.5							
61	Dodick	2019	Placebo	121									1.7	7.4							
217	Ferrari	2019	Fremanezumab-Q	276									0.5	2							
217	Ferrari	2019	Fremanezumab-M	285									1	1							
217	Ferrari	2019	Placebo	277									3	1							
148	Rothrock	2019	BTA 150U	220			0.5				0		3	3			5				
148	Rothrock	2019	Topiramate 100 mg	142			31				8		2	13			13				
49	Detke	2018	Galcanezumab 120 mg	273									2								

TABLE 65 Details for nervous system disorders of SOC (%) (*continued*)

ID	Author	Year	Intervention	Participants	Neck rigidity	Dysesthesia	Paraesthesia	Hypertonia	Hypoesthesia	Difficulty with memory	Difficulty with concentration	Taste perversion	Migraine	Dizziness	Aphasia	Dysgeusia	Cognitive disorder	Headache	Somnolence	Drowsiness	Facial paralysis
49	Detke	2018	Galcanezumab 240 mg	282									1								
49	Detke	2018	Placebo	558									1								
45	Dodick	2018	Erenumab 70 mg	283									2.1								
45	Dodick	2018	Placebo	289									2.8								
181	Stauffer	2018	Galcanezumab 120 mg	206									1	2.6							
181	Stauffer	2018	Galcanezumab 240 mg	220									2.3	2.3							
181	Stauffer	2018	Placebo	432									0.9	2.6							
201	Vladimir	2018	Galcanezumab 120 mg	226										3.5							
201	Vladimir	2018	Galcanezumab 240 mg	228										3.1							
201	Vladimir	2018	Placebo	461										2.2							
196	Reuter	2018	Erenumab 140 mg	119										3							
196	Reuter	2018	Placebo	124										2							
173	Silberstein	2017	Fremanezumab-Q	376										2							
173	Silberstein	2017	Fremanezumab-M	379										3							
173	Silberstein	2017	Placebo	375										1							
185	Tepper	2017	Erenumab 70 mg	190									2								
185	Tepper	2017	Erenumab 140 mg	188									3								
185	Tepper	2017	Placebo	282									1								
77	Goadsby	2017	Erenumab 70 mg	314									1.3								
77	Goadsby	2017	Erenumab 140 mg	319									0.9								

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TABLE 65 Details for nervous system disorders of SOC (%) (*continued*)

ID	Author	Year	Intervention	Participants	Neck rigidity	Dysesthesia	Paraesthesia	Hypertonia	Hypoesthesia	Difficulty with memory	Difficulty with concentration	Taste perversion	Migraine	Dizziness	Aphasia	Dysgeusia	Cognitive disorder	Headache	Somnolence	Drowsiness	Facial paralysis
77	Goadsby	2017	Placebo	319									3.1								
88	Hong Sun	2016	Erenumab 7 mg	108									1					4			
88	Hong Sun	2016	Erenumab 21 mg	105									3					1			
88	Hong Sun	2016	Erenumab 70 mg	106									3					3			
88	Hong Sun	2016	Placebo	153									1					1			
44	Dodick	2014	Galcanezumab 150 mg	107										5							
44	Dodick	2014	Placebo	110										3							
94	Kalita	2013	Divalproate 250–1000 mg	143																4.9	
94	Kalita	2013	Amitriptyline 50 mg	144																47.3	
41	Couch	2011	Amitriptyline 100 mg	194			1.5							10.1					27.3		
41	Couch	2011	Placebo	197			1							5.6					8.6		
143	Lipton	2011	Topiramate 100 mg	176			32.4		6.8			9.7		11.4					5.1		
143	Lipton	2011	Placebo	185			0.7		2.7			1.6		7.6					1.6		
59	Dodick	2010	BTA 150U	687														2.9			
59	Dodick	2010	Placebo	692														1.6			
47	Dodick	2009	Topiramate 100 mg	177			29.9		10.7		6.8	5.6		8.5				5.1	11.9		
47	Dodick	2009	Amitriptyline 100 mg	169			4.7		3.6		3	3.6		10.7				0	17.8		
170	Silberstein	2007	Topiramate 100 mg	160			28.8		9.4	6.9	9.4	9.4		3.8					5.6		
170	Silberstein	2007	Placebo	161			7.5		0	6.2	2.5	2.5		7.5					4.3		
215	Diener	2007	Topiramate 200 mg	254			30				4			0.7		3					

TABLE 65 Details for nervous system disorders of SOC (%) (*continued*)

ID	Author	Year	Intervention	Partici-pants	Neck rigidity	Dyses-thesia	Paraes-thesia	Hyper-tonia	Hypoe-sthesia	Difficulty with memory	Difficulty with conce-ntration	Taste perversion	Mig-raine	Diz-ziness	Aphasia	Dys-geusia	Cognitive disorder	Head-ache	Somn-olence	Drows-iness	Facial paralysis
215	Diener	2007	Placebo	258			21				5			0.7		4					
21	Aurora	2006	BTA 105 to 260U	187	10.2		2.1	7	3.7				3.2	2.1				5.9			1.6
21	Aurora	2006	Placebo	182	3.3		0	1.1	1.6				0.5	0				4.9			0
216	Elkind (study 1)	2006	BTA 7U	105														1			
216	Elkind (study 1)	2006	BTA 25U	101														2			
216	Elkind (study 1)	2006	BTA 50U	106														7.6			
216	Elkind (study 1)	2006	Placebo	106														1.9			
216	Elkind (study 2)	2006	BTA 25U	173										1.2				4.6			
216	Elkind (study 2)	2006	BTA 50U	180										5				5.6			
216	Elkind (study 3)	2006	BTA 25U	50										0							
216	Elkind (study 3)	2006	BTA 50U	51										5.9							
216	Elkind (study 3)	2006	Placebo	100										0							
53	Diener	2002	Flunarizine 5 mg	263										1.5					1.9		
53	Diener	2002	Flunarizine 10 mg	275										1.1					2.5		
53	Diener	2002	Propranolol 160 mg	270										3.3					0.7		
109	Lucking	1988	Flunarizine 10 mg	160					2.4												
109	Lucking	1988	Propranolol 40 mg	170					2.2												

Fremanezumab-Q, fremanezumab quarterly; Fremanezumab-M, fremanezumab monthly.

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TABLE 66 Details for infection and infestation of SOC (%)

Study ID	Author	Year of publication	Intervention	Partic-ipants	Infe-ction	Nasoph-aryngitis	Sinus infection	Sinus-itis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influ-enza	Pyrexia	COVID-19	Viral infection	Viral gastr-oenteritis	Flu syndrome	Gastroe-nteritis
666	Hu	2022	Galcanezumab 120 mg	261		2.7			5.4				2.3					
666	Hu	2022	Placebo	259		3.5			5				1.2					
555	Ashina	2022	Eptinezumab 100 mg	299		2				0.33				7				
555	Ashina	2022	Eptinezumab 300 mg	294		3				2				6				
555	Ashina	2022	Placebo	298		1				1				5				
158	Sakai	2021	Fremanezumab-M	188		16.6					0	2.1						
158	Sakai	2021	Fremanezumab-Q	190		21.1					2.5	1.1						
158	Sakai	2021	Placebo	191		18.8					1	1.6						
8	Ailani	2021	Atogepant 10 mg	221		1.8		1.8	4.1	1.4		1.4						0.9
8	Ailani	2021	Atogepant 30 mg	228		3.5		1.3	5.7	3.9		0.9						2.2
8	Ailani	2021	Atogepant 60 mg	231		3.5		2.2	3.9	3.9		2.2						1.3
8	Ailani	2021	Placebo	222		3.6		1.4	4.5	3.6		0.9						1.8
157	Sakai	2021	Fremanezumab-M	121		14						5						
157	Sakai	2021	Fremanezumab-Q	118		12.7						1.7						
157	Sakai	2021	Placebo	117		13.7						0.9						
203	Wang	2021	Erenumab 70 mg	335		0.6			2.7				3					
203	Wang	2021	Erenumab 140 mg	224		3.6			1.8				2.2					
203	Wang	2021	Placebo	335		2.4			2.1				4.5					
777	Winner	2021	Eptinezumab 100 mg	238					0.8			0.8						
777	Winner	2021	Placebo	242					0.8			0.8						
105	Lipton	2020	Eptinezumab 100 mg	356		5.3		2	4.2	2.2								

TABLE 66 Details for infection and infestation of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Partic-ipants	Infe-ction	Nasoph-aryngitis	Sinus infection	Sinus-itis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influ-enza	Pyrexia	COVID-19	Viral infection	Viral gastr-oenteritis	Flu syndrome	Gastroe-nteritis
105	Lipton	2020	Eptinezumab 300 mg	350		9.4		2.6	5.4	3.4								
105	Lipton	2020	Placebo	366		6		4.1	5.5	1.6								
19	Ashina	2020	Eptinezumab 30 mg	219		6.4		3.2	11.4			1.4						
19	Ashina	2020	Eptinezumab 100 mg	223		7.6		2.7	9.9			1.8						
19	Ashina	2020	Eptinezumab 300 mg	224		6.3		4.9	10.3			3.6						
19	Ashina	2020	Placebo	222		5.4		6.3	7.2			2.3						
156	Sakai	2020	Galcanezumab 120 mg	115								7.8						
156	Sakai	2020	Galcanezumab 240 mg	114								0.9						
156	Sakai	2020	Placebo	230								1.3						
221	Mulleners	2020	Galcanezumab 120 mg	232		9		2	2	2		3						1
221	Mulleners	2020	Placebo	230		7		2	2	1		5						2
888	Croop	2020	Rimegepant 75 mg	370		4			2	2								
888	Croop	2020	Placebo	371		2			3	2								
61	Dodick	2019	Eptinezumab 100 mg	122		6.6		2.5	6.6									
61	Dodick	2019	Eptinezumab 300 mg	121		7.4		6.6	10.7									
61	Dodick	2019	Eptinezumab 30 mg	122		2.5		4.9	5.7									

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TABLE 66 Details for infection and infestation of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Partic-ipants	Infe-ction	Nasoph-aryngitis	Sinus infection	Sinus-itis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influ-enza	Pyrexia	COVID-19	Viral infection	Viral gastr-oenteritis	Flu syndrome	Gastroe-nteritis
61	Dodick	2019	Eptinezumab 10 mg	130		4.6		6.2	6.9									
61	Dodick	2019	Placebo	121		5		5	5									
217	Ferrari	2019	Fremanezumab-Q	276		5			1	1		0.5						1
217	Ferrari	2019	Fremanezumab-M	285		2			3	1		2						1
217	Ferrari	2019	Placebo	277		4			1	2		0.5						3
148	Rothrock	2019	BTA 150U	220				6										
148	Rothrock	2019	Topiramate 100 mg	142				7										
49	Detke	2018	Galcanezumab 120 mg	273		6		1	3	2		2	2					
49	Detke	2018	Galcanezumab 240 mg	282		3		3	3	1		1	0					
49	Detke	2018	Placebo	558		5		1	2	1		1	2					
45	Dodick	2018	Erenumab 70 mg	283		5.3		2.1	6.4			3.9						
45	Dodick	2018	Placebo	289		5.9		2.1	4.8			3.5						
60	Dodick	2018	Fremanezumab-M	290		3.8		1.4	5.5	2.4								
60	Dodick	2018	Fremanezumab-Q	291		3.8		0.7	3.8	3.4								
60	Dodick	2018	Placebo	293		3.1		2.7	5.1	1.4								
181	Stauffer	2018	Galcanezumab 120 mg	206		7.8		4.6		3.9		2.4						
181	Stauffer	2018	Galcanezumab 240 mg	220		2.7		3.6		5.9		1.8						
181	Stauffer	2018	Placebo	432		6.3		3		3.5		1.2						
201	Vladimir	2018	Galcanezumab 120 mg	226		8.4			5.8			1.3						
201	Vladimir	2018	Galcanezumab 240 mg	228		7			5.3			4.4						

TABLE 66 Details for infection and infestation of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Partic-ipants	Infe-ction	Nasoph-aryngitis	Sinus infection	Sinus-itis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influ-enza	Pyrexia	COVID-19	Viral infection	Viral gastr-oenteritis	Flu syndrome	Gastroe-nteritis
201	Vladimir	2018	Placebo	461		8.9			3.5			3						
196	Reuter	2018	Erenumab 140 mg	119		4			3									
196	Reuter	2018	Placebo	124		10			0									
173	Silberstein	2017	Fremanezumab-Q	376		5		3	5									
173	Silberstein	2017	Fremanezumab-M	379		4		1	4									
173	Silberstein	2017	Placebo	375		5		3	4									
185	Tepper	2017	Erenumab 70 mg	190		3			3									
185	Tepper	2017	Erenumab 140 mg	188		2			3									
185	Tepper	2017	Placebo	282		6			1									
77	Goadsby	2017	Erenumab 70 mg	314		9.9		2.2	6.7	1.6		1.3						
77	Goadsby	2017	Erenumab 140 mg	319		11		3.4	4.7	2.2		2.5						
77	Goadsby	2017	Placebo	319		10		2.2	5.6	2.2		1.9						
88	Hong Sun	2016	Erenumab 7 mg	108		9			1			1						
88	Hong Sun	2016	Erenumab 21 mg	105		5			2			4						
88	Hong Sun	2016	Erenumab 70 mg	106		6			3			1						
88	Hong Sun	2016	Placebo	153		8			2			3						
44	Dodick	2014	Galcanezumab 150 mg	107		4		3	17							2		
44	Dodick	2014	Placebo	110		7		5	9							4		
94	Kalita	2013	Divalproate 250–1000 mg	143						1.5								
94	Kalita	2013	Amitriptyline 50 mg	144						1.1								
143	Lipton	2011	Topiramate 100 mg	176				9.1	9.1						9.7			
143	Lipton	2011	Placebo	185				8.1	6.5						9.2			

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TABLE 66 Details for infection and infestation of SOC (%) (*continued*)

Study ID	Author	Year of publication	Intervention	Partic-ipants	Infe-ction	Nasoph-aryngitis	Sinus infection	Sinus-itis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influ-enza	Pyrexia	COVID-19	Viral infection	Viral gastr-oenteritis	Flu syndrome	Gastroe-nteritis
47	Dodick	2009	Topiramate 100 mg	177				7.9	7.9						7.9			
47	Dodick	2009	Amitriptyline 100 mg	169				10.7	6.5						6.5			
170	Silberstein	2007	Topiramate 100 mg	160				4.4	13.8									
170	Silberstein	2007	Placebo	161				5	12.4									
216	Elkind (study 1)	2006	BTA 7U	105			3.8		11.4								10.5	
216	Elkind (study 1)	2006	BTA 25U	101			6.9		9.9								4	
216	Elkind (study 1)	2006	BTA 50U	106			3.8		10.4								6.6	
216	Elkind (study 1)	2006	Placebo	106			2.8		11.3								8.5	
216	Elkind (study 2)	2006	BTA 25U	173	11.6		9.2		8.1								6.9	
216	Elkind (study 2)	2006	BTA 50U	180	8.3		8.3		6.7								7.8	
216	Elkind (study 3)	2006	BTA 25U	50	6		4		12								4	
216	Elkind (study 3)	2006	BTA 50U	51	5.9		7.8		15.7								5.9	
216	Elkind (study 3)	2006	Placebo	100	3		4		9								7	
53	Diener	2002	Flunarizine 5 mg	263											4.5			
53	Diener	2002	Flunarizine 10 mg	275											6.5			
53	Diener	2002	Propranolol 160 mg	270														

Fremanezumab-Q, fremanezumab quarterly; Fremanezumab-M, fremanezumab monthly.

TABLE 67 Details for general disorders and administration site condition of SOC (%)

Study ID	Author	Year	Inte-rvention	Partic-ipants	Influenza-like illness	I-S pain	I-S reac-tion	I-S haemor-rhage	Pain	Pain in extre-mity	I-S rash	I-S paraes-thesia	I-S bruis-ing	Infusion-S extra-vasation	I-S discol-oration	I-S disco-mfort	I-S indura-tion	I-S warmth	I-S pruri-tus	I-S oed-ema	I-S eryt-hema	I-S swell-ing	Asth-enia	Fati-gue	Non-cardiac chest pain	I-S hyper-sensitivity	I-S haema-toma
666	Hu	2022	GAL 120	261		7.3	3.8									2.3			5		1.9						
666	Hu	2022	PBO	259		6.2	0.4									0			0		0						
555	Ashina	2022	EPT 100	299																				1			
555	Ashina	2022	EPT 300	294																				2			
555	Ashina	2022	PBO	298																				1			
158	Sakai	2021	FRE-M	188		7.4	29.3										17.6		5.3		15.4						
158	Sakai	2021	FRE-Q	190		12.6	26.8										12.1		1.6		12.1						
158	Sakai	2021	PBO	191		8.9	25.1										12.6		2.6		11						
8	Ailani	2021	ATO 10	221																				1.4			
8	Ailani	2021	ATO 30	228																				3.1			
8	Ailani	2021	ATO 60	231																				3.9			
8	Ailani	2021	PBO	222																				1.8			
157	Sakai	2021	FRE-M	121		9.1	25.6	0.8									14.9		5.8		15.7	3.3					
157	Sakai	2021	FRE-Q	118		13.6	29.7	3.4									11.9		1.7		11.9	1.7					
157	Sakai	2021	PBO	117		6	21.4	0.9									10.3		0		12.8	0					
197	Reuter	2021	ERE 140	388																				9.8			
197	Reuter	2021	TOP 100	388																				17.3			
203	Wang	2021	ERE 70	335																	1.2						
203	Wang	2021	ERE 140	224																	0.4						
203	Wang	2021	PBO	335																	2.4						
777	Winner	2021	EPT 100	238										0.8												2.1	
777	Winner	2021	PBO	242										0.8												0	
105	Lipton	2020	EPT 100	356																				2.2			
105	Lipton	2020	EPT 300	350																				1.7			

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TABLE 67 Details for general disorders and administration site condition of SOC (%) (*continued*)

Study ID	Author	Year	Inte-rvention	Partic-ipants	Influenza-like illness	I-S pain	I-S reac-tion	I-S haemor-rhage	Pain	Pain in extre-mity	I-S rash	I-S paraes-thesia	I-S bruis-ing	Infusion-S extra-vasation	I-S discol-oration	I-S disco-mfort	I-S indura-tion	I-S warmth	I-S pruri-tus	I-S oed-ema	I-S eryt-hema	I-S swell-ing	Asth-enia	Fati-gue	Non-cardiac chest pain	I-S hyper-sensitivity	I-S haema-toma
105	Lipton	2020	PBO	366																				1.9			
19	Ashina	2020	EPT 30	219																				2.3			
19	Ashina	2020	EPT 100	223																				3.6			
19	Ashina	2020	EPT 300	224																				3.6			
19	Ashina	2020	PBO	222																				< 1			
156	Sakai	2020	GAL 120	115		6.1													8.7		14.8	10.4					
156	Sakai	2020	GAL 240	114		7													20.2		27.2	10.5					
156	Sakai	2020	PBO	230		1.3													0		2.2	1.3					
221	Mulleners	2020	GAL 120	232		6	3					1	2				2		0	0	3	0					
221	Mulleners	2020	PBO	230		2	0						0						1	1	3			2			0
217	Ferrari	2019	FRE-Q	276		4				0.5	1	1	0.5				4	0.5	1		7		0.5	3			
217	Ferrari	2019	FRE-M	285		3				1	1	1	2				5	1	2		6		1	3			
217	Ferrari	2019	PBO	277		3				1	0.5	1	0.5				4	0	1		5		1	1			
148	Rothrock	2019	BTA 150	220																				0.5			
148	Rothrock	2019	TOP 100	142																				13			
49	Detke	2018	GAL 120	273		6	3												0		1			2			
49	Detke	2018	GAL 240	282		7	5												2		5			2			
49	Detke	2018	PBO	558		4	2												0		1			2			
45	Dodick	2018	ERE 70	283		6																		3.5			
45	Dodick	2018	PBO	289		4.2																		2.1			
60	Dodick	2018	FRE-M	290		30		1									24				17.9			0.7			
60	Dodick	2018	FRE-Q	291		29.6		3.1									19				18.9			2.1			
60	Dodick	2018	PBO	293		25.9		2									15				14			1.4			
181	Stauffer	2018	GAL 120	206		16	3.4						1						4.4		4.9						
181	Stauffer	2018	GAL 240	220		20.5	5.5						1.8						4.6		4.1						

TABLE 67 Details for general disorders and administration site condition of SOC (%) (*continued*)

Study ID	Author	Year	Inte-rvention	Partic-ipants	Influenza-like illness	I-S pain	I-S reac-tion	I-S haemor-rhage	Pain	Pain in extre-mity	I-S rash	I-S paraes-thesia	I-S bruis-ing	Infusion-S extra-vasation	I-S discol-oration	I-S disco-mfort	I-S indura-tion	I-S warmth	I-S pruri-tus	I-S oed-ema	I-S eryt-hema	I-S swell-ing	Asth-enia	Fati-gue	Non-cardiac chest pain	I-S hyper-sensitivity	I-S haema-toma
181	Stauffer	2018	PBO	432		17.4	0.9						1.4						0.2		2.6						
201	Vladimir	2018	GAL 120	226		9.3	3.1												2.7		2.7	2.2		2.7			
201	Vladimir	2018	GAL 240	228		8.8	7.9												3.1		3.1	0.4		2.2			
201	Vladimir	2018	PBO	461		8.5	0												0		0.9	0		2.6			
196	Reuter	2018	ERE 140	119		6															3			3			
196	Reuter	2018	PBO	124		6															3			2			
173	Silberstein	2017	FRE-Q	376		30		2									20				21						
173	Silberstein	2017	FRE-M	379		26		2									24				20						
173	Silberstein	2017	PBO	375		28		3									18				16						
185	Tepper	2017	ERE 70	190		4																					
185	Tepper	2017	ERE 140	188		4																					
185	Tepper	2017	PBO	282		1																					
77	Goadsby	2017	ERE 70	314		3.2																		1.9			
77	Goadsby	2017	ERE 140	319		0.3																		2.2			
77	Goadsby	2017	PBO	319		0.3																		2.5			
88	Hong Sun	2016	ERE 7	108																				5			
88	Hong Sun	2016	ERE 21	105																				2			
88	Hong Sun	2016	ERE 70	106																				4			
88	Hong Sun	2016	PBO	153																				2			
44	Dodick	2014	GAL 150	107		17				4											5						
44	Dodick	2014	PBO	110		6				5											0						
41	Couch	2011	AMI 100	194																			8.2	7.7	1.5		
41	Couch	2011	PBO	197																			4.5	4.1	0.5		
143	Lipton	2011	TOP 100	176																				14.8			

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TABLE 67 Details for general disorders and administration site condition of SOC (%) (*continued*)

Study ID	Author	Year	Inte-rvention	Partic-ipants	Influenza-like illness	I-S pain	I-S reac-tion	I-S haemor-rhage	Pain	Pain in extre-mity	I-S rash	I-S paraes-thesia	I-S bruis-ing	Infusion-S extra-vasation	I-S discol-oration	I-S disco-mfort	I-S indura-tion	I-S warmth	I-S pruri-tus	I-S oed-ema	I-S eryt-hema	I-S swell-ing	Asth-enia	Fati-gue	Non-cardiac chest pain	I-S hyper-sensitivity	I-S haema-toma
143	Lipton	2011	PBO	185																				8.6			
47	Dodick	2009	TOP 100	177																				16.9			
47	Dodick	2009	AMI 100	169																				24.3			
170	Silberstein	2007	TOP 100	160																				11.9			
170	Silberstein	2007	PBO	161																				9.9			
215	Diener	2007	TOP 200	254																				7			
215	Diener	2007	PBO	258																				4			
21	Aurora	2006	BTA 260	187		2.1		0	1.6																		
21	Aurora	2006	PBO	182		0.5		2.2	0																		
216	Elkind (study 2)	2006	BTA 25	173		5.2			7.5																		
216	Elkind (study 2)	2006	BTA 50	180		2.2			7.8																		
216	Elkind (study 3)	2006	BTA 25	50					4																		
216	Elkind (study 3)	2006	BTA 50	51					2																		
216	Elkind (study 3)	2006	PBO	100					5																		
53	Diener	2002	FLU 5	263																				3.8			
53	Diener	2002	FLU 10	275																				1.5			
53	Diener	2002	PRO 160	270																				3.7			
109	Lucking	1988	FLU 10	160																				8.1			
109	Lucking	1988	PRO 40	170																				8.1			

AMI 100, amitriptyline 100 mg; ATO 10, atogepant 10 mg; ATO 30, atogepant 30 mg; ATO 60, atogepant 60 mg; BTA 150, BTA 150U; BTA 260, BTA 105–260U; BTA 25, BTA 25U; BTA 50, BTA 50U; EPT 100, eptinezumab 100 mg; EPT 300, eptinezumab 300 mg; EPT 30, eptinezumab 30 mg; EPT 10, eptinezumab 10 mg; ERE 140, erenumab 140 mg; ERE 70, erenumab 70 mg; ERE 7, erenumab 7 mg; ERE 21, erenumab 21 mg; FLU 5, flunarizine 5 mg; FLU 10, flunarizine 10 mg; FRE-M, fremanezumab monthly; FRE-Q, fremanezumab quarterly; GAL 120, galcanezumab 120 mg; GAL 240, galcanezumab 240 mg; GAL 150, galcanezumab 150 mg; I-S, Injection Site; PBO, placebo; PRO 160, propranolol 160 mg; PRO 40, propranolol 40 mg; TOP 100, topiramate 100 mg; TOP 200, topiramate 200 mg.

TABLE 68 Any AEs reported from 29 trials

Intervention	Dose	Frequency	Total participants	Participants with AEs (%)[a]
Erenumab[36,45,142–144]	140 mg	Monthly	1238	408 (33)
Rimegepant[148]	75 mg	Once daily	370	133 (36)
Topiramate[88,135,142]	100 mg	Twice daily	707	264 (37)
Eptinezumab[89,94,131,149,151]	100 mg	Single dose on day 0	1238	517 (42)
Erenumab[36,45,130,134,144]	70 mg	Monthly	1228	574 (47)
Erenumab[130]	7 mg	Monthly	108	54 (50)
Erenumab[130]	21 mg	Monthly	105	54 (51)
Eptinezumab[89,94,131,149,151]	300 mg	Single dose on day 0	989	509 (51)
Placebo[35–37,45,89–91,94,95,97,126,127,129–131,133,134,140,141,143,144,146,148–151]	–	Matched with active treatments	7569	3831 (51)
Atogepant[129]	30 mg	Once daily	228	119 (52)
Atogepant[129]	10 mg	Once daily	221	117 (53)
Atogepant[129]	60 mg	Once daily	231	124 (54)
Eptinezumab[89,131]	30 mg	Single dose on day 0	341	184 (54)
Eptinezumab[89]	10 mg	Single dose on day 0	130	74 (57)
OnabotulinumtoxinA (BTA)[88,97]	150U	Every 12 weeks	907	534 (59)
Galcanezumab[95,127,140,141,146,150]	120 mg	Monthly	1313	786 (60)
Fremanezumab[35,37,90,91,126]	Monthly (225 mg)	Monthly	1263	774 (61)
Fremanezumab[35,37,90,91,126]	Quarterly (675 mg)	Single dose on day 0	1251	798 (64)
Galcanezumab[95,127,140,141,146]	240 mg	Monthly	844	566 (67)
Galcanezumab[133]	150 mg	Every 2 weeks	107	77 (72)
Amitriptyline[135]	25–100 mg	Twice daily	169	150 (89)

a The treatments are listed in order of increasing AEs percentage.

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TABLE 69 Number of participants with AEs in a series of three sequential studies, evaluating different doses of BTA safety (%)

					Eye disorders (%)		Vascular disorders (%)	Nervous system disorders (%)		Infection and infestation (%)				General disorders and administration site conditions (%)		Respiratory disorders (%)		
Author	Year of publication	Intervention	Dose (units)	Participants	Blepharoptosis	Eyelid oedema	Hypertension	Dizziness	Headache	Infection	Flu syndrome	Sinus infection	Upper respiratory tract infection	Injection site pain	Pain	Bronchitis	Any AEs (%)	Treatment-related AEs (%)
Elkind (study 1)[145]	2006	BTA	7.5U	105	2 (1.9)	1 (1)	0	0	1 (1)	0	11 (10.5)	4 (3.8)	12 (11.4)	0	0	0	52 (49.5)	7 (6.6)
Elkind (study 1)[145]	2006	BTA	25U	101	5 (5)	0	0	0	2 (2)	0	4 (4)	7 (6.9)	10 (9.9)	0	0	0	47 (46.5)	22 (21.78)
Elkind (study 2)[145]	2006	BTA	25U	173	7 (4)	0	0	2	8	20	12	16	14	9	13	6	134	43
Elkind (study 3)[145]	2006	BTA	25U	50	0	0	1 (2)	0	0	3 (6)	2 (4)	2 (4)	6 (12)	0	2 (4)	1 (2)	35 (70)	-
Elkind (study2)[145]	2006	BTA	50U	180	16 (8.9)	0	0	9 (5)	10 (5.6)	15 (8.3)	14 (7.8)	15 (8.3)	12 (6.7)	4 (2.2)	14 (7.8)	10 (5.6)	139 (77.2)	53 (29.44)
Elkind (study 3)[145]	2006	BTA	50U	51	3 (5.9)	0	1 (2)	3 (5.9)	0	3 (5.9)	3 (5.9)	4 (7.8)	8 (15.7)	0	1 (2)	2 (3.9)	35 (68.6)	-
Elkind (study 1)[145]	2006	BTA	50U	106	8 (7.6)	7 (6.6)	0	0	8 (7.6)	0	7 (6.6)	4 (3.8)	11 (10.4)	0	0	0	60 (56.6)	32 (30.18)
Elkind (study 1)[145]	2006	Placebo	-	106	0	0	0	0	2 (1.9)	0	9 (8.5)	3 (2.8)	12 (11.3)	0	0	0	50 (47.2)	7 (6.6)
Elkind (study 3)[145]	2006	Placebo	-	100	0	0	5 (5)	0	0	3 (3)	7 (7)	4 (4)	9 (9)	0	5 (5)	7 (7)	60 (60)	-

TABLE 70 Number of participants with AEs in two studies, evaluating different doses of BTA safety (%)

			Injury (%)	Skin and subcutaneous (%)	Eye disorders (%)		Musculoskeletal and connective tissue disorders (%)				Nervous system disorders (%)						General disorders and injection site condition (%)				Gastrointestinal disorders (%)			
Author	Intervention	Participants	Ecchymosis	Skin tightness	Blepharoptosis	Eyelid oedema	Muscular weakness	Back pain	Neck pain	Arm pain	Neck rigidity	Hypertonia	Hypesthesia	Migraine	Dizziness	Headache	Asthenia	Injection-site pain	Injection site haemorrhage	Pain	Dysphagia	Nausea	Any AEs (%)	Treatment-related AEs (%)
Aurora, 2006[132]	BTA 105 to 260U	187	2 (1)	14 (8)	29 (16)	12 (6)	49 (26)	3 (2)	32 (17)	14 (7)	19 (10)	13 (7)	7 (4)	6 (3)	4 (2)	11 (6)	0	4 (2)	0	3 (2)	0	0	152 (81)	113 (60)
Relja, 2007[138]	BTA 225U	129	0	6 (5)	18 (14)	3 (2)	35 (27)	0	30 (23)	6 (5)	22 (17)	4 (3)	0	1 (1)	2 (2)	2 (2)	5 (4)	3 (2)	0	5 (4)	4 (3)	4 (3)	99 (77)	87 (67)
Relja, 2007[138]	BTA 150U	125	0	9 (7)	12 (10)	0	35 (28)	0	24 (19)	6 (5)	20 (16)	3 (2)	0	3 (2)	3 (2)	5 (4)	3 (2)	9 (7)	2 (2)	3 (2)	3 (2	2 (2)	97 (78)	79 (63)
Relja, 2007[138]	BTA 75U	123	0	7 (6)	3 (2)	2 (2)	30 (2)	0	22 (18)	7 (6)	13 (11)	3 (2)	0	2 (2)	3 (2)	4 (3)	4 (3)	4 (3)	3 (2)	3 (2)	1 (1	1 (1)	95 (77)	77 (63)
Relja, 2007[138]	Placebo	118	0	2 (2)	0	0	2 (2)	0	6 (5)	0	5 (4)	0	0	1 (1)	3 (3)	3 (3)	3 (3)	2 (2)	0	2 (2)	0	1 (1)	64 (54)	37 (31)
Aurora, 2006[132]	Placebo	182	3 (2)	1	3 (2)	0	2 (1)	1	8 (4)	2 (1)	6 (3)	2 (1)	3 (2)	1	0	9 (5)	0	1	4 (2)	0	0	0	109 (60)	39 (21)

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TABLE 71 Number of participants with AEs, evaluating safety of sodium valproate vs. topiramate (%)

Author	Year	Intervention	Dose	Participants	General AEs (%)	Liver AEs (%)	Immunologic AEs (%)	Skin AEs (%)	Any AEs (%)
Fazlalizadeh[147]	2008	Sodium valproate	200 mg	285	19 (6.66)	14 (4.91)	0	7 (2.46)	40 (14%)
Fazlalizadeh[147]	2008	Topiramate	100 mg	284	29 (10.21)	6 (2.11)	6 (2.11)	0	41 (14.4)

TABLE 72 Number of participants with AEs, evaluating safety of amitriptyline vs. divalproate (%)

				Investigations (%)	Reproductive system (%)	Skin and subcutaneous (%)	Gastrointestinal disorders (%)			Ear disorders (%)	Nervous system disorders (%)	
Author	Year	Intervention	Participants	Weight increase	Menstrual irregularity	Hair loss	Dry mouth	Vomiting	Gastrointestinal symptoms	Giddiness	Drowsiness	Any AEs (%)
Kalita[137]	2013	Amitriptyline (12.5– 50 mg)	144	71 (58.7)	0	2 (1.4)	78 (56.5)	1 (0.7)	12 (8.3)	4 (3.6)	69 (47.3)	81 (56.3)
Kalita[137]	2013	Divalproate (250–1000 mg)	143	79 (61.7)	6 (4.8)	55 (38.5)	13 (9.1)	0	18 (12.6)	3 (2.1)	7 (4.9)	68 (47.6)

TABLE 73 Number of participants with AEs, evaluating safety of amitriptyline (%)

			Investigations (%)	Skin and subcutaneous (%)		Gastrointestinal disorders (%)			Eye disorders (%)	Psychiatric disorders (%)				Renal and urinary disorders (%)	Nervous system disorders (%)			Cardiac disorders (%)	General disorders and administration site conditions (%)			Any AEs (%)
Author	Intervention	Participants	Weight increase	Rash	Sweat discoloration	Nausea	Dry mucous membrane	Constipation	Visual disturbance	Agitation	Nervousness	Insomnia	Depression	Urinary retention	Paraesthesia	Dizziness	Somnolence	Tachycardia	Asthenia	Fatigue	Non-cardiac chest pain	
Couch, 2011[22]	Amitriptyline 100 mg	194	3 (1.5)	1(0.5)	6 (3)	4 (2)	68 (35)	23 (11)	4 (2)	14 (7)	10 (5)	7 (3.6)	4 (2)	6 (3)	3 (1.5)	20 (10)	53 (27)	7(3.6)	16 (8)	15 (7.7)	3 (1.5)	111 (57)
Couch, 2011[22]	Placebo	197	2 (1)	3 (1.5)	5 (2.5)	3 (1.5)	14 (7)	8 (4)	5 (2.5)	8 (4)	16 (8)	14 (7)	2 (1)	0	2 (1)	11 (5.5)	17 (8.6)	6 (3)	9 (4.5)	8 (4)	1 (0.5)	53 (27)

TABLE 74 Number of participants with AEs, evaluating safety of propranolol and flunarizine (%)

Author	Intervention	Participants	Investigations (%)	Injury (%)	Gastrointestinal disorders (%)			Psychiatric disorders (%)	Nervous system disorders (%)			General disorders (%)	Vascular disorders (%)	Respiratory disorder (%)	Ear and labyrinth disorders (%)	Any AEs (%)
			Weight increase	Injury	Abdominal pain	Nausea	Gastrointestinal disorders	Depression	Dizziness	Hypoesthesia	Somnolence	Fatigue	Hypotension	Rhinitis	Vertigo	
Lucking, 1998[128]	Propranolol 40 mg	170	8 (3.6)	0	0	0	22 (9.8)	0	0	5 (2.2)	0	18 (8.1)	0	0	16 (7.2)	16 (7.2)
Diener, 2002[136]	Propranolol 160 mg	270	7 (2.6)	7 (2.6)	5 (1.9)	22 (8)	0	5 (1.9)	9 (3.3)	0	2 (0.7)	10	4 (1.5)	6 (2.2)	0	88 (27)
Diener, 2002[136]	Flunarizine 5 mg	263	26 (9.9)	5 (1.9)	3 (1.1)	34 (13)	0	7 (2.7)	4 (1.5)	0	5 (1.9)	10 (3.8)	3 (1.1)	4 (1.5)	0	88 (33.5)
Diener, 2002[136]	Flunarizine 10 mg	275	18 (5.6)	4 (1.5)	4 (1.5)	47 (17)	0	2(0.7)	3 (1.1)	0	7 (2.5)	14 (5.9)	3 (1.1)	6 (2.2)	0	88 (32)
Lucking, 1998[128]	Flunarizine 10 mg	160	6 (2.8)	0	0	0	15 (7.1)	0	0	5 (2.4)	0	17 (8.1)	0	0	11 (5.2)	11 (5.2)

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TABLE 75 Number of participants with AEs, evaluating safety of topiramate (%)

			Investigations (%)	Injury (%)	Gastrointestinal disorders (%)				Psychiatric disorders (%)		Metabolism and nutrition disorders (%)	Musculoskeletal and connective tissue (%) disorders	Nervous system disorders (%)						Infection (%)		General disorders (%)	
Author	Intervention	Participants	Weight decrease	Injury	Diarrhoea	Dry mouth	Nausea	Abdominal pain	Confusion	Depression	Anorexia	Back pain	Paraesthesia	Hypoesthesia	Difficulty with attention	Taste perversion	Dizziness	Somnolence	Sinusitis	Upper respiratory tract infection	Fatigue	Any AEs (%)
Lipton, 2011[139]	Topiramate 100 mg	176	0	3 (2)	11 (6)	12 (7)	19 (11)	0	10 (6)	0	15 (9)	10 (6)	57 (32)	12 (7)	0	17 (10)	20 (11)	9 (5)	16 (9)	16 (9)	26 (15)	145 (82)
Silberstein, 2007[28]	Topiramate 100 mg	160	0	8 (5)	0	15 (9)	14 (8)	0	0	0	8 (5)	0	46 (29)	15 (9)	15 (9	15 (9)	6 (4)	9 (6)	7 (4)	22 (14)	19 (12)	132 (83)
Diener, 2007[152]	Topiramate 200 mg	254	23 (9)	0	0	0	11 (4)	6 (2)	0	13 (5)	13 (5)	0	77 (30)	0	11 (4)	8 (3)	1	0	0	0	18 (7)	173 (68)
Lipton, 2011[139]	Placebo	185	0	17 (9)	6 (3)	5 (3)	17 (9)	0	3 (2)	0	5 (3)	10 (5)	13 (7)	5 (3)	0	3 (2)	14 (8)	3 (2)	15 (8)	12 (7)	16 (9)	136 (74)
Silberstein, 2007[28]	Placebo	161	0	2 (1)	0	5 (3)	13 (8)	0	0		9 (6)	0	12 (8)	0	4 (2.5)	4 (3)	12 (8)	7 (4)	8 (5)	20 (13)	16 (10)	113 (70)
Diener, 2007[152]	Placebo	258	18 (7)	0	0	0	10 (4)	5 (2)	0	13 (5)	8 (3)	0	55 (21)	0	12 (5)	9 (3)	1	0	0	0	10 (4)	151 (59)

Appendix 6 Further results for serious adverse events

TABLE 76 Classification of SAEs by SOC

SOC	SAEs
Cardiac disorders	Acute myocardial infarction, atrial fibrillation, syncope
Ear and labyrinth disorders	Labyrinthitis, sudden hearing loss, vertigo, vestibular neuronitis
Eye disorders	Angle closure glaucoma, diplopia, optic neuritis, retinal detachment, rhegmatogenous retinal detachment
Gastrointestinal disorders	Abdominal pain, alcoholic pancreatitis, appendicitis, diverticulitis, oesophagitis, gastric ulcer haemorrhage, gastritis, haemorrhoids, intestinal haemorrhage, irritable bowel syndrome, mechanical ileus, obstructive defaecation, pancreatitis, pancreatitis acute, parotitis, small intestinal obstruction, vomiting
General disorders and administration site conditions	Abdominal adhesions, asthenia, chest pain, oedema peripheral, malaise, nasal septum deviation, non-cardiac chest pain, tooth impacted, vocal cord thickening
Hepatobiliary disorders	Cholecystitis, cholecystitis acute, cholelithiasis, common bile duct stone
Immune system disorders	Anaphylactic reaction, anaphylactic shock, hypersensitivity
Infections and infestations	Acute pyelonephritis, bacterial pharyngitis, bacteriuria, clostridium difficile colitis, COVID-19 pneumonia, gastroenteritis, gastrointestinal infection, infected dermal cyst, influenza, kidney infection, nasopharyngitis, papilloma viral infection, parasitic gastroenteritis, pyelonephritis, pyrexia, sepsis, tonsillitis, urinary tract infection, viral gastroenteritis, viral infection
Injury	Accident, ankle fracture, brain contusion, cartilage injury, clavicle fracture, concussion, contusion, fall, foot fracture, hand fracture, humerus fracture, injury, ligament rupture, limb injury, lower limb fracture, meniscus injury, radius fracture, respiratory fume inhalation, rib fracture, road traffic accident, skin laceration, sternal fracture, tendon injury, thoracic vertebral fracture, traumatic orbital fracture, ulna fracture, wrist fracture
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatraemia
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, Behçet syndrome, costochondritis, flank pain, intervertebral disc protrusion, osteoarthritis, periarthritis, post-traumatic neck syndrome
Neoplasms: benign, malignant and unspecified (including cysts and polyps)	Adenocarcinoma of the cervix, brain neoplasm, breast cancer, colon cancer, fibroma, gall bladder polyp, ovarian cyst, polycystic ovaries, rectal polyp, ruptured ovarian cyst, uterine leiomyoma, breast neoplasm, fibroadenoma of breast, malignant melanoma, neoplasm malignant, vulval cancer
Nervous system disorders	Cerebellar syndrome, cerebral venous thrombosis, cervical radiculopathy, hypoaesthesia, lumbar spinal stenosis, migraine, migraine aggravated, migraine with aura, nervous system disorders, neuropathy, seizure, speech disorder, transient ischaemic attack
Neurological	Spinal pain
Poisoning and procedural complications	Overdose, intentional overdose
Pregnancy, puerperium and perinatal conditions	Pregnancy

continued

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TABLE 76 Classification of SAEs by SOC (*continued*)

SOC	SAEs
Psychiatric disorders	Confusional state, depression, disorientation, major depression, psychogenic seizure, suicidal ideation, suicide attempt
Psychiatry	Panic attack
Renal and urinary disorders	Bladder dysfunction, calculus urinary, nephrolithiasis, renal calculus, renal colic, urinary incontinence
Reproductive system and breast disorders	Cervical dysplasia, dysmenorrhoea, endometriosis, menorrhagia, menstrual disorder and vaginal haemorrhage, metrorrhagia, ovarian disorder, spontaneous abortion, threatened abortion
Respiratory, thoracic and mediastinal	Asthma, chronic obstructive pulmonary disease, COPD and apnoea related to COPD, dyspnoea, epistaxis, pneumonia, post-surgical laryngospasm with hypoxic brain injury
Skin and subcutaneous tissue disorders	Erythema nodosum
Vascular disorders	Hypertensive crisis, orthostatic hypotension, peripheral vascular disease, pulmonary embolism

COPD, chronic obstructive pulmonary disease.

Note
Serious adverse events in bold font were not found in the CTCAE Version 5.0, and thus were categorised by our clinical team.

TABLE 77 Arm level data on any SAEs and treatment-related SAEs (%)

Study ID	Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death	SAEs definitions
8	Ailani, 2021	Atogepant 10 mg	221	0.9	0.5	0	Standard
8	Ailani, 2021	Atogepant 30 mg	228	0	0	0	Standard
8	Ailani, 2021	Atogepant 60 mg	231	0	0	0	Standard
8	Ailani, 2021	Placebo	222	0.9	0	0	Standard
19	Ashina, 2020	Eptinezumab 100 mg	223	1.79	0	0	Standard
19	Ashina, 2020	Eptinezumab 30 mg	219	1.83	0	0	Standard
19	Ashina, 2020	Eptinezumab 300 mg	224	1.34	0	0	Standard
19	Ashina, 2020	Placebo	222	2.8	0	0	Standard
44	Dodick, 2014	Galcanezumab 150 mg	107	0	–	0	Standard
44	Dodick, 2014	Placebo	110	0.91		0	Standard
45	Dodick, 2018	Erenumab 70 mg	283	1.1	–	0	Standard
45	Dodick, 2018	Placebo	289	1.7	–	0	Standard
47	Dodick, 2009	Amitriptyline 100 mg	169	4.7	0.5	0	Standard
47	Dodick, 2009	Topiramate 100 mg	177	2.3	0	0	Standard
49	Detke, 2018	Galcanezumab 120 mg	273	0.18	–	0	Standard

TABLE 77 Arm level data on any SAEs and treatment-related SAEs (%) (*continued*)

Study ID	Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death	SAEs definitions
49	Detke, 2018	Galcanezumab 240 mg	282	1.8	–	0	Standard
49	Detke, 2018	Placebo	558	0.7	–	0	Standard
53	Diener, 2002	Flunarizine 10 mg	275	1.8	–	0	No definition
53	Diener, 2002	Flunarizine 5 mg	263	0.4	–	0	No definition
53	Diener, 2002	Propranolol 160 mg	270	0.7	–	0	No definition
59	Dodick, 2010	BTA 150U	687	4.8	0.1	0	Standard
59	Dodick, 2010	Placebo	692	2.3	0	0	Standard
60	Dodick, 2018	Fremanezumab-M	289	1	0	0	Standard
60	Dodick, 2018	Fremanezumab-Q	291	1	0	0.3	Standard
60	Dodick, 2018	Placebo	293	2.4	0	0	Standard
61	Dodick, 2019	Eptinezumab 10 mg	130	0.8	0	0	Standard
61	Dodick, 2019	Eptinezumab 100 mg	122	3.3	0	0	Standard
61	Dodick, 2019	Eptinezumab 30 mg	122	0	0	0	Standard
61	Dodick, 2019	Eptinezumab 300 mg	121	5.8	0	0	Standard
61	Dodick, 2019	Placebo	121	0.8	0	0	Standard
77	Goadsby, 2017	Erenumab 140 mg	319	2.51	–	0	Standard
77	Goadsby, 2017	Erenumab 70 mg	314	2.5	–	0	Standard
77	Goadsby, 2017	Placebo	319	2.2	–	0	Standard
88	Hong Sun, 2016	Erenumab 21 mg	105	1	0	0	Standard
88	Hong Sun, 2016	Erenumab 7 mg	108	0	0	0	Standard
88	Hong Sun, 2016	Erenumab 70 mg	106	0	0	0	Standard
88	Hong Sun, 2016	Placebo	153	1	0		Standard
105	Lipton, 2020	Eptinezumab 100 mg	356	0.84	–	0	Standard
105	Lipton, 2020	Eptinezumab 300 mg	350	1.1	–	0	Standard
105	Lipton, 2020	Placebo	366	0.81	–	0	Standard
109	Lucking, 1998	Flunarizine 10 mg	160	0	0	0	No definition
109	Lucking, 1998	Propranolol 40 mg	170	0	0	0	No definition

continued

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TABLE 77 Arm level data on any SAEs and treatment-related SAEs (%) (*continued*)

Study ID	Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death	SAEs definitions
111	Relja, 2007	BTA 150U	125	1.62	–	0	No definition
111	Relja, 2007	BTA 225U	129	1.5	–	0	No definition
111	Relja, 2007	BTA 75U	123	0.81	–	0	No definition
111	Relja, 2007	Placebo	118	1.7	0	0	No definition
143	Lipton, 2011	Placebo	185	2.7	0.5	0	No definition
143	Lipton, 2011	Topiramate 100 mg	176	1.7	1.1	0	No definition
148	Rothrock, 2019	BTA 150U	220	2	0	0	Standard
148	Rothrock, 2019	Topiramate 100 mg	142	4	1	0	Standard
156	Sakai, 2020	Galcanezumab 120 mg	115	2.6	–	0	Standard
156	Sakai, 2020	Galcanezumab 240 mg	114	0.9	–	0	Standard
156	Sakai, 2020	Placebo	230	0	0	0	Standard
157	Sakai, 2021	Fremanezumab-M	121	0	0	0	Standard
157	Sakai, 2021	Fremanezumab-Q	118	0	0	0	Standard
157	Sakai, 2021	Placebo	117	0	0	0	Standard
158	Sakai, 2021	Fremanezumab-M	188	1.6	0	0	Standard
158	Sakai, 2021	Fremanezumab-Q	190	0.5	0	0	Standard
158	Sakai, 2021	Placebo	191	0.5	0	0	Standard
170	Silberstein, 2007	Placebo	161	0	0	0	No definition
170	Silberstein, 2007	Topiramate 100 mg	160	0	0	0	No definition
173	Silberstein, 2017	Fremanezumab-M	379	1.32	0	0	Standard
173	Silberstein, 2017	Fremanezumab-Q	376	0.8		0.26	Standard
173	Silberstein, 2017	Placebo	375	1.6	–	0	Standard
181	Stauffer, 2018	Galcanezumab 120 mg	206	2.91	0	0	Standard
181	Stauffer, 2018	Galcanezumab 240 mg	220	0	0	0	Standard
181	Stauffer, 2018	Placebo	432	1.16	0	0	Standard
185	Tepper, 2017	Erenumab 140 mg	188	1	–	0	Standard

TABLE 77 Arm level data on any SAEs and treatment-related SAEs (%) (*continued*)

Study ID	Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death	SAEs definitions
185	Tepper, 2017	Erenumab 70 mg	190	3	–	0	Standard
185	Tepper, 2017	Placebo	282	2	–	–	Standard
196	Reuter, 2018	Erenumab 140 mg	119	1.68	0	0	Standard
196	Reuter, 2018	Placebo	124	0.8	0	0	Standard
197	Reuter, 2021	Erenumab 140 mg	388	2.58	0.3	0	Standard
197	Reuter, 2021	Topiramate 100 mg	388	4.9	0.5	0	Standard
201	Vladimir, 2018	Galcanezumab 120 mg	226	2.2	–	0	Standard
201	Vladimir, 2018	Galcanezumab 240 mg	228	3.1	–	0	Standard
201	Vladimir, 2018	Placebo	461	1.1	–	0	Standard
203	Wang, 2021	Erenumab 140 mg	224	0	0	0	Standard
203	Wang, 2021	Erenumab 70 mg	335	2.99	0.3	0	Standard
203	Wang, 2021	Placebo	335	1.94	0	0	Standard
215	Diener, 2007	Placebo	258	4	0	0	No definition
215	Diener, 2007	Topiramate 200 mg	254	3	0.39	0	No definition
216	Elkind, 2006 (study 1)	BTA 25U	101	–	0	0	No definition
216	Elkind, 2006 (study 2)	BTA 25U	173	–	0	0	No definition
216	Elkind, 2006 (study 3)	BTA 25U	50	–	0	0	No definition
216	Elkind, 2006 (study 1)	BTA 50U	106	–	0	0	No definition
216	Elkind, 2006 (study 2)	BTA 50U	180	–	0	0	No definition
216	Elkind, 2006 (study 3)	BTA 50U	51	–	0	0	No definition
216	Elkind, 2006 (study 1)	BTA 7U	105	–	0	0	No definition
216	Elkind, 2006 (study 1)	Placebo	106	–	0	0	No definition
216	Elkind, 2006 (study 3)	Placebo	100	–	0	0	No definition
217	Ferrari, 2019	Fremanezumab-M	285	3.86	0	0	Standard
217	Ferrari, 2019	Fremanezumab-Q	276	3.62	0	0	Standard
217	Ferrari, 2019	Placebo	277	1	0	0	Standard
221	Mulleners, 2020	Galcanezumab 120 mg	232	1	–	0	Standard

continued

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TABLE 77 Arm level data on any SAEs and treatment-related SAEs (%) (*continued*)

Study ID	Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death	SAEs definitions
221	Mulleners, 2020	Placebo	230	1	–	0	Standard
555	Ashina, 2022	Eptinezumab 100 mg	299	1.67	0	0	Standard
555	Ashina, 2020	Eptinezumab 300 mg	294	2.38	0.68		Standard
555	Ashina, 2022	Placebo	298	1.34	0	0	Standard
666	Hu, 2022	Galcanezumab 120 mg	261	0.76	–	0	Standard
666	Hu, 2022	Placebo	259	1.54	–	0	Standard
777	Winner, 2021	Eptinezumab 100 mg	238	0	0	0	Standard
777	Winner, 2021	Placebo	242	0	0	0	Standard
888	Croop, 2020	Placebo	371	1	0.26	0	Standard
888	Croop, 2020	Rimegepant 75 mg	370	0.81	0	0	Standard
999	Fazlalizadeh, 2008	Sodium valproate 200 mg	285	–	–	0	No definition
999	Fazlalizadeh, 2008	Topiramate 100 mg	284	–	–	0	No definition

TABLE 78 Details for neoplasms: benign, malignant and unspecified of SOC (%)

Author, year	Interventions	Partici-pants	Breast cancer	Fibroade-noma of breast	Breast neopl-asm	Polycy-stic ovaries	Thyroid adenoma	Vulval cancer	Benign colonic neoplasm	Anal polyp	Uterine leiomy-oma	Gall bladder polyp	Lentigo maligna	Malignant melanoma in situ	Malignant melanoma	Pelvic pain	Squamous cell carcinoma	Papillary thyroid cancer	Ruptured ovarian cyst	Adenocar-cinoma of the cervix	Ovarian cyst	Colon cancer	Rectal polyp	Brain neopl-asm	Fibroma
Hong Sun, 2016	Erenumab 70 mg	106																	0						
Hong Sun, 2016	Erenumab 7 mg	108																	0.1						
Hong Sun, 2016	Erenumab 21 mg	105																	0						
Dodick, 2009	Amitriptyline 100 mg	169			0.6																			0.6	
Dodick, 2010	BTA 150U	687	0.44						0.15		0.3			0.15	0.15		0.15							0.15	
Rothrock, 2019	BTA 150U	220	0.45																						
Dodick, 2019	Eptinezumab 100 mg	122									0.82														
Ashina, 2020	Eptinezumab 300 mg	224	0.45		0.45																				
Dodick, 2019	Eptinezumab 300 mg	121									0.83					0.83									
Tepper, 2017	Erenumab 70 mg	190																							0.53
Goadsby, 2017	Erenumab 70 mg	314																			0.31				
Ferrari, 2019	Fremanezumab-Q	276						0		0.36	0														
Detke, 2018	Galcanezumab 120 mg	273																				0.36			
Vladimir, 2018	Galcanezumab 120 mg	226										0								0.44			0.44		
Croop, 2020	Rimegepant 75 mg	370													0.27										

continued

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TABLE 78 Details for neoplasms: benign, malignant and unspecified of SAEs (%) (*continued*)

Author, year	Interventions	Partici-pants	Breast cancer	Fibroade-noma of breast	Breast neopl-asm	Polycy-stic ovaries	Thyroid adenoma	Vulval cancer	Benign colonic neoplasm	Anal polyp	Uterine leiomy-oma	Gall bladder polyp	Lentigo maligna	Malignant melanoma in situ	Malignant melanoma	Pelvic pain	Squamous cell carcinoma	Papillary thyroid cancer	Ruptured ovarian cyst	Adenocar-cinoma of the cervix	Ovarian cyst	Colon cancer	Rectal polyp	Brain neopl-asm	Fibroma
Reuter, 2021	Topiramate 100 mg	388		0.26																					
Rothrock, 2019	Topiramate 100 mg	142	0.7																						
Sakai, 2021	Placebo	191	0.5																						
Silberstein, 2017	Placebo	375									0.26														
Dodick, 2010	Placebo	692																0.28							
Ferrari, 2019	Placebo	277	0.36				0.36	0.36			0.36														
Ashina, 2020	Placebo	222	0.45																						
Dodick, 2018	Placebo	289									0.3														
Dodick, 2018	Placebo	293											0.34												
Vladimir, 2018	Placebo	461										0.2								0			0		

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 79 Details for nervous system disorders of SOC (%)

Author, year	Interventions	Partici-pants	Migraine with aura	Dizzi-ness	Migraine aggravated	Neuro-pathy	Hypoes-thesia	Intracranial aneurysm	Multiple sclerosis	Optic neuritis	Transient ischaemic attack	Tonic-clonic seizure	Spinal pain	Serotonin syndrome	Migr-aine	Head-ache	Convul-sion	Seizure	Cervical radiculopathy
Hong Sun, 2016	Erenumab 70 mg	106													0.1				
Dodick, 2009	Amitriptyline 100 mg	169			0.6														
Dodick, 2010	BTA 150U	687													0.59		0.15		
Dodick, 2019	Eptinezumab 100 mg	122														0.82			
Ashina, 2022	Eptinezumab 100 mg	299													0			0	0.33
Ashina, 2020	Eptinezumab 300 mg	294													0			0.34	0
Dodick, 2019	Eptinezumab 300 mg	121												0.83			0.83		
Goadsby, 2017	Erenumab 140 mg	319											0.26		0				
Reuter, 2018	Erenumab 140 mg	119													0.84				
Dodick, 2018	Erenumab 70 mg	283													0.4				
Goadsby, 2017	Erenumab 70 mg	314											0		0.31				
Dodick, 2018	Fremanezumab-M	289										0.35							
Ferrari, 2019	Fremanezumab-M	285					0		0.35	0.35									
Ferrari, 2019	Fremanezumab-Q	276					0	0.35											
Vladimir, 2018	Galcanezumab 240 mg	228									0.44				0				
Reuter, 2021	Topiramate 100 mg	388	0												0.26				
Silberstein, 2017	Placebo	375													0.26				

continued

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TABLE 79 Details for nervous system disorders of SAEs (%) (*continued*)

Author, year	Interventions	Partici-pants	Migraine with aura	Dizzi-ness	Migraine aggravated	Neuro-pathy	Hypoes-thesia	Intracranial aneurysm	Multiple sclerosis	Optic neuritis	Transient ischaemic attack	Tonic-clonic seizure	Spinal pain	Serotonin syndrome	Migr-aine	Head-ache	Convul-sion	Seizure	Cervical radiculopathy
Dodick, 2010	Placebo	692													0.28				
Tepper, 2017	Placebo	282													0.35				
Ferrari, 2019	Placebo	277					0.36								0.36				
Ashina, 2020	Placebo	222													0.45				
Dodick, 2018	Placebo	289													0.3				
Dodick, 2018	Placebo	293		0.34											0.34				
Vladimir, 2018	Placebo	461									0				0.2				
Wang, 2021	Placebo	335													0.3				
Ashina, 2022	Placebo	298													0.34			0	0
Lipton, 2011	Placebo					0.5									0.5				

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 80 Details for injury, poisoning and procedural complications of SOC (%) – part 1

Author, year	Interventions	Partici-pants	Respiratory fume inhalation	Seroma	Incarcerated incisional hernia	Foot fracture	Clavicle fracture	Accident	Cartilage injury	Wrist fracture	Ulna fracture	Thoracic vertebral fracture	Lower limb fracture	Injury	Hand fracture	Humerus fracture	Ankle fracture	Traumatic orbital fracture	Meniscus injury	Radius fracture	Fall	Tendon injury	Ankle fracture
Rothrock, 2019	BTA 150U	220						0.45															
Ashina, 2022	Eptinezumab 100 mg	299														0.33							
Tepper, 2017	Erenumab 140 mg	188							0.53														
Goadsby, 2017	Erenumab 140 mg	319																					0.26
Reuter, 2018	Erenumab 140 mg	119																0.84					
Reuter, 2021	Erenumab 140 mg	388																			0.26	0.26	
Silberstein, 2017	Fremanezumab-M	379									0.26									0.26	0.26		
Ferrari, 2019	Fremanezumab-M	285	0.35																				
Silberstein, 2017	Fremanezumab-Q	376								0.26													
Ferrari, 2019	Fremanezumab-Q	276				0.36	0.36																
Dodick, 2018	Fremanezumab-Q	291																				0.34	
Sakai, 2020	Galcanezumab 120 mg	115																	0.9				
Stauffer, 2018	Galcanezumab 120 mg	206		0.49	0.49																		
Vladimir, 2018	Galcanezumab 240 mg	228																	0.44				
Dodick, 2009	Topiramate 100 mg	177												0.5									

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TABLE 80 Details for injury, poisoning and procedural complications of SAEs (%) (*continued*)

Author, year	Interventions	Partici-pants	Respiratory fume inhalation	Seroma	Incarcerated incisional hernia	Foot fracture	Clavicle fracture	Accident	Cartilage injury	Wrist fracture	Ulna fracture	Thoracic vertebral fracture	Lower limb fracture	Injury	Hand fracture	Humerus fracture	Ankle fracture	Traumatic orbital fracture	Meniscus injury	Radius fracture	Fall	Tendon injury	Ankle fracture
Reuter, 2021	Topiramate 100 mg	388															0.26						
Rothrock, 2019	Topiramate 100 mg	142						0.7															
Silberstein, 2017	Placebo	375					0.26	0.26															
Ferrari, 2019	Placebo	277										0.36						0.35					
Dodick, 2018	Placebo	293								0.34											0.34		
Goadsby, 2017	Placebo	319																			0.26		
Vladimir, 2018	Placebo	461				0.2																	
Mulleners, 2020	Placebo	230											0.43										
Ashina, 2022	Placebo	298													0.34	0							
Diener, 2002	Propranolol 160 mg													0.36									
Diener, 2002	Flunarizine 10 mg													0.37									

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 81 Details for injury, poisoning and procedural complications of SOC (%) – part 2

Author, year	Interventions	Partici-pants	Ligament rupture	Sternal fracture	Skin laceration	Limb injury	Stomal hernia	Proce-dural pain	Postproce-dural constipation	Postprocedural complication	Abdominal wound dehiscence	Road traffic accident	Head injury	Concu-ssion	Brain contu-sion	Contu-sion	Rib fracture	Radius fracture	Overdose	Intentional overdose
Rothrock, 2019	BTA 150U	220												0.45						
Ashina, 2020	Eptinezumab 30 mg	219					0.46													
Ashina, 2020	Eptinezumab 100 mg	223						0.45	0.45											
Ashina, 2020	Eptinezumab 300 mg	224								0.45	0.45									
Dodick, 2019	Eptinezumab 300 mg	121											0.83	0.83						
Reuter, 2021	Erenumab 140 mg	388	0.26	0.26	0.26	0.26								0		0.26				
Tepper, 2017	Erenumab 70 mg	190																0.53		
Sakai, 2021	Fremanezumab-M	188													0.53					
Ferrari, 2019	Fremanezumab-M	285															0.36			
Silberstein, 2017	Fremanezumab-Q	376										0.26								
Ferrari, 2019	Fremanezumab-Q	276										0.36					0.35			
Reuter, 2021	Topiramate 100 mg	388												0.26						
Rothrock, 2019	Topiramate 100 mg	142												0.7						
Dodick, 2014	Placebo	110						0.91												
Dodick, 2018	Placebo	293										0.34								
Goadsby, 2017	Placebo	319																		0.26
Vladimir, 2018	Placebo	461										0.2					0.2	0.2		
Croop, 2020	Placebo	371																	0.27	
Ashina, 2022	Placebo	298										0.34		0.34						

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

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TABLE 82 Details for respiratory, thoracic and mediastinal disorders of SOC (%)

Author, year	Interventions	Partici-pants	Pneu-monia	Postsurgical laryngospasm with hypoxic brain injury	COPD and apnoea related to COPD	COPD	Asthma	Respira-tory distress	Dysp-noea	Vocal cord thickening	Pulmonary embolism	Pulmonary sarcoidosis	Sleep apnoea syndrome	Hypoxia	Epistaxis
Ailani, 2021	Atogepant 10 mg	221					0.45								
Dodick, 2010	BTA 150U	687	0.44										0.15	0.15	
Rothrock, 2019	BTA 150U	220	0.45		0.45										
Dodick, 2019	Eptinezumab 300 mg	121						0.83							
Sakai, 2021	Fremanezumab-M	188					0.53								
Ferrari, 2019	Fremanezumab-M	285								0.35					
Silberstein, 2017	Fremanezumab-Q	376	0.26			0.26	0		0						
Rothrock, 2019	Topiramate 100 mg	142	0.7		0.7										
Silberstein, 2017	Placebo	375	0			0	0.26		0.26						
Dodick, 2010	Placebo	692	0.28									0.28			
Detke, 2018	Placebo	558													0.18
Ailani, 2021	Placebo	222		0.45			0								
Ashina, 2020	Placebo	222				0.45							0.45		
Stauffer, 2018	Placebo	432									0.23				
Croop, 2020	Placebo	371	0.27												

COPD, chronic obstructive pulmonary disease; Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 83 Details for gastrointestinal disorders of SOC (%)

Author, year	Interventions	Partici-pants	Mecha-nical ileus	intestinal haemorr-hage	Haemor-rhoids	Irritable bowel syndrome	Esoph-agitis	Pancre-atitis acute	Pancre-atitis acute	Colitis ischae-mic	Colitis	Pancr-eatitis	Gastroes-ophageal reflux	Inguinal hernia	Parotitis	Gastric ulcer haemorrhage	Vomi-ting	Diverti-culitis	Abdo-minal pain	Gas-tritis	Small intestinal obstruction	Obstructive defaecation	Alcoholic pancreatitis
Dodick, 2009	Amitriptyline 100 mg	169					0.6																
Dodick, 2010	BTA 150U	687							0.15	0.15	0.15												
Tepper, 2017	Erenumab 140 mg	188																	0.53				
Reuter, 2021	Erenumab 140 mg	388	0.26																			0.26	
Sakai, 2021	Fremanezumab-M	188		0.53																			
Ferrari, 2019	Fremanezumab-Q	276											0.36	0.36									
Dodick, 2018	Fremanezumab-Q	291		0.34																			
Mulleners, 2020	Galcanezumab 120 mg	232			0.43																		
Stauffer, 2018	Galcanezumab 120 mg	206						0.5													0.5		
Vladimir, 2018	Galcanezumab 120 mg	226																		0.44			
Detke, 2018	Galcanezumab 240 mg	282										0.35											
Reuter, 2021	Topiramate 100 mg	388				0.26														0.26			
Detke, 2018	Placebo	558																		0.18			0.18
Tepper, 2017	Placebo	282										0.35			0.35		0.35		0				
Ailani, 2021	Placebo	222														0.45							

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

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TABLE 84 Details for renal and urinary disorders of SOC (%)

Author, year	Interventions	Partici-pants	Nephro-lithiasis	Urinary incontinence	Kidney injury	Calculus urinary	Renal calculus	Renal colic	Bladder dysfunction
Dodick, 2009	Amitriptyline 100 mg	169					0.6		
Dodick, 2010	BTA 150U	687				0.15			
Ashina, 2020	Eptinezumab 30 mg	219	0.46		0.46				
Silberstein, 2017	Fremanezumab-M	379				0.26			
Ferrari, 2019	Fremanezumab-M	285	0.7						
Ferrari, 2019	Fremanezumab-Q	276						0.35	
Vladimir, 2018	Galcanezumab 120 mg	226							0.44
Vladimir, 2018	Galcanezumab 240 mg	228							
Detke, 2018	Galcanezumab 240 mg	282	0.35					0.35	
Rothrock, 2019	Topiramate 100 mg	142	0.7						
Silberstein, 2017	Placebo	375	0.26						
Diener, 2002	Flunarizine 10 mg			0.37					

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 85 Details for infections and infestations of SOC (%) – part 1

Author, year	Interventions	Partici-pants	Gastroint-estinal infection	Viral infection	Nasoph-aryngitis	Tonsillitis	Upper respiratory tract infection bacterial	Sepsis	Pyelone-phritis	Kidney infection	Vaginal abscess	Viral gastroe-nteritis	Gastroe-nteritis	Pharyngitis streptococcal	Infected dermal cyst	Sinusitis
Dodick, 2009	Amitriptyline 100 mg	169											0.6			
Dodick, 2010	BTA 150U	687								0.5						
Dodick, 2019	Eptinezumab 300 mg	121									0.83	0.83				
Goadsby, 2017	Erenumab 140 mg	319						0.26	0.26	0.26		0.26				
Wang, 2021	Erenumab 70 mg	335											0.3			
Mulleners, 2020	Galcanezumab 120 mg	232				0.43										
Hu, 2022	Galcanezumab 120 mg	261											0.38		0.38	
Croop, 2020	Rimegepant 75 mg	370											0.27			
Reuter, 2021	Topiramate 100 mg	388	0.26		0.26				0.26				0.26			
Dodick, 2010	Placebo	692					0.28	0.28					0.28	0.28		
Ferrari, 2019	Placebo	277														0.35
Reuter, 2018	Placebo	124	0.8													
Wang, 2021	Placebo	335		0.3									0.3			
Croop, 2020	Placebo	371							0.27							

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TABLE 86 Details for infections and infestations of SOC (%) – part 2

Author, year	Interventions	Partici-pants	Peri tonsillitis	Diverti-culitis	Dengue fever	Cellulitis	Labyrin-thitis	*Clostridium difficile* colitis	Influenza	Papilloma viral infection	Appen-dicitis	Parasitic gastroen-teritis	Bacter-iuria	Pyrexia	Acute pyelon-ephritis	COVID-19 pneumonia	Urinary tract infection	Bacterial pharyngitis
Ashina, 2022	Eptinezumab 100 mg	299														0.33		
Ashina, 2020	Eptinezumab 300 mg	294														0.68		
Goadsby, 2017	Erenumab 140 mg	319						0.26										
Reuter, 2021	Erenumab 140 mg	388								0.26								
Tepper, 2017	Erenumab 70 mg	190									0.53							
Dodick, 2018	Erenumab 70 mg	283															0.4	
Goadsby, 2017	Erenumab 70 mg	314													0.31			
Wang, 2021	Erenumab 70 mg	335					0.3											
Dodick, 2018	Fremanezumab-M	289									0.35							
Sakai, 2021	Fremanezumab-Q	190							0.5									
Ferrari, 2019	Fremanezumab-Q	276		0.35														
Vladimir, 2018	Galcanezumab 120 mg	226																0.44
Vladimir, 2018	Galcanezumab 240 mg	228							0.44					0.44				
Reuter, 2021	Topiramate 100 mg	388							0.26		0.26	0.26	0.26					
Tepper, 2017	Placebo	282															0.35	
Ferrari, 2019	Placebo	277	0.35		0.35													
Ashina, 2020	Placebo	222				0.45												
Wang, 2021	Placebo	335				0.3												
Croop, 2020	Placebo	371									0.27							
Hu, 2022	Placebo	259														0.38		

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 87 Details for cardiac disorders of SOC (%)

Author, year	Interventions	Participants	Atrial fibrillation	Acute coronary syndrome	Tachycardia	Atrial fibrillation	Palpitations	Pericarditis	Syncope	Acute myocardial infarction
Dodick, 2010	BTA 150U	687		0.15	0.15			0.15		0.15
Rothrock, 2019	BTA 150U	220			0.45				0.45	
Ferrari, 2019	Fremanezumab-M	285				0.35				
Ferrari, 2019	Fremanezumab-Q	276	0.36							
Vladimir, 2018	Galcanezumab 240 mg	228								0.44
Reuter, 2021	Topiramate 100 mg	388							0.26	
Detke, 2018	Placebo	558								0.18
Ferrari, 2019	Placebo	277					0.36			
Ashina, 2020	Placebo	222							0.45	

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

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TABLE 88 Details for congenital, familial and genetic disorders and reproductive system and breast disorders of SOC (%)

Author, year	Interventions	Partici-pants	Congenital diaphragmatic hernia	Metror-rhagia	Menomet-rorrhagia	Ovarian disorder	Abortion threatened	Spontan-eous abortion	Uterine Prolapse	Endome-triosis	Menstrual disorder and vaginal haemorrhage	Dysmen-orrhoea	Menorrhagia	Cervical dysplasia
Dodick, 2009	Amitriptyline 100 mg	169											0.6	
Dodick, 2010	BTA 150U	687						0.15						
Lipton, 2020	Eptinezumab 300 mg	350					0.38							
Reuter, 2021	Erenumab 140 mg	388										0.26		0.26
Dodick, 2018	Fremanezumab-M	289											0.35	
Ferrari, 2019	Fremanezumab-M	285			0.35					0.35				
Ferrari, 2019	Fremanezumab-Q	276										0.35	0.35	
Dodick, 2009	Topiramate 100 mg	177				0.5					0.5		0.5	
Reuter, 2021	Topiramate 100 mg	388								0.26				
Dodick, 2010	Placebo	692								0.28				
Lipton, 2020	Placebo	366			0.27									
Ferrari, 2019	Placebo	277	0.36	0.36										
Ashina, 2020	Placebo	222							0.45					
Dodick, 2018	Placebo	293						0.34						
Goadsby, 2017	Placebo	319								0.26				
Wang, 2021	Placebo	335						0.5						
Lipton, 2011	Placebo							0.5						
Diener, 2002	Propranolol 160 mg										0.3			

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 89 Details for hepatobiliary disorders of SOC (%)

Author, year	Interventions	Participants	Cholelithiasis	Hepatic cholestatic	Cerebral venous thrombosis	Cholecystitis acute
Dodick, 2009	Amitriptyline 100 mg	169	0.6			
Ashina, 2020	Eptinezumab 30 mg	219		0.46		
Dodick, 2019	Eptinezumab 100 mg	122	0.5			
Ashina, 2020	Eptinezumab 100 mg	223	0.45			
Ashina, 2022	Eptinezumab 100 mg	299	0.33			
Goadsby, 2017	Erenumab 140 mg	319	0.63		0.26	
Ferrari, 2019	Fremanezumab-Q	276	0.36			0.36
Vladimir, 2018	Galcanezumab 240 mg	228	0.44			
Reuter, 2021	Topiramate 100 mg	388	0.26			
Dodick, 2010	Placebo	692	0.28			
Tepper, 2017	Placebo	282	0.35			
Dodick, 2018	Placebo	289				0.3
Stauffer, 2018	Placebo	432	0.5			
Diener, 2002	Flunarizine 10 mg		0.37			

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

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TABLE 90 Details for psychiatric disorders of SOC (%)

Author, year	Interventions	Participants	Major depression	Depression	Stress	Conversion disorder	Suicidal ideation	Disorien-tation	Substance-induced mood disorders	Panic attack	Menor-rhagia	Suicide attempt	Psychogenic seizure
Dodick, 2010	BTA 150U	687		0.3	0.15	0.15							
Dodick, 2019	Eptinezumab 10 mg	130					0.77						
Dodick, 2019	Eptinezumab 100 mg	122							0.82		0.82		
Ashina, 2020	Eptinezumab 100 mg	223					0.45			0.45		0.45	
Ashina, 2020	Eptinezumab 300 mg	294											0.34
Reuter, 2021	Erenumab 140 mg	388	0.26										
Silberstein, 2017	Fremanezumab-M	379					0.26						
Vladimir, 2018	Galcanezumab 240 mg	228						0.44					
Croop, 2020	Rimegepant 75 mg	370										0.27	
Reuter, 2021	Topiramate 100 mg	388		0.26									
Vladimir, 2018	Placebo	461										0.2	
Ashina, 2022	Placebo	298					0.34						
Diener, 2002	Flunarizine 10 mg			0.37									

Fremanezumab-M, fremanezumab monthly.

TABLE 91 Details for musculoskeletal and connective tissue disorders of SOC (%)

Author, year	Interventions	Partici-pants	Costocho-ndritis	Tendonitis	Vertebral osteophyte	Rhabdo-myolysis	Periart-hritis	Post-traumatic neck syndrome	Back pain	Behcet syndrome	Interver-tebral disc protrusion	Osteoa-rthritis	Lumbar spinal stenosis	Arthralgia	Flank pain
Dodick, 2010	BTA 150U	687							0.15						
Ashina, 2020	Eptinezumab 30 mg	219				0.46									
Ashina, 2020	Eptinezumab 300 mg	294									0.34				
Tepper, 2017	Erenumab 140 mg	188									0.52				
Reuter, 2021	Erenumab 140 mg	388									0.26				
Tepper, 2017	Erenumab 70 mg	190	0.53								0				
Dodick, 2018	Erenumab 70 mg	283									0.4				
Goadsby, 2017	Erenumab 70 mg	314						0.31	0.31						
Silberstein, 2017	Fremanezumab-M	379							0.26						
Ferrari, 2019	Fremanezumab-Q	276							0.35						
Stauffer, 2018	Galcanezumab 120 mg	206		0.46											
Reuter, 2021	Topiramate 100 mg	388											0.26		
Dodick, 2010	Placebo	692									0.28				
Tepper, 2017	Placebo	282									0.35				
Ashina, 2020	Placebo	222									0.45				
Dodick, 2018	Placebo	289													0.3
Goadsby, 2017	Placebo	319										0.26		0.26	
Stauffer, 2018	Placebo	432			0.23										
Mulleners, 2020	Placebo	230								0.43					
Ashina, 2022	Placebo	298					0.34								

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

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TABLE 92 Details for investigations of SOC (%)

Author, year	Interventions	Participants	Weight decreased	International normalised ratio abnormal
Ferrari, 2019	Fremanezumab-Q	276		0.35
Reuter, 2021	Topiramate 100 mg	388	0.26	

Fremanezumab-Q, fremanezumab quarterly.

TABLE 93 Details for metabolism and nutrition disorders of SOC (%)

Author, year	Interventions	Participants	Hypokalaemia	Hypoglycaemia	Dehydration	Hyponatraemia	Decreased appetite
Dodick, 2010	BTA 150U	687	0.15				
Detke, 2018	Galcanezumab 240 mg	282	0.35				
Reuter, 2021	Topiramate 100 mg	388					0.26
Rothrock, 2019	Topiramate 100 mg	142			0.7		
Dodick, 2018	Placebo	289				0.3	
Dodick, 2018	Placebo	293		0.34			

TABLE 94 Details for vascular disorders of SOC (%)

Author, year	Interventions	Participants	Hypertensive crisis	Peripheral arterial occlusive disease	Deep vein thrombosis	Pulmonary embolism
Dodick, 2010	BTA 150U	687	0.15			
Silberstein, 2017	Fremanezumab-M	379	0.26			
Detke, 2018	Galcanezumab 240 mg	282				0.35
Rothrock, 2019	Topiramate 100 mg	142		0.7	0.7	
Stauffer, 2018	Placebo	432			0.23	

Fremanezumab-M, fremanezumab monthly; Fremanezumab-Q, fremanezumab quarterly.

TABLE 95 Details for general disorders and administration site conditions of SOC (%)

Author, year	Interventions	Partici-pants	Non-cardiac chest pain	Malaise	Nasal septum deviation	Tooth impacted	Chest pain	Abdominal adhesions	Asthenia	Oedema peripheral
Dodick, 2010	BTA 150U	687	0.15							
Tepper, 2017	Erenumab 140 mg	188	0					0.53		
Goadsby, 2017	Erenumab 140 mg	319	0.31							
Tepper, 2017	Erenumab 70 mg	190	0.53							
Goadsby, 2017	Erenumab 70 mg	314	0.26							
Wang, 2021	Erenumab 70 mg	335							0.3	
Sakai, 2020	Galcanezumab 120 mg	115				0.9				
Sakai, 2020	Galcanezumab 240 mg	114			0.9					
Silberstein, 2017	Placebo	375								0.26
Goadsby, 2017	Placebo	319	0.26							
Hu, 2022	Placebo	259			0.38					
Lipton, 2011	Placebo						0.5			
Diener, 2002	Flunarizine 5 mg			0.38						

TABLE 96 Details for eye disorders of SOC (%)

Author, year	Interventions	Partici-pants	Diplopia	Retinal tear	Rhegmatogenous retinal detachment	Angle closure glaucoma	Retinal detachment	Optic neuritis
Ailani, 2021	Atogepant 10 mg	221						0.45
Ashina, 2022	Eptinezumab 100 mg	299					0.33	
Ferrari, 2019	Fremanezumab-M	285		0.35				
Reuter, 2021	Topiramate 100 mg	388			0.26	0.26	0.26	
Silberstein, 2017	Placebo	375	0.26					

Fremanezumab-M, fremanezumab monthly.

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TABLE 97 Details for ear and labyrinth disorders, immune system disorders, and blood and lymphatic system disorders of SOC (%)

			Ear and labyrinth disorders			Immune system disorders			Blood and lymphatic system disorders
Author, year	Interventions	Participants	Vestibular neuronitis	Sudden hearing loss	Vertigo	Hypersensitivity	Anaphylactic reaction	Anaphylactic shock	Thrombocytopenia
Hong Sun, 2016	Erenumab 70 mg	106			0.1				
Ashina, 2020	Eptinezumab 300 mg	224			0.45				
Ashina, 2020	Eptinezumab 300 mg	294					0.68		
Goadsby, 2017	Erenumab 140 mg	319	0.26						
Ferrari, 2019	Fremanezumab-M	285					0.35		
Sakai, 2020	Galcanezumab 120 mg	115		0.9					
Reuter, 2021	Topiramate 100 mg	388						0.26	
Silberstein, 2017	Placebo	375				0.26			
Dodick, 2010	Placebo	692							0.28
Dodick, 2018	Placebo	289				0.3			
Dodick, 2018	Placebo	293				0.3			
Goadsby, 2017	Placebo	319				0.26			

Fremanezumab-M, fremanezumab monthly.

TABLE 98 Any SAEs reported from 29 trials

Treatments	Doses	Frequency	Total participants (*n*)	Participants with any SAEs[a] (%)
Atogepant[129]	30 mg	Once daily	228	0
Atogepant[129]	60 mg	Once daily	231	0
Erenumab[130]	21 mg	Monthly	105	0
Galcanezumab[133]	150 mg	Every 2 weeks	107	0
Eptinezumab[89]	10 mg	Single dose on day 0	130	1 (0.77)
Rimegepant[148]	75 mg	Once daily	370	3 (0.81)
Atogepant[129]	10 mg	Once daily	221	2 (0.9)
Erenumab[130]	7 mg	Monthly	108	1 (0.93)
Eptinezumab[89,131]	30 mg	Single dose on day 0	341	4 (1.17)
Fremanezumab[35,37,90,91,126]	Quarterly, 625 mg	Single dose on day 0	1251	15 (1.2)
Eptinezumab[89,94,131,149,151]	100 mg	Single dose on day 0	1238	16 (1.29)
Galcanezumab[95,127,140,141]	240 mg	Monthly	844	12 (1.42)
Placebo[35–37,45,89–91,94,95,97,126,127,129,131,133,134,140,141,143,144,146,148–151,155]	-	Matched with active treatments	7570	109 (1.42)
Galcanezumab[95,127,140,141,146,150]	120 mg	Monthly	1313	20 (1.52)
Fremanezumab[35,37,90,91,126]	Monthly, 225 mg	Monthly	1262	22 (1.74)
Erenumab[36,45,142–144]	140 mg	Monthly	1238	22 (1.78)
Eptinezumab[89,94,131,151]	300 mg	Single dose on day 0	989	21 (2.12)
Erenumab[36,45,134,144]	70 mg	Monthly	1228	28 (2.28)
BTA[88,97]	150U	Every 12 weeks	907	37 (4.08)
Topiramate[88,135,142]	100 mg	Twice daily	707	29 (4.1)
Amitriptyline[135]	25–100 mg	Twice daily	169	8 (4.73)

a Treatments are listed in order of increasing SAEs percentage.

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Appendix 7 Literature searches for cost-effectiveness studies

Overview

TABLE 99 Overview of literature searches for cost-effectiveness studies

Bibliographic databases		
Database	**Date searched**	**Number of records**
MEDLINE All, 1946–3 September 2021 (via Ovid)	6 September 2021	568
EMBASE Classic + EMBASE, 1947–3 September 2021 (via Ovid)	6 September 2021	2531
EconLit (via *EBSCO*host)	6 September 2021	66
NHS EED (via CRD website)	6 September 2021	116
HTA database (via CRD website)	6 September 2021	123
International HTA database (via INAHTA website)	6 September 2021	138
Cost-effectiveness Analysis Registry (via Tufts Medical Center website)	6 September 2021	32
EconPapers [via Research Papers in Economics (RePEc)]	6 September 2021	30
Total number of records retrieved: 3604 **Duplicates removed (EndNote): 677** **Final number for screening: 2927**		
Other sources		
Source	**Date searched**	**Documents retrieved**
NICE website	7 September 2021	25
SMC website	7 September 2021	5
AWMSG website	7 September 2021	0
CADTH website	7 September 2021	14; plus 1 record of ongoing review
Google	13 September 2021	5
Google Scholar	13 September 2021	1
Total number sought for retrieval: 50 **Reports not retrieved/available: 0** **Final number for screening: 50 (+1 ongoing review)**		
Bibliographic databases – update search (with three additional drug terms where applicable), November 2022		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	10 November 2022	644
EMBASE (via Ovid)	10 November 2022	2767
EconLit (via *EBSCO*host)	10 November 2022	76
NHS EED (via CRD)	As these databases are no longer updated, searches were not re-run; however the original search results were rescreened for any studies relating to riboflavin, coenzyme Q10 or magnesium (0 found)	
HTA database (via CRD)		
International HTA database (via INAHTA website)	10 November 2022	157
Cost-effectiveness Analysis Registry (via Tufts Medical Center website)	10 November 2022	34

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TABLE 99 Overview of literature searches for cost-effectiveness studies (*continued*)

EconPapers [via Research Papers in Economics (RePEc)]	14 November 2022	27
Total number of records retrieved: 3705 **Duplicates removed within this set (EndNote): 546** **Duplicates removed against previous searches (EndNote): 2819** **Final number for screening: 340**		
Other sources – update search (with three additional drug terms), November 2022		
Source	**Date searched**	**Documents retrieved**
NICE website	15 November 2022	6
SMC website	16 November 2022	0
AWMSG website	16 November 2022	0; 2 records of ongoing NICE TAs
CADTH website	16 November 2022	4; plus 2 records of ongoing/ suspended reviews
Google	16 November 2022	3
Google Scholar	16 November 2022	8
Total number sought for retrieval: 21 **Reports not retrieved/available: 0** **Final number for screening: 21 (+3 ongoing reviews and 1 suspended review)**		
Citation tracking		
Source	Date searched	Number of records
Reference lists – included studies (Web of Science and Citation Finder)	16 May 2022 and 25 May 2022	255
Forwards citation tracking: Web of Science	30 November 2022	62
Forwards citation tracking: Google Scholar (for studies not found in Web of Science only)	30 November 2022	49
Total number of records retrieved: 366 **Duplicates removed (both within this set and against previous searches) (EndNote): 160** **Final number for screening: 206**		
Checking for retraction notices, errata and comments relating to included articles		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	22 November 2022	1, not related to included studies
EMBASE (via Ovid)	22 November 2022	0
Retraction Watch website	22 November 2022	0
Total number of records retrieved: 0		
Additional search for utility data		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	21 November 2022	860
Cost-effectiveness Analysis Registry (via Tufts Medical Center website)	21 November 2022	118
ISPOR Presentations Database (via ISPOR website)	21 November 2022	32
ScHARRHUD	21 November 2022	2
EQ-5D website	22 November 2022	0
Total number of records retrieved: 1012		

AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; NHS EED, National Health Service Economic Evaluation Database.

Search strategies: original searches, September 2021

MEDLINE (via Ovid)

Date searched: 6 September 2021

Database: Ovid MEDLINE(R) ALL <1946 to 3 September 2021>

Search strategy:

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1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. (112,847)
2 Headache/ or exp Headache Disorders/ (61,218)
3 1 or 2 [population: migraine/headache] (124,069)
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. (216,382)
5 Calcitonin Gene-Related Peptide/ai (436)
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ (216,971)
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ (700)
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. (506)
9 (brogepant or brogepant or atogepant or gepant?).ab,kf,ti,nm. (213)
10 exp Botulinum Toxins/ (17,099)
11 (botulin* adj toxin*).ab,kf,ti,nm. (21,932)
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. (25,143)
13 (antidepress* or anti depress*).ab,kf,ti. (73,848)
14 exp Antidepressive Agents/ (153,091)
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. (17,952)
16 exp 'Serotonin and Noradrenaline Reuptake Inhibitors'/ (5001)
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. (2907)
18 exp Angiotensin Converting Enzyme Inhibitors/ (45,311)
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. (37,925)
20 acei.ab,kf,ti. (4337)
21 lisinopril.ab,kf,ti,nm. (3085)
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. (14,463)
23 (ARB or ARBs).ab,kf,ti. (7863)
24 exp Angiotensin Receptor Antagonists/ (25,388)
25 candesartan.ab,kf,ti,nm. (3374)
26 ((beta adj3 block*) or betablock*).ab,kf,ti. (55,677)
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagonist* or block*)).ab,kf,ti. (34,501)
28 exp Adrenergic beta-Antagonists/ (85,429)
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. (67,109)
30 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kf,ti. (41,544)
31 (CCB or CCBs).ab,kf,ti. (2617)
32 exp Calcium Channel Blockers/ (88,521)
33 (flunarizine or verapamil).ab,kf,ti,nm. (27,699)
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. (53,578)
35 exp Anticonvulsants/ (147,133)
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. (31,187)
37 Pizotyline/ (250)
38 (pizotifen or pizotyline).ab,kf,ti,nm. (418)

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39 (alpha adj4 agonist*).ab,kf,ti. (15,366)
40 exp Adrenergic alpha-Agonists/ (164,048)
41 (clonidine or guanfacine).ab,kf,ti,nm. (19,179)
42 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [Interventions: named drugs/drug classes or types] (1,098,078)
43 Economics/ (27,362)
44 exp 'Costs and Cost Analysis'/ (248,833)
45 Economics, Nursing/ (4006)
46 Economics, Medical/ (9151)
47 Economics, Pharmaceutical/ (3015)
48 exp Economics, Hospital/ (25,285)
49 Economics, Dental/ (1919)
50 exp 'Fees and Charges'/ (30,859)
51 exp Budgets/ (13,884)
52 budget*.ti,ab,kf. (32,036)
53 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (248,167)
54 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 (323,416)
55 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (179,847)
56 (value adj2 (money or monetary)).ti,ab,kf. (2646)
57 exp models, economic/ (15,779)
58 economic model*.ab,kf. (3649)
59 markov chains/ (15,222)
60 markov.ti,ab,kf. (24,937)
61 monte carlo method/ (30,091)
62 monte carlo.ti,ab,kf. (53,356)
63 exp Decision Theory/ (12,574)
64 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (28,316)
65 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 [economic evaluations/cost/economic models filter] (791,472)
66 3 and 42 and 65 [population + named drug interventions + economic filter] (209)
67 exp Migraine Disorders/dt, pc (9891)
68 'migrain*'.ab,hw,kf,ti. (42,481)
69 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kf,ti. (173,556)
70 ((pharmacolog* or pharmaceutical or drug? or medical) adj1 (treatment? or therap* or management)).ab,hw,kf,ti. (455,613)
71 68 and (69 or 70) (4510)
72 67 or 71 (12,167)
73 65 and 72 [economics filter + general terms for migraine prevention/drug treatment] (477)
74 66 or 73 (568)

The migraine/headache search terms (lines 1–3) and Botox search terms (lines 10–12) are based on those used in:

Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, *et al.* Botulinum toxins for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2018;**6**:CD011616. https://doi.org/10.1002/14651858.CD011616.pub2

The search filter for economic and cost studies (lines 43–65) is the CADTH filter for Economic Evaluations/Cost/Economic Models – Ovid MEDLINE:

Strings attached: CADTH database search filters (Internet). Ottawa: CADTH; 2016. Available from: www.cadth.ca/resources/finding-evidence/.

EMBASE (via Ovid)

Date searched: 6 September 2021

Database: EMBASE Classic+EMBASE <1947 to 3 September 2021>

Search Strategy:

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1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kw,ti. (186,676)
2 'headache and facial pain'/ or exp chronic daily headache/ or headache/ or exp migraine/ or vascular headache/ (294,055)
3 headache/si not exp 'headache and facial pain'/dm, dt, pc, th (78,809)
4 (1 or 2) not 3 [population: migraine/headache; not as side effect only] (253,367)
5 antimigraine agent/ (2568)
6 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kw,ti. (274,669)
7 exp calcitonin gene related peptide receptor antagonist/ (3872)
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kw,ti,tn. (1445)
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kw,ti,tn. (465)
10 botulinum toxin/ or botulinum toxin A/ (39,609)
11 (botulin* adj toxin*).ab,kw,ti,tn. (23,,041)
12 (botulinum* or botox* or onabotulinum*).ab,kw,ti,tn. (34504)
13 (antidepress* or anti depress*).ab,kw,ti. (108,538)
14 exp antidepressant agent/ (515,062)
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kw,ti,tn. (22,238)
16 exp serotonin noradrenalin reuptake inhibitor/ (200,859)
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kw,ti. (4807)
18 exp dipeptidyl carboxypeptidase inhibitor/ (184,019)
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kw,ti. (55,283)
20 acei.ab,kw,ti. (9041)
21 lisinopril.ab,kw,ti,tn. (4455)
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kw,ti. (22,206)
23 (ARB or ARBs).ab,kw,ti. (15,636)
24 exp angiotensin receptor antagonist/ (100,617)
25 candesartan.ab,kw,ti,tn. (4072)
26 ((beta adj3 block*) or betablock*).ab,kw,ti. (83,000)
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagonist* or block*)).ab,kw,ti. (44,164)
28 exp beta adrenergic receptor blocking agent/ (316,392)
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kw,ti,tn. (69,423)
30 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kw,ti. (55,268)
31 (CCB or CCBs).ab,kw,ti. (4499)
32 exp calcium antagonist/ (289,477)

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33 (flunarizine or verapamil).ab,kw,ti,tn. (29,545)
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kw,ti. (84,420)
35 exp anticonvulsive agent/ (451,825)
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kw,ti,tn. (43,812)
37 pizotifen/ (1970)
38 (pizotifen or pizotyline).ab,kw,ti,tn. (443)
39 (alpha adj4 agonist*).ab,kw,ti. (12,525)
40 exp alpha 2 adrenergic receptor stimulating agent/ (114,971)
41 (clonidine or guanfacine).ab,kw,ti,tn. (19,862)
42 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [named drug or drug class interventions] (1,819,269)
43 Economics/ (244,858)
44 Cost/ (63,187)
45 exp Health Economics/ (917,483)
46 Budget/ (31,270)
47 budget*.ti,ab,kw. (43,208)
48 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. (313,082)
49 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 (458,270)
50 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. (252,987)
51 (value adj2 (money or monetary)).ti,ab,kw. (3646)
52 Statistical Model/ (167,169)
53 economic model*.ab,kw. (5435)
54 Probability/ (123,900)
55 markov.ti,ab,kw. (32,912)
56 monte carlo method/ (44,164)
57 monte carlo.ti,ab,kw. (55,487)
58 Decision Theory/ (1821)
59 Decision Tree/ (15,564)
60 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. (39,985)
61 or/43-60 [Filter for economic studies] (1,788,926)
62 4 and 42 and 61 (2163)
63 exp migraine/dt, pc [Drug Therapy, Prevention] (18,205)
64 'migrain*'.ab,hw,kw,ti. (79,663)
65 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kw,ti. (247,454)
66 ((pharmacolog* or pharmaceutical or drug? or medical) adj1 (treatment? or therap* or management)).ab,hw,kw,ti. (1,207,792)
67 64 and (65 or 66) (12,279)
68 63 or 67 (27,128)
69 61 and 68 [economics filter + general terms for migraine prevention/drug treatment] (2170)
70 62 or 69 (3083)
71 conference abstract.pt. (4,170,650)
72 70 not 71 (2531)

The search filter for economic and cost studies (lines 43–61) is the CADTH filter for Economic Evaluations/Cost/Economic Models – OVID EMBASE:

Strings attached: CADTH database search filters (Internet). Ottawa: CADTH; 2016. Available from: www.cadth.ca/resources/finding-evidence/

EconLit (via EBSCOhost)

Date searched: 6 September 2021

Database: EconLit with Full Text

Search modes – Boolean/Phrase

Search Screen – Advanced Search

#	Query	Results
S5	S1 AND S4	66
S4	S2 OR S3	255,123
S3	AB (therap* or treat* or prevent* or prophyla* or management) OR TI (therap* or treat* or prevent* or prophyla* or management)	134,407
S2	TX pharmac* OR health* or medic* or drug or drugs	138,404
S1	AB (headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*) OR SU (headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*) OR TI (headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*)	88

NHS Economic Evaluation Database (NHS EED) and HTA database (via CRD) www.crd.york.ac.uk/CRDWeb/

Date searched: 6 September 2021

Search	Hits
(headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*) [All fields] IN NHSEED	116
(headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*) [All fields] IN HTA	123

International HTA database (via INAHTA website) https://database.inahta.org/

Date searched: 6 September 2021

Line	Query	Hits
4	#1 OR #2 OR #3	138
3	'Headache Disorders'[mhe]	57
2	'Headache'[mh]	30
1	headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*	135

Cost-effectiveness Analysis Registry (via Tufts Medical Center website) https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Date searched: 6 September 2021

Basic search screen: Methods selected

Results of each search were copied and pasted into Excel, to easily identify unique results, which were then found in PubMed for easy export/import into EndNote.

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Search term/s	Results
headache	24
head ache	0
migraine	21, of which 8 unique/13 already found with 'headache' search
Total unique results:	32

EconPapers [via Research Papers in Economics (RePEc)] https://econpapers.repec.org/
Date searched: 6 September 2021

Advanced search screen: https://econpapers.repec.org/scripts/search.pf

30 documents matched the search for (headache* OR 'head ache*' OR migrain*) AND (pharmac* OR medic* OR drug OR drugs OR therap* OR treat* OR prevent* OR prophyla*) in *titles and keywords* in working papers, articles, books and chapters.

National Institute for Health and Care Excellence website www.nice.org.uk/
Date searched: 7 September 2021

Browsed Guidance section: Conditions and diseases > Neurological conditions > Headaches

23 published products on this topic:

25 documents relating to 6 published guidelines or other evidence reviews were judged to contain potentially useful information for the cost-effectiveness review.

Scottish Medicines Consortium website www.scottishmedicines.org.uk/
Date searched: 7 September 2021

Search box on homepage:

Migraine 12 results

headache 6 results, none unique

5 documents relating to 5 drugs were judged to contain potentially useful information for the cost-effectiveness review

All Wales Medicines Strategy Group (AWMSG) website https://awmsg.nhs.wales/
Date searched: 7 September 2021

Search box on homepage:

migraine 3 results, all refer to NICE technology appraisals identified above

headache 0 results

0 documents for retrieval

Canadian Agency for Drugs and Technologies in Health (CADTH) website https://cadth.ca/

Date searched: 7 September 2021

Search box on homepage, results limited to 'Reports' tab.

migraine 30 results, of which 8 potentially relevant

headache 40 results, of which 1 potentially relevant and not already identified

14 documents relating to 9 projects/reviews were judged to contain potentially useful information for the cost-effectiveness or clinical reviews; 1 ongoing reimbursement review also identified.

Google www.google.co.uk

Date searched: 13 September 2021

Results (10 per page) were browsed until yielding very few results containing all search terms.

Documents were retrieved if judged to be potentially useful for the cost-effectiveness review, and if they had not already been identified via the bibliographic databases or HTA websites searches.

Search string	Number of results browsed	Documents retrieved
migraine prevention OR prophylaxis technology assessment	30	0
migraine prevention OR prophylaxis economic	60	3 (2 × ICER reports; Clarke *et al.*, 1996)
migraine prevention OR prophylaxis cost-effectiveness	60	2 [NCPE Ireland report on fremanezumab, after which checked www.ncpe.ie for further reports on migraine (using 'migraine' in website search box) and identified a further report on erenumab]
Total documents retrieved:		5

Google Scholar https://scholar.google.co.uk

Date searched: 13 September 2021

Results (10 per page) were browsed until yielding very few results containing all search terms.

Documents were retrieved if judged to be potentially useful for the cost-effectiveness review, and if they had not already been identified via the bibliographic databases, HTA websites or Google searches.

Search string	Number of results browsed	Documents retrieved
migraine prevention OR prophylaxis technology assessment	20	0
migraine prevention OR prophylaxis economic	60	1 (Serrano *et al.*, 2013)
migraine prevention OR prophylaxis cost-effectiveness	70	0
migraine prevention OR prophylaxis costs	20	0
Total documents retrieved:		1

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Search strategies: update searches, November 2022

MEDLINE (via Ovid)

Date searched: 10 November 2022

Ovid MEDLINE(R) ALL <1946 to 9 November 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 12,1183
2 Headache/ or exp Headache Disorders/ 64,883
3 1 or 2 [population: migraine/headache, based on Cochrane botox review] 132,533
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 224,447
5 Calcitonin Gene-Related Peptide/ai 463
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 227,782
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ 890
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 728
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 302
10 exp Botulinum Toxins/ 18,168
11 (botulin* adj toxin*).ab,kf,ti,nm. 23,254
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 26,590
13 (antidepress* or anti depress*).ab,kf,ti. 78,227
14 exp Antidepressive Agents/ 158,386
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18,644
16 exp 'Serotonin and Noradrenaline Reuptake Inhibitors'/ 5339
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. 3142
18 exp Angiotensin Converting Enzyme Inhibitors/ 46,784
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 39,275
20 acei.ab,kf,ti. 4756
21 lisinopril.ab,kf,ti,nm. 3161
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 15,381
23 (ARB or ARBs).ab,kf,ti. 8696
24 exp Angiotensin Receptor Antagonists/ 27,199
25 candesartan.ab,kf,ti,nm. 3451
26 ((beta adj3 block*) or betablock*).ab,kf,ti. 57,496
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagonist* or block*)).ab,kf,ti. 34,884
28 exp Adrenergic beta-Antagonists/ 86,681
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. 68,133
30 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kf,ti. 42,422
31 (CCB or CCBs).ab,kf,ti. 2832
32 exp Calcium Channel Blockers/ 90,332
33 (flunarizine or verapamil).ab,kf,ti,nm. 28,047
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 55,700
35 exp Anticonvulsants/ 152,024
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 32,859
37 Pizotyline/ 252
38 (pizotifen or pizotyline).ab,kf,ti,nm. 425
39 (alpha adj4 agonist*).ab,kf,ti. 15,650
40 exp Adrenergic alpha-Agonists/ 166,822
41 (clonidine or guanfacine).ab,kf,ti,nm. 19,417
42 Riboflavin/ or Ubiquinone/ or Magnesium/ or exp Magnesium Compounds/ [additional drugs identified 2022] 104,342

43 (riboflavin or vitamin b2 or vitamin b 2 or coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10 or magnesium).ab,kf,ti,nm. [additional drugs identified 2022] 147,923
44 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 [Interventions: named drugs/drug classes or types] 1,275,996
45 Economics/ 27,469
46 exp 'Costs and Cost Analysis'/ 261,027
47 Economics, Nursing/ 4013
48 Economics, Medical/ 9230
49 Economics, Pharmaceutical/ 3084
50 exp Economics, Hospital/ 25,645
51 Economics, Dental/ 1920
52 exp 'Fees and Charges'/ 31,239
53 exp Budgets/ 14,053
54 budget*.ti,ab,kf. 34,526
55 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 269,051
56 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 359,511
57 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 198,450
58 (value adj2 (money or monetary)).ti,ab,kf. 2893
59 exp models, economic/ 16,156
60 economic model*.ab,kf. 4009
61 markov chains/ 15,834
62 markov.ti,ab,kf. 27,574
63 monte carlo method/ 31,696
64 monte carlo.ti,ab,kf. 57,654
65 exp Decision Theory/ 12,981
66 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 34,084
67 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 [economic evaluations/cost/economic models filter from CADTH www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#e-co] 858,537
68 3 and 44 and 67 [population + named drug interventions + economic filter] 268
69 exp Migraine Disorders/dt, pc 10,729
70 'migrain*'.ab,hw,kf,ti. 45,173
71 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kf,ti. 189,003
72 ((pharmacolog* or pharmaceutical or drug? or medical) adj1 (treatment? or therap* or management)).ab,hw,kf,ti. 477,844
73 70 and (71 or 72) 4964
74 69 or 73 13,104
75 67 and 74 [economics filter + general terms for migraine prevention/drug treatment] 532
76 68 or 75 644

EMBASE (via Ovid)

Date searched: 10 November 2022

EMBASE Classic+EMBASE <1947 to 9 November 2022>

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1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kw,ti. 202,354
2 'headache and facial pain'/ or exp chronic daily headache/ or headache/ or exp migraine/ or vascular headache/ 322,004
3 headache/si not exp 'headache and facial pain'/dm, dt, pc, th 84,245
4 (1 or 2) not 3 278,483
5 antimigraine agent/ 2699
6 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kw,ti. 287,217
7 exp calcitonin gene related peptide receptor antagonist/ 5139
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kw,ti,tn. 2207
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kw,ti,tn. 797
10 botulinum toxin/ or botulinum toxin A/ 42,654
11 (botulin* adj toxin*).ab,kw,ti,tn. 23,636
12 (botulinum* or botox* or onabotulinum*).ab,kw,ti,tn. 36,798
13 (antidepress* or anti depress*).ab,kw,ti. 114,256
14 exp antidepressant agent/ 568,155
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kw,ti,tn. 23,369
16 exp serotonin noradrenalin reuptake inhibitor/ 211,940
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kw,ti. 5037
18 exp dipeptidyl carboxypeptidase inhibitor/ 195,496
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kw,ti. 57,500
20 acei.ab,kw,ti. 9819
21 lisinopril.ab,kw,ti,tn. 4705
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kw,ti. 22,240
23 (ARB or ARBs).ab,kw,ti. 17,026
24 exp angiotensin receptor antagonist/ 111,581
25 candesartan.ab,kw,ti,tn. 4182
26 ((beta adj3 block*) or betablock*).ab,kw,ti. 84,862
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagonist* or block*)).ab,kw,ti. 43,408
28 exp beta adrenergic receptor blocking agent/ 333,504
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kw,ti,tn. 71,299
30 (calcium adj2 (block* or antagonis* or inhibit*)).ab,kw,ti. 54,855
31 (CCB or CCBs).ab,kw,ti. 4827
32 exp calcium antagonist/ 340,528
33 (flunarizine or verapamil).ab,kw,ti,tn. 30,070
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kw,ti. 88,096
35 exp anticonvulsive agent/ 491290
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kw,ti,tn. 46,687
37 pizotifen/ 2006
38 (pizotifen or pizotyline).ab,kw,ti,tn. 450
39 (alpha adj4 agonist*).ab,kw,ti. 12,572
40 exp alpha 2 adrenergic receptor stimulating agent/ 126,725
41 (clonidine or guanfacine).ab,kw,ti,tn. 20,327
42 exp riboflavin/ or ubidecarenone/ or magnesium/ or magnesium citrate/ or magnesium sulfate/ or magnesium oxide/ or magnesium derivative/ [additional drugs identified 2022] 160,786
43 (riboflavin or vitamin b2 or vitamin b 2 or coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10 or magnesium).ab,kw,ti,tn. [additional drugs identified 2022] 119,146
44 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 2,136,027

45 Economics/ 246,769
46 Cost/ 64,938
47 exp Health Economics/ 1,002,939
48 Budget/ 32,775
49 budget*.ti,ab,kw. 45,859
50 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 305,827
51 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 505,669
52 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. 269,096
53 (value adj2 (money or monetary)).ti,ab,kw. 3909
54 Statistical Model/ 172,230
55 economic model*.ab,kw. 5843
56 Probability/ 137,823
57 markov.ti,ab,kw. 34,476
58 monte carlo method/ 47,954
59 monte carlo.ti,ab,kw. 58,507
60 Decision Theory/ 1848
61 Decision Tree/ 18,902
62 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 45,947
63 or/45-62 [Filter for economic studies from CADTH: www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#health] 1,934,921
64 4 and 44 and 63 2509
65 exp migraine/dt, pc [Drug Therapy, Prevention] 19,315
66 'migrain*'.ab,hw,kw,ti. 86,560
67 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kw,ti. 269,120
68 ((pharmacolog* or pharmaceutical or drug? or medical) adj1 (treatment? or therap* or management)).ab,hw,kw,ti. 1,299,091
69 66 and (67 or 68) 14,004
70 65 or 69 29,664
71 63 and 70 2398
72 64 or 71 3457
73 conference abstract.pt. 4,588,873
74 72 not 73 2767

EconLit (via EBSCOhost)

Date searched: 10 November 2022

Database: EconLit with Full Text

Search modes – Boolean/Phrase

Search Screen – Advanced Search

#	Query	Results
S5	S1 AND S4	76
S4	S2 OR S3	275, 263

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#	Query	Results
S3	AB (therap* or treat* or prevent* or prophyla* or management) OR TI (therap* or treat* or prevent* or prophyla* or management)	143, 783
S2	TX pharmac* OR health* or medic* or drug or drugs	151, 216
S1	AB (headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*) OR SU (headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*) OR TI (headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*)	99

International HTA database (via INAHTA website) https://database.inahta.org/

Date searched: 10 November 2022

Line	Query	Hits
4	#1 OR #2 OR #3	157
3	'Headache Disorders'[mhe]	69
2	'Headache'[mh]	32
1	headache* or 'head ache*' or migrain* or cephalgi* or cephalalgi* or hemicrani*	154

Cost-effectiveness Analysis Registry (via Tufts Medical Center website) https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Date searched: 10 November 2022

Basic search screen: Methods selected

Results of each search were copied and pasted into Excel, to easily identify unique results, which were then found in PubMed for easy export/import into EndNote.

Search term/s	Results
headache	22
head ache	0
migraine	23, of which 12 unique/11 already found with 'headache' search
Total unique results:	**34**

EconPapers [via Research Papers in Economics (RePEc)] https://econpapers.repec.org/

Date searched: 14 November 2022

Advanced search screen: https://econpapers.repec.org/scripts/search.pf

27 documents matched the search for (headache* OR 'head ache*' OR migrain*) AND (pharmac* OR medic* OR drug OR drugs OR therap* OR treat* OR prevent* OR prophyla*) in *titles and keywords* in working papers, articles, books and chapters that were added to EconPapers in the last 2 years.

National Institute for Health and Care Excellence website www.nice.org.uk/

Date searched: 15 November 2022

Browsed Guidance section: Conditions and diseases > Neurological conditions > Headaches

20 published products on this topic:

6 documents relating to 1 technology appraisal guidance and 1 clinical guideline new/updated since the previous search and judged to contain potentially useful information

Scottish Medicines Consortium website www.scottishmedicines.org.uk/
Date searched: 16 November 2022

Search box on homepage:

migraine 13 results

headache 6 results, 0 unique/new since previous search

0 documents were new/updated since the previous search and judged to contain potentially useful information

All Wales Medicines Strategy Group (AWMSG), via All Wales Therapeutics and Toxicology Centre website https://awttc.nhs.wales/
Date searched: 16 November 2022

Search box on homepage:

migraine 6 results, of which 3 refer to NICE technology appraisals identified above, 2 refer to ongoing NICE technology appraisals and 1 is a review article (not AWMSG)

headache 9 results, of which 0 are relevant/AWMSG documents

0 documents for retrieval, 2 ongoing NICE appraisals identified

Canadian Agency for Drugs and Technologies in Health (CADTH) website https://cadth.ca/
Date searched:

Search box on homepage, results limited to 'Reports' tab.

migraine 87 results, of which 4 potentially relevant

headache 556 results, browsed first 60 results (sorted by relevance), by which point no relevant results were appearing (non-headache conditions). 0 potentially relevant and not already identified

4 documents relating to 2 projects/reviews were judged to contain potentially useful information for the cost-effectiveness or clinical reviews; 1 ongoing reimbursement review and 1 suspended review were also identified.

Google www.google.co.uk
Date searched: 16 November 2022

Results (10 per page) were browsed until yielding very few results containing all search terms.

Documents were retrieved if judged to be potentially useful for the cost-effectiveness review, and if they had not already been identified via the bibliographic databases or HTA websites searches.

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Search string	Number of results browsed	Documents retrieved
migraine prevention OR prophylaxis technology assessment date range: 1 Sept 2021 – 16 Nov 2022	30	3
migraine prevention OR prophylaxis economic date range: 1 Sept 2021 – 16 Nov 2022	40	0
migraine prevention OR prophylaxis cost-effectiveness date range: 1 Sept 2021 – 16 Nov 2022	50	0
Total documents retrieved:		**3**

Google Scholar https://scholar.google.co.uk

Date searched: 16 November 2022

Results (10 per page) were browsed until yielding very few results containing all search terms.

Documents were retrieved if judged to be potentially useful for the cost-effectiveness review, and if they had not already been identified via the bibliographic databases, HTA websites or Google searches.

Search string	Number of results browsed	Documents retrieved
migraine prevention OR prophylaxis technology assessment Since 2021	30	1
migraine prevention OR prophylaxis economic Since 2021	50	2
migraine prevention OR prophylaxis cost-effectiveness Since 2021	50	5
migraine prevention OR prophylaxis costs Since 2021	30	0
Total documents retrieved		**8**

Reference lists search (included studies; journal articles only)

Web of Science Core Collection: Science Citation Index Expanded–1970–present; ***Social Sciences Citation Index (SSCI)–1900–present; Arts and Humanities Citation Index (AHCI)–1975–present; Conference Proceedings Citation Index – Science (CPCI-S)–1990–present; Conference Proceedings Citation Index – Social Science and Humanities (CPCI-SSH)–1990–present; Emerging Sources Citation Index (ESCI)–2015–present.

Date searched: 30 November 2022

Searched for each included study by combinations of author and title keywords

6/9 included study papers had records in Web of Science, yielding **219** reference list results.

Citation Finder https://citation-finder.vercel.app/

Date searched: 30 November 2022

Reference lists from Batty *et al.*, 2013 (36 references) and Ruggeri *et al.*, 2013 (30 references) were copied into Citation Finder, where **36** results were available/downloadable and exported to EndNote

The reference list from Vekov et al., 2019 could not be checked, due to being in non-Roman alphabet.

Forward citations search (included studies; journal articles only)

Web of Science Core Collection: Science Citation Index Expanded-1970–present; SSCI–1900–present; AHCI–1975–present; CPCI-S–1990–present; CPCI-SSH–1990–present; ESCI–2015–present.

Date searched: 30 November 2022

Searched for each included study by combinations of author and title keywords

6/9 included study papers had records in Web of Science, yielding **62** citing paper results

Google Scholar https://scholar.google.co.uk/

Date searched: 30 November 2022

2/3 study papers not found in Web of Science were found via Google Scholar; 1 had 0 citing papers in Google Scholar, 1 had **49** citing papers. Vekov *et al.*, 2019 was not found.

Searches to check for retraction notices, errata and comments relating to included journal articles

MEDLINE (Ovid) search strategy, date searched: 30 November 2022

Database: Ovid MEDLINE(R) ALL <1946 to 29 November 2022>

Search strategy:

---------- ---------- ---------- ---------- ---------- ---------- ----------

1 ('23647483' or '31302899' or '32787820' or '31578100' or '29571276' or '33491167' or '30142988').ui. (7) [these are the 7 included journal articles available in MEDLINE]
2 (cin or comment or con or concern or cri or crf or ecf or eci or efr or ein or erratum or expression or republished or retracted or retraction or rin or rof or rpf or rpi or rrf or rri or uin or uof or update).cm. (2,147,964)
3 1 and 2 (0)
4 ((cost-effectiveness or economic or price range) and (onabotulinum* or erenumab)).mp. and (migraine or headache).ti. [mp = title, book title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (34)
5 (retracted publication or retraction of publication).pt. (25,344)
6 expression of concern.pt. or expression of concern.af. (2922)
7 (ecf or eci or rin or rof).cm. (27,157)
8 (retraction or retracted).ti. (16,522)
9 5 or 6 or 7 or 8 (33,054)
10 (comment or 'corrected and republished article' or published erratum).pt. (1,113,471)
11 (cin or con).cm. ['comment in' or 'comment on'] (1,748,037)
12 (cri or crf or ecf or eci or efr or ein or rin or rof or rpf or rpi or rrf or rri or uin or uof).cm. (430,242)

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13 (comment on or erratum or corrigendum or withdrawn).ti. (94,317)
14 9 or 10 or 11 or 12 or 13 (2,171,292)
15 4 and 14 (1)

0 retractions or comments.

1 erratum found – not related to any included studies.

EMBASE (Ovid) search strategy, date searched: 30 November 2022

Checking for Ruggeri et al., 2013 and Vekov et al., 2019 only, as these are not available in MEDLINE.

EMBASE Classic+EMBASE <1947 to 29 November 2022>

1 ('369487386' or '630983838').rr.0[accession nos. of the 2 included journal articles not available in MEDLINE]
2 (cost-effectiveness or economic or price range).rt.745
3 (onabotulinum* or erenumab or CGRP).rt.61
4 (migraine or headache).rt.386
5 2 and 3 and 40
6 (cost-effectiveness or economic or price range).ti.96,194
7 (onabotulinum* or erenumab or CGRP).ti.5625
8 (migraine or headache).ti.63,709
9 6 and 7 and 828
10 erratum/ or 'expression of concern'/ or retraction notice/262,872
11 Retracted article/13,016
12 yes.ne.5454
13 (erratum or tombstone).pt.269,407
14 10 or 11 or 12 or 13272,633
15 (retraction or retracted).ti.16,297
16 (comment on or erratum or corrigendum or withdrawn).ti.236,791
17 14 or 15 or 16312,777
18 9 and 170

No errata, retractions or comments found.

Retraction Watch Database http://retractiondatabase.org/RetractionSearch.aspx

Date searched: 22 November 2022

Searched for 'migraine' in Title field (as all included studies include this word in the title): 7 results, none of which are in the included studies.

Additional search for utility data to inform the economic model

MEDLINE (Ovid)

Date searched: 21 November 2022

Ovid MEDLINE(R) ALL <1946 to 18 November 2022>

1 exp Migraine Disorders/ 31,004
2 'migrain*'.ab,kf,ti. 41,133
3 1 or 2 [migraine PRECISE] 45,319

4 Quality-Adjusted Life Years/ 15,238
5 (quality-adjusted or adjusted life year$).ti,ab,kf. 21,931
6 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 13,787
7 (illness state$1 or health state$1).ti,ab,kf. 7951
8 (hui or hui1 or hui2 or hui3).ti,ab,kf. 1874
9 (multiattribute$ or multi attribute$).ti,ab,kf. 1221
10 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 19,025
11 utilities.ti,ab,kf. 8926
12 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. 16,014
13 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 5587
14 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 25,680
15 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 2259
16 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. 14,819
17 quality of life/ and ec.fs. 10,872
18 quality of life/ and (health adj3 status).ti,ab,kf. 11,245
19 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 7420
20 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. 50,021
21 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. 4925
22 *quality of life/ and (quality of life or qol).ti. 62,829
23 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. 38,413
24 quality of life/ and health-related quality of life.ti,ab,kf. 42,320
25 models, economic/ 11,038
26 or/4-25 [Filter FSF – sensitivity maximizing filter to identify HSU studies, from Arber *et al.*, 2017 https://doi.org/10.1017/S0266462317000897] 209,664
27 3 and 26 860

Lines 4–26 are 'filter FSF1 – sensitivity maximizing' from Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. Performance of Ovid MEDLINE search filters to identify health state utility studies. *Int J Technol Assess Health Care* 2017;**33**:472–80. https://doi.org/10.1017/S0266462317000897

Cost-effectiveness Analysis Registry (via Tufts Medical Center website) https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Date searched: 21 November 2022

Basic search screen: Utilities selected

Search term/s	Results
migraine	118

ISPOR Presentations Database

www.ispor.org/heor-resources/presentations-database/search

Date searched: 21 November 2022

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Search term/s (keyword field)	Results
migrain* AND (utilit* OR HSUV*)	32, of which 8 duplicates = 24 unique results
migrain* AND disutilit*	3 duplicates/already found above = 0 unique
migrain* AND (EQ-5D OR euroqol)	21, of which 10 duplicates, 3 already found above = 8 unique
Total: 32 posters/records downloaded (posters downloaded where available)	

ScHARRHUD

www.scharrhud.org/index.php

Date searched: 21 November 2022

Search: migrain* in Any field 3 results, of which 1 already found by MEDLINE search above

Total: 2 records downloaded

EQ-5D website

Search for EQ-5D documents: https://euroqol.org/publications/search-for-eq-5d-documents/

Date searched: 22 November 2022

migraine 0 results

headache 0 results

Appendix 8 Cost-effectiveness review – further information

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TABLE 100 Characteristics of included studies

Author, year, country	Objective(s)	Study design	Study population	Subgroups	Sample size (*n*)	Intervention	Comparators	Type of economic evaluation
Journal articles								
Batty, 2013[167] UK	To evaluate the cost-effectiveness of BTA compared with placebo for the prophylaxis of headaches in adults with CM	Model-based economic evaluation	Participants in the Phase III PREEMPT Trial were considered for the model	The groups were: (1) Licensed population, of all CM participants (*n* = 401), (2) Participants who previously received 1 or more oral drugs (only topiramate was a licensed treatment for migraine) (*n* = 983), and (3) Participants who previously received 3 or more oral drugs (*n* = 439)	1384	BTA	Placebo	CUA
Giannouchos, 2019[168] Greece	To evaluate the differences in costs and outcomes of erenumab versus BTA in CM participants	Model-based economic evaluation	Participants with CM who failed initial preventive treatment with BTA or erenumab. Adults with a mean age 41 years; and 86% were females	None	Not reported	Erenumab	BTA	CUA
Hansson-Hedblom, 2020[169] Norway and Sweden	To describe the economic consequences of migraine using cost of illness survey data and the cost-effectiveness of BTA for the treatment of CM	Model-based economic evaluation	Participants in Phase III PREEMPT trial	As in other study using PREEMPT trial participants	Not reported	BTA	Placebo	CUA
Hollier-Hann, 2020[170] UK	To evaluate the cost-effectiveness of BTA compared with placebo for the prophylaxis of headaches in adults with CM	Model-based economic evaluation	Participants with CM who have previously received three or more oral preventive therapies in PREEMPT trial	None	439	BTA	Placebo	CUA

TABLE 100 Characteristics of included studies (*continued*)

Author, year, country	Objective(s)	Study design	Study population	Subgroups	Sample size (*n*)	Intervention	Comparators	Type of economic evaluation
Lipton, 2018[171] USA	To estimate value-based pricing ranges for erenumab 140 mg, administered subcutaneously every 4 weeks, in patients who have failed at least 1 prior preventive treatment compared to BSC	Model-based economic evaluation	Participants that were either naıve to preventive treatment or previously treated with preventive medication but failed due to lack of efficacy or intolerability. The populations considered in the model are subgroups of participants who have previously failed 1 prior preventive therapy	CM and EM group	Not reported	Erenumab	Placebo (vs. BTA as a scenario analysis)	CUA
Mahon, 2021[172] Sweden	To determine the cost-effectiveness of erenumab for the preventive treatment of migraine	Model-based economic evaluation	Participants with CM and EM. The base-case analysis for 'total migraine' assumed that 66.7% of the participants had CM and 33.3% had EM, which aligns with the reported percentage of participants with CM for whom prophylactic treatment fails	None	Not reported	Erenumab	Placebo (vs. BTA as a scenario analysis)	CUA
Ruggeri, 2013[173] Italy	To evaluate the cost-effectiveness of BTA versus placebo in participants with CM	Model-based economic evaluation	Participants with CM from PREEMPT trial	None	1384 patients. (*n* = 686 – BTA; *n* = 698 – placebo)	BTA	Placebo	CUA
Sussman, (2018[174] USA	To assess the cost-effectiveness of erenumab for the prophylactic treatment of EM and CM	Model-based economic evaluation	Participant with EM and CM. The analyses were done separately	CM and EM groups	Not stated	Erenumab	Placebo (vs. BTA as a scenario analysis)	CUA

continued

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TABLE 100 Characteristics of included studies (*continued*)

Author, year, country	Objective(s)	Study design	Study population	Subgroups	Sample size (*n*)	Intervention	Comparators	Type of economic evaluation
Vekov, 2019[175] Bulgaria	To develop a model based on costs and health benefits of CGRP inhibitors	Model-based economic evaluation	Participants with EM and CM	CM and EM groups. For the CM group only participants who have not improved with standard preventive therapy were included	667	Erenumab	Preventative treatment	CUA
Other reports								
CADTH (BTA), 2019[176] Canada	To compare cost-effectiveness of BTA with existing treatments	Canada	Model- based economic evaluation	Participants with CM from PREEMPT trial. Adult participants with CM, defined as headache 15 or more days per month and headache lasting 4 hours a day or longer	1384	BTA	BSC	CUA
CADTH (erenumab), 2019[177] Canada	To compare cost-effectiveness of erenumab with existing treatments	Canada	Model- based economic evaluation	Adult participants with CM, defined as headache 15 or more days per month and headache lasting 4 hours a day or longer. (Study 295, STRIVE trial and LIBERTY trial)	Not stated	Erenumab	BSC (vs. BTA in scenario analysis)	CUA
ICER^ (CGRP), 2018[178] USA	To compare cost-effectiveness of CGRP inhibitors as the preventative treatments for participants with EM or CM	USA	Model- based economic evaluation	Patients with CM who fail initial preventive treatment with BTA or other treatment for the prevention of migraine attack	Not stated	Erenumab, fremanezumab	BSC (no preventative care)	CUA
NICE: erenumab, 2019[180] UK	To compare cost-effectiveness of erenumab with existing treatments	UK	Model- based economic evaluation	Patients with CM who fail initial preventive treatment with BTA or other treatment for the prevention of migraine attack	439	Erenumab	BSC and BTA	CUA
NICE: fremanezumab, 2019[179] UK	To compare cost-effectiveness of fremanezumab with existing treatments	UK	Model- based economic evaluation	Patients with CM who fail initial preventive treatment with BTA or other treatment for the prevention of migraine attack	439	Fremanezumab	BSC and BTA	CUA

TABLE 100 Characteristics of included studies (*continued*)

Author, year, country	Objective(s)	Study design	Study population	Subgroups	Sample size (*n*)	Intervention	Comparators	Type of economic evaluation
NICE: galcanezumab, 2020[181] UK	To compare cost-effectiveness of galcanezumab with existing treatments	UK	Model- based economic evaluation	Patients with CM who fail initial preventive treatment with BTA or other treatment for the prevention of migraine attack	439	Galcanezumab	BSC and BTA	CUA
Warwick Evidence, 2011[182] UK	To compare cost-effectiveness of BTA with existing treatments	UK	Model- based economic evaluation	Patients in the Phase III PREEMPT trial were considered for the model	1384	BTA	Placebo	CUA

BSC, best supportive care; BTA, onabotulinumtoxinA; CADTH, Canadian Agency for Drugs and Technology in Health; CM, chronic migraine; CUA, cost-utility analysis; EM, episodic migraine; ICER^, Institute for Clinical and Economic Review; PREEMPT, patients in the Phase III REsearch Evaluating Migraine Prophylaxis Therapy.

TABLE 101 Details of the economic models and model inputs

Authors, year	Model type	Perspective	Time horizon	Cost included in the model	Source of cost and resource inputs	Currency, price year
Journal articles						
Batty, 2013[167]	A Markov model with 13 health states, including death. The 12 states were split into 2 parallel stages: on treatment and off treatment. A 12-week cycle length was employed. The model also considered negative and positive stopping rule for the treatment	NHS	2 years	Cost of BTA; consultant time to take participant history, tailor prophylactic and acute treatment; consultant time to administer the injections; cost of care including GP visits, ED visits, hospitalisation and triptan costs	Resource used was informed by IBMS, with unit costs taken from NHS reference cost, cost of triptans per attack was based on the weighted average costs in the UK in 2010	UK £ 2010
Giannouchos, 2019[168]	Decision tree model	Payer and societal perspective	1 year	Direct costs included the cost of the 2 drugs and administration, the use of acute drugs under usual care, and hospitalisation costs, physician, and ED visits. Indirect costs for the societal perspective analysis included wages lost on workdays	Resource utilisation data were obtained from 4 previously published studies and the cost inputs were obtained from publicly available data for the Greek healthcare sector and on the governmental pricing system derived from a public Greek hospital	Euro € 2019

continued

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TABLE 101 Details of the economic models and model inputs (*continued*)

Authors, year	Model type	Perspective	Time horizon	Cost included in the model	Source of cost and resource inputs	Currency, price year
Hansson-Hedblom, 2020[169]	A Markov model with 13 health states, including death as mentioned in Batty AJ, *et al.*	Payer and societal perspective	10 years	Direct cost included cost of BTA, neurology consultant appointment, specialist nurse appointment, cost of care including GP visits, ED visits, hospitalisation and triptan costs. Indirect cost involved productivity cost		SEK, 2018 for Sweden; NOK, 2018 for Norway
Hollier-Hann, 2020[170]	CUA using Markov model with 13 health states, including death as mentioned in Batty AJ, *et al.*	NHS	2 years	Cost of BTA; consultant time to take participant history, tailor prophylactic and acute treatment; consultant time to administer the injections; cost of care including GP visits, ED visits, hospitalisation and triptan costs	Resource used was informed by IBMS, with unit costs taken from NHS reference cost, cost of triptans per attack was based on the weighted average costs in the UK in 2010	UK £ 2010
Lipton, 2018[171]	A Markov model was implemented based on the clinical data from the Episodic Migraine (EM) and Chronic Migraine (CM) studies for the subgroups of participants with prior treatment failures. The cycle length was 28 days	US societal perspective	10 years	Direct medical costs included cost of medicine and administration, GP visits, ED visits, hospitalisations, and specialist neurologist consultations based on published unit costs. Cost of medicines to treat acute attacks. Indirect costs included productivity cost associated with presenteeism and absenteeism	Average annual medical resource use is taken from a published 2009 analysis of survey data from 7437 migraine participants in the USA	USD $ 2017
Mahon, 2021[172]	A hybrid decision tree plus Markov model was developed	Swedish societal perspective	10 years	Direct cost included cost of medicine and administration, ED visit, hospitalisation, GP visit, consultant visit, nurse/physician visit, triptan medication and other medications. Indirect cost related to absenteeism and presenteeism were included	Resource utilisation and efficacy data were sourced from four trials (CM295, STRIVE, ARISE and LIBERTY). Study 178, which had an open label phase of 256 weeks, was used to inform long-term assumptions regarding those who continued on treatment. Resource usage costs were obtained from the price list of Sweden. Productivity costs were included from the published literature	SEK, 2018

TABLE 101 Details of the economic models and model inputs (*continued*)

Authors, year	Model type	Perspective	Time horizon	Cost included in the model	Source of cost and resource inputs	Currency, price year
Ruggeri, 2013[173]	A Markov model with 13 health states, including death as mentioned in Batty AJ, *et al.*	Italian National Health Service and a societal perspective	2 years	Direct cost included cost of medicine and administration, GP visit or outpatient cost, ED visit, hospitalisation and cost of triptans. Indirect costs included productivity cost	Resource utilisation data were derived from IBMS study. Costs were obtained from the local government data	Euro € 2013
Sussman, 2018[174]	A hybrid Monte Carlo participant simulation and Markov cohort model was constructed. Both EM and CM participants must have failed at least 1 previous therapy prior to model entry since CGRP pathway antagonists are expected to be used as second-line therapies. Participants in the EM cohort must have had between 4 and 14 MMDs and participants in the CM cohort must have had at least 15 MMDs at baseline	US societal and payers perspective	2 years	Direct cost included – acute medication cost, physician visit, ED visit, AEs and hospitalisation cost. Indirect costs included productivity cost	Data inputs for the model were derived from the erenumab pivotal and open labelled extended trials, and BTA pivotal trial, published literature, and publicly available sources	USD $ 2017
Vekov, 2019[175]	A hybrid model including a Monte Carlo simulation and a Markov cohort model. The input data to the model are the primary and secondary clinical end-points in the randomised trials NCT02066415 and NCT02483585. They measure the change in the number of days with migraine per month at weeks 12 and 24, the number of days per month with symptomatic migraine therapy	Payers' perspective	2 years	Only the cost of medicines was included; other healthcare costs were assumed to be equal for both therapies and hence excluded	Resource utilisation (medicine usage) data were obtained from the randomised trial NCT02066415	Bulgarian Lev (BGN) 2019
Other reports						
CADTH (BTA), 2019[176]	Hybrid model with decision tree for 12-week assessment period, classifying patients as responders and non-responders, and Markov model for post-assessment with 12-week cycle lengths	Canadian public healthcare payer perspective	3 years	Direct costs included cost of medicine and administration, GP visits or outpatient cost, ED visits, hospitalisation and cost of triptans. Indirect costs included productivity cost	Resource used was informed by IBMS, with unit costs taken from NHS reference costs, cost of triptans per attack was based on the weighted average costs in the UK in 2010	CAD $ 2019

continued

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TABLE 101 Details of the economic models and model inputs (*continued*)

Authors, year	Model type	Perspective	Time horizon	Cost included in the model	Source of cost and resource inputs	Currency, price year
CADTH (erenumab), (2019)[177]	Hybrid model with decision tree for 12-week assessment period, classifying participants as responders and non-responders, and Markov model for post-assessment with 12-week cycle lengths	Canadian public healthcare payer perspective	3 years	Direct costs included cost of medicine and administration, GP visits or outpatient cost, ED visits, hospitalisation and cost of triptans. Indirect costs included productivity cost	Resource used was informed by the trial, and cost data were obtained from manufacturer and other local data resources	CAD $ 2019
ICER^ (CGRP), (2018)[178]	Markov model comprising CGRP inhibitor versus no preventive treatment arms. The intervention arm of the model includes 3 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	Health system payer perspective	2 years	Direct medical care cost including cost of medicine, GP visit, outpatient visit, ED visit and hospitalisation	Resource used was informed by IBMS, with unit costs taken from the local data resources	USD $ 2018
NICE: erenumab, (2019)[180]	A decision tree plus Markov model included 2 health states – on treatment and discontinuation of treatment once patients were classified as responders or non-responders	NHS perspective	Lifetime	Migraine-specific cost related to hospitalisation and ED visits, healthcare professional visits and use of acute medication	Resource used was informed by National Health and Wellness survey conducted in migraine population, with unit costs taken from the local data resources	UK £ 2018
NICE: fremanezumab, (2019)[179]	A decision tree plus Markov model included 2 health states – on treatment and discontinuation of treatment once patients were classified as responders or non-responders	NHS perspective	10 years	Migraine-specific cost related to hospitalisation and ED visits, healthcare professional visits and use of acute medication	Resource used was informed by National Health and Wellness survey conducted in migraine population, with unit costs taken from the local data resources	UK £ 2019
NICE: galcanezumab, (2020)[181]	A decision tree plus Markov model included 2 health states – on treatment and discontinuation of treatment once patients were classified as responders or non-responders	NHS perspective	Lifetime	Migraine-specific cost related to hospitalisation and ED visits, healthcare professional visits and use of acute medication	Trial-specific (CONQUER) data and the resource utilisation data from Lipton *et al.* (2018)	UK £ 2020

TABLE 101 Details of the economic models and model inputs (*continued*)

Authors, year	Model type	Perspective	Time horizon	Cost included in the model	Source of cost and resource inputs	Currency, price year
Warwick Evidence, (2011)[182]	A Markov model with 13 health states, including death. The 12 states were split into 2 parallel stages: on treatment and off treatment. Each treatment state was subdivided into categories based on the number of headache days per 28 days. 3 health states for EM (0–3, 4–9 and 10–14 headache days per 28 days), and 3 health states for CM (15–19, 20–23 and 24 + headache days per 28 days). A 12-week cycle length was employed. The model also considered negative and positive stopping rule for the treatment	NHS perspective	2 years	Migraine-specific cost related to hospitalisation and ED visits, healthcare professional visit and use of acute medication	Resource used was informed by IBMS, with unit costs taken from NHS reference costs, cost of triptans per attack was based on the weighted average costs in the UK in 2010	UK £ 2011

BTA, onabotulinumtoxinA; BGN, Bulgarian Lev; CAD, Canadian Dollar; CADTH, Canadian Agency for Drugs and Technology in Health; CM, chronic migraine; CUA, cost-utility analysis; ED, emergency department; EM, episodic migraine; IBMS, International Burden of Migraine Study; ICER^, Institute for Clinical and Economic Review; NOK, Norwegian Krone; SEK, Swedish Krona; USD, US Dollar.

TABLE 102 Details of model inputs and results

Authors, year	Discount rate (%)	Utilities (QALYs) and outcomes			Results/ICER	WTP threshold	Sensitivity analyses
		Preference-based measure used to estimate utilities	Whose utility values?	Other outcomes			
Journal articles							
Batty, 2013[167]	3.5	MSQ v2.1 was used to collect HRQoL information at baseline and 24 weeks after the intervention. The MSQ scores were mapped to EuroQol EQ-5D to produce utility values	Utility values from the participants of the PREEMPT trial	Headache per day/ year, cost per headache day avoided	At 2 years, BTA treatment was associated with an increase in costs of £1367 and an increase in QALYs of 0.1 compared to placebo, resulting in an ICER of £15,028. Treatment with BTA reduced headache days by 38 days per year at a cost of £18 per headache day avoided	£20,000–30,000/QALY	Both deterministic and PSA were performed

continued

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TABLE 102 Details of model inputs and results (*continued*)

Authors, year	Discount rate (%)	Utilities (QALYs) and outcomes			Results/ICER	WTP threshold	Sensitivity analyses
		Preference-based measure used to estimate utilities	Whose utility values?	Other outcomes			
Giannouchos, 2019[168]	None	QALYs were calculated by using the health utility data (MSQ to EQ-5D) for participants with CM from 10 countries obtained from the IBMS	General public	Number of migraines avoided	CM treatment with erenumab compared to BTA resulted in ICERs of €218,870 and €231,554 per QALY gained and €620 and €656 per migraine avoided, from the societal and the payer's perspective, respectively. Using a cost-effectiveness threshold equal to three times the local GDP per capita (€49,000), for erenumab the ICERs fall below this threshold	EURO 49,000/QALY	Both PSA and deterministic sensitivity analyses were performed
Hansson-Hedblom, 2020[169]	3	The IBMS study was used to map EQ-5D scores from MSQ score	Utility values from the participants of PREEMPT trial		In Sweden, BTA was associated with 0.223 additional QALYs at an additional cost of EUR 4126 compared to placebo, resulting in an ICER of EUR 18,506. In Norway, BTA was associated with 0.216 additional QALYs at an additional cost of EUR 4301 compared to placebo, resulting in an ICER of EUR 19,954	SEK 280,000 (Sweden) and NOK 495,000 (Norway)	Both PSA and deterministic sensitivity analyses were performed
Hollier-Hann, 2020[170]	3.5	Utility values were directly obtained from the EQ-5D data collected in the REPOSE study. EQ-5D was administered at baseline and each follow-up visit (at intervals of approx. 12 weeks)	UK tariff	Headache per day/ year, cost per headache day avoided	BTA treatment resulted in incremental costs of £1204 and an incremental QALY gain of 0.07 compared with placebo in CM participants who have previously failed 3 or more preventive treatments, corresponding to an ICER of £16,306 per QALY gained	£20,000–30,000/QALY	Both PSA and deterministic sensitivity analyses were performed
Lipton, 2018[171]	3	MSQ responses from the erenumab EM and CM pivotal studies were mapped to the EQ-5D-3L, then pooled to generate one complete migraine data set	General public		Erenumab resulted in incremental QALYs of 0.185 vs. BSC and estimated cost offsets due to reduced MMDs of $8482 over 10 years, with an average duration of treatment of 2 years	$100,000–200,000/QALY	Both PSA and deterministic sensitivity analyses were performed

TABLE 102 Details of model inputs and results (*continued*)

Authors, year	Discount rate (%)	Utilities (QALYs) and outcomes			Results/ICER	WTP threshold	Sensitivity analyses
		Preference-based measure used to estimate utilities	Whose utility values?	Other outcomes			
Mahon, 2021[172]	3	Two trials included in this study used the MSQ score which was mapped onto EQ-5D	Not stated	Cost per migraine day avoided	Erenumab treatment resulted in ICERs of SEK 34,696 and SEK 301,565 per QALY gained in the total migraine and EM populations, respectively. Erenumab was dominant in the CM population	SEK 300,000/QALY	Both PSA and deterministic sensitivity analyses were performed
Ruggeri, 2013[173]	3	The IBMS study was used to map EQ-5D scores from MSQ score	UK tariff	Headache per day/year, cost per headache day avoided	BTA compared with placebo gained an incremental 0.04 more QALYs per participant; the incremental cost per participant was €208; the ICER was €4899 per QALY gained	€20,000–30,000/QALY	Both PSA and deterministic sensitivity analyses were performed
Sussman, 2018[174]	3	EQ-5D scores were used	Not stated	Headache-related disability, lost work productivity, anxiety and depression	From a societal perspective treatment with erenumab compared with no preventive treatment ranges from a dominant strategy among CM participants to an ICER of $122,167 for EM participants. When excluding indirect costs (i.e. payer perspective), the ICERs are cost-effective among CM participants ($23,079 and $65,720 vs. no preventive treatment and BTA, respectively), but not among EM participants	USD 50,000/QALY	Both PSA and deterministic sensitivity analyses were performed
Vekov, 2019[175]	5	EQ-5D scores were used	Not stated	HIT-6, MIDAS	Erenumab was not cost-effective compared to placebo (standard prevention therapy) with ICER of 637,000 BGN per QALY	Three times the national annual GDP per capita	PSA
Other reports							
CADTH (BTA), 2019[176]	3	MSQ was used to collect HRQoL information at baseline and 24 weeks after the intervention. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values from the participants of PREEMPT trial were used	Headache per day/year, cost per headache day avoided	ICER was CAD 134,601/QALY gained for BTA vs. BSC. At a WTP of CAD 50,000 per QALY, BTA was associated with a 9% probability of being the optimal intervention. A price reduction of more than 75% is required to achieve an ICER of less than CAD 50,000/QALY	CAD 50,000	Sensitivity analysis showed that utility values had the greatest influence on model results

continued

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TABLE 102 Details of model inputs and results (*continued*)

Authors, year	Discount rate (%)	Utilities (QALYs) and outcomes			Results/ICER	WTP threshold	Sensitivity analyses
		Preference-based measure used to estimate utilities	Whose utility values?	Other outcomes			
CADTH (erenumab), 2019[177]	3	MSQ was used to collect HRQoL information at baseline and 24 weeks after the intervention. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values from the participants of PREEMPT trial were used	Headache per day/ year, cost per headache day avoided	Erenumab dominated BTA in the population for whom the previous treatment including BTA had failed	CAD 50,000	Sensitivity analyses involved analysing different time horizons were performed
ICER^ (CGRP), 2018[178]	3	MSQ was used to collect HRQoL information at baseline and 24 weeks after the intervention. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values from the participants of PREEMPT trial were used	Headache per day/ year, cost per headache day avoided	The ICER for erenumab vs. no preventative treatment was USD 86,000/QALY and fremanezumab vs. no preventative treatment was USD 115,000/QALY, both way above the baseline WTP of USD 50,000/QALY	USD 50,000	Sensitivity analyses were performed using topiramate as the alternative treatment to BTA and this resulted in an estimated ICER of USD 28,960/QALY
NICE: erenumab, 2019[180]	3.5	MSQ was used to collect HRQoL information at baseline and 24 weeks after the intervention. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values obtained from erenumab trials (Study 295, STRIVE and ARISE) data	Headache per day/ year, cost per headache day avoided	The blended dose of erenumab was cost-effective in treating CM population vs. BTA and vs. BSC with an ICER of £18,893 and £17,212 per QALY gained, respectively. Erenumab 140 mg is cost-effective treatment vs. both BTA and BSC, with an ICER of £17,832 and £13,340 per QALY gained, respectively	£20,000–30,000/QALY	Both PSA and deterministic sensitivity analyses were performed including using the whole migraine population and a societal perspective
NICE: fremanezumab, 2019[179]	3.5	MSQ was used to collect HRQoL information. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values obtained from patient level MSQ data from FOCUS trial	Headache per day/ year, cost per headache day avoided	Fremanezumab had higher costs, but also gained more QALYs than both BSC and BTA. The ICERs showed that fremanezumab was a cost-effective treatment compared to BSC (£11,825/QALY gained) and BTA (£16,227/QALY gained)	£20,000–30,000/QALY	Both PSA and deterministic sensitivity analyses were performed

TABLE 102 Details of model inputs and results (*continued*)

Authors, year	Discount rate (%)	Utilities (QALYs) and outcomes			Results/ICER	WTP threshold	Sensitivity analyses
		Preference-based measure used to estimate utilities	Whose utility values?	Other outcomes			
NICE: galcanezumab, 2020[181]	3.5	MSQ was used to collect HRQoL information. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values obtained from patient level MSQ data from CONQUER trial	Headache per day/ year, cost per headache day avoided	The actual ICERS were confidential and masked. However, the report indicated that ICER for galcanezumab fell below the lower threshold (£20,000/QALY gained) as defined by standard WTP for UK	£20,000–30,000/QALY	Both PSA and deterministic sensitivity analyses were performed
Warwick Evidence, 2011[182]	3.5	MSQ was used to collect HRQoL information. The MSQ scores then were mapped into EQ-5D to produce utility values	Utility values obtained from patient level MSQ data from PREEMPT Trial	Headache per day/ year, cost per headache day avoided	The reported ICER was £5828/QALY gained	£20,000–30,000/QALY	Both PSA and deterministic sensitivity analyses were performed

BSC, best supportive care; BTA, onabotulinumtoxinA; BGN, Bulgarian Lev; CAD, Canadian Dollar; CADTH, Canadian Agency for Drugs and Technology in Health; CM, chronic migraine; EM, episodic migraine; EQ-5D, EuroQol EQ-5D; GDP, gross domestic product; IBMS, International Burden of Migraine Study; ICER^, Institute for Clinical and Economic Review; NOK, Norwegian Krone; PREEMPT, patients in the Phase III REsearch Evaluating Migraine Prophylaxis Therapy; SEK, Swedish Krona; USD, US dollar.

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TABLE 103 Other study details

Author, year	Limitations	Generalisability
Journal articles		
Batty, 2013[167]	Placebo was not representative of standard care	Transferable
Giannouchos, 2019[168]	Limitations were mostly presented for the assumptions made in the model	Context-specific
Hansson-Hedblom, 2020[169]	The clinical trial may not be representative of everyday practice and physicians and participants may adjust treatment practices. The model was limited by only using MMDs, and other dimensions of migraine, such as duration and severity, were not considered	Context-specific
Hollier-Hann, 2020[170]	Limitations included the assumptions made for the model including that treatment response, HRQoL, and resource utilisation were based on MMD frequency alone	Transferable
Lipton, 2018[171]	The model was created based on primary efficacy data from a mixed population of participants (EM and CM). There were also limited data beyond week 12 for CM participants. Also, treatment response, HRQoL and resource utilisation were based on MMD frequency alone	Context-specific
Mahon, 2021[172]	Limitations included the assumptions made for the model including that treatment response, HRQoL and resource utilisation were based on MMD frequency alone	Context-specific
Ruggeri, 2013[173]	Same limitations as Lipton *et al.* (see above) and also the study used the UK tariff for the utility scores in the base model	Transferable
Sussman, 2018[174]	Same limitations as Lipton *et al.* (see above).	Context-specific
Vekov, 2019[175]	Limitations were not stated	Context-specific
Reports		
CADTH (BTA), 2019[176]	The severity of CM was not captured in the model and there was no good quality of comparative evidence	Context-specific
CADTH (erenumab), 2019[177]	There was no good quality of comparative evidence	Context-specific
ICER^ (CGRP), 2018[178]	Since the data were obtained from the trial, there was uncertainty about the long-term effectiveness of the drugs	Context-specific
NICE: erenumab, 2019[180]	Uncertainty due to not having long-term effectiveness data	Context-specific
NICE: fremenzumab, 2019[179]	Uncertainty due to not having long-term effectiveness data. There was also a lack of granularity within the published data for BTA, which led to limitations within the NMA conducted to compare the efficacy of fremanezumab and BTA	Context-specific
NICE: galcanezumab, 2020[181]	The limitations included the model's inability to capture the natural progression of diseases, the use of short-term estimates of mean change in MHDs, and response rates for extrapolating to different time horizons	Context-specific
Warwick Evidence, 2011[182]	Limitations included the trials limitation to deal with correlated data, predicted ED-5D scores and the integrity around utility scores	Context-specific

BTA, onabotulinumtoxinA; CADTH, Canadian Agency for Drugs and Technology in Health; CM, chronic migraine; EM, episodic migraine; EQ-5D, European-Quality of Life Five dimensions; ICER^, Institute for Clinical and Economic Review.

TABLE 104 Quality assessment criteria of included studies

	Journal articles								
	Batty *et al.*[167]	Giannouchos *et al.*[168]	Hansson-Hedblom *et al.*[169]	Hollier-Hann *et al.*[170]	Lipton *et al.*[171]	Mahon *et al.*[172]	Ruggeri *et al.*[173]	Sussman *et al.*[174]	Vekov *et al.*[175]
CHEERS 2022 (n = 27)									
Yes	25	23	23	23	22	25	23	25	12
No	2	2	2	3	2	2	2	2	10
Partial	1	3	3	2	4	1	3	1	6
Unclear	0	0	0	0	0	0	0	0	0
Not applicable	0	0	0	0	0	0	0	0	0
Philips criteria (n = 57)									
Yes	51	50	50	49	51	51	50	51	20
No	3	4	4	6	4	3	3	3	16
Partial	3	3	2	2	2	2	2	3	9
Unclear	0	0	0	0	0	0	1	0	10
Not applicable	0	0	1	0	0	1	1	0	2

	Other reports						
	CADTH (BTA)[176]	CADTH (Erenumab)[177]	ICER^ (CGRP)[178]	NICE (Erenumab)[180]	NICE (Fremenzumab)[179]	NICE (Galcanezumab)[181]	Warwick Evidence (BTA)[182]
CHEERS 2022 (n = 27)							
Yes	26	26	25	26	26	26	24
No	1	0	1	1	1	1	1
Partial	0	1	1	0	0	0	3
Unclear	0	0	0	0	0	0	0
Not applicable	0	0	0	0	0	0	0
Philips criteria (n = 57)							
Yes	50	49	52	53	54	55	55
No	3	2	1	2	1	0	0
Partial	4	6	4	1	1	1	2
Unclear	0	0	0	1	1	1	0
Not applicable	0	0	0	0	0	0	0

CADTH, Canadian Agency for Drugs and Technology in Health; ICER^, Institute for Clinical and Economic Review.

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Appendix 9 Model inputs for the economic model

TABLE 105 Deterministic transition probabilities used in the base-case analysis

Transitions	Placebo	BTA	Eptinezumab 100	Eptinezumab 300	Fremanezumab (monthly)	Fremanezumab (quarterly)	Galcanezumab	Topiramate
0–3 MHD–0–3 MHD	0.56200	0.68563	0.67243	0.69976	0.68342	0.66996	0.67054	0.62965
0–3 MHD–4–9 MHD	0.28100	0.16337	0.16182	0.14079	0.15336	0.16373	0.16336	0.19681
0–3 MHD–10–14 MHD	0.05400	0.03862	0.03823	0.03368	0.03640	0.03863	0.03847	0.04386
0–3 MHD–15–19 MHD	0.01500	0.01660	0.01614	0.01934	0.01743	0.01586	0.01604	0.01363
0–3 MHD–20–23 MHD	0.03400	0.02601	0.02585	0.02090	0.02386	0.02629	0.02605	0.03053
0–3 MHD–24–28 MHD	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
0–3 MHD–0–3 Off TX	0.05400	0.06977	0.08553	0.08553	0.08553	0.08553	0.08553	0.08553
4–9 MHD–0–3 MHD	0.17200	0.40152	0.39196	0.43971	0.41116	0.38764	0.38866	0.31857
4–9 MHD–4–9 MHD	0.49100	0.33880	0.33422	0.31423	0.32618	0.33606	0.33601	0.37326
4–9 MHD–10–14 MHD	0.23800	0.15606	0.15482	0.13033	0.14497	0.15701	0.15615	0.18513
4–9 MHD–15–19 MHD	0.02800	0.02325	0.02281	0.02362	0.02314	0.02274	0.02283	0.02300
4–9 MHD–20–23 MHD	0.02800	0.02483	0.02460	0.02122	0.02324	0.02490	0.02471	0.02738

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TABLE 105 Deterministic transition probabilities used in the base-case analysis (*continued*)

Transitions	Placebo	BTA	Eptinezumab 100	Eptinezumab 300	Fremanezumab (monthly)	Fremanezumab (quarterly)	Galcanezumab	Topiramate
4–9 MHD–24–28 MHD	0.00600	0.00249	0.00249	0.00179	0.00221	0.00255	0.00254	0.00355
4–9 MHD–4–9 Off TX	0.03700	0.05305	0.06910	0.06910	0.06910	0.06910	0.06910	0.06911
10–14 MHD–0–3 MHD	0.08400	0.21276	0.20761	0.23435	0.21836	0.20519	0.20576	0.16652
10–14 MHD–4–9 MHD	0.27500	0.26762	0.26233	0.27559	0.26766	0.26118	0.26200	0.25391
10–14 MHD–10–14 MHD	0.34300	0.27936	0.27567	0.25747	0.26835	0.27729	0.27666	0.29818
10–14 MHD–15–19 MHD	0.18700	0.12471	0.12346	0.10850	0.11744	0.12480	0.12437	0.14399
10–14 MHD–20–23 MHD	0.04700	0.04675	0.04622	0.04159	0.04436	0.04662	0.04634	0.04928
10–14 MHD–24–28 MHD	0.01900	0.00789	0.00789	0.00567	0.00699	0.00809	0.00804	0.01126
10–14 MHD–10–14 Off TX	0.04500	0.06092	0.07683	0.07683	0.07683	0.07683	0.07683	0.07686
15–19 MHD–0–3 MHD	0.02100	0.08076	0.07868	0.09103	0.08364	0.07756	0.07782	0.05973
15–19 MHD–4–9 MHD	0.12700	0.16688	0.16293	0.18265	0.17086	0.16118	0.16204	0.14218
15–19 MHD–10–14 MHD	0.27500	0.28304	0.27802	0.28198	0.27961	0.27766	0.27780	0.27311
15–19 MHD–15–19 MHD	0.30900	0.21684	0.21418	0.19665	0.20713	0.21577	0.21541	0.24132
15–19 MHD–20–23 MHD	0.12700	0.13237	0.13077	0.11949	0.12624	0.13174	0.13100	0.13715

TABLE 105 Deterministic transition probabilities used in the base-case analysis (*continued*)

Transitions	Placebo	BTA	Eptinezumab 100	Eptinezumab 300	Fremanezumab (monthly)	Fremanezumab (quarterly)	Galcanezumab	Topiramate
15–19 MHD–24–28 MHD	0.06200	0.02575	0.02573	0.01850	0.02283	0.02639	0.02623	0.03673
15–19 MHD–15–19 Off TX	0.07900	0.09435	0.10970	0.10970	0.10970	0.10970	0.10970	0.10978
20–23 MHD–0–3 MHD	0.00000	0.03029	0.02942	0.03564	0.03192	0.02885	0.02899	0.01989
20–23 MHD–4–9 MHD	0.06400	0.06680	0.06541	0.06992	0.06723	0.06502	0.06526	0.06167
20–23 MHD–10–14 MHD	0.09200	0.17809	0.17350	0.20102	0.18456	0.17104	0.17200	0.13944
20–23 MHD–15–19 MHD	0.32800	0.26864	0.26370	0.27076	0.26654	0.26312	0.26398	0.26828
20–23 MHD–20–23 MHD	0.31100	0.34413	0.33962	0.31612	0.33018	0.34164	0.33991	0.34896
20–23 MHD–24–28 MHD	0.18700	0.07768	0.07762	0.05580	0.06884	0.07959	0.07912	0.11078
20–23 MHD–20–23 Off TX	0.01800	0.03437	0.05073	0.05073	0.05073	0.05073	0.05073	0.05098
24–28 MHD–0–3 MHD	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
24–28 MHD–4–9 MHD	0.00000	0.00891	0.00860	0.01140	0.00972	0.00835	0.00845	0.00514
24–28 MHD–10–14 MHD	0.02400	0.04885	0.04757	0.05550	0.05075	0.04686	0.04713	0.03775
24–28 MHD–15–19 MHD	0.09200	0.08665	0.08464	0.09417	0.08847	0.08382	0.08443	0.07881
24–28 MHD–20–23 MHD	0.13900	0.50391	0.49180	0.55323	0.51651	0.48619	0.48697	0.38584

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TABLE 105 Deterministic transition probabilities used in the base-case analysis (*continued*)

Transitions	Placebo	BTA	Eptinezumab 100	Eptinezumab 300	Fremanezumab (monthly)	Fremanezumab (quarterly)	Galcanezumab	Topiramate
24–28 MHD–24–28 MHD	0.70000	0.29077	0.29055	0.20887	0.25771	0.29795	0.29619	0.41468
24–28 MHD–24–28 Off TX	0.04500	0.06092	0.07683	0.07683	0.07683	0.07683	0.07684	0.07777
0–3 Off TX–0–3 Off TX	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
4–9 Off TX–4–9 Off TX	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
10–14 Off TX–10–14 Off TX	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
15–19 Off TX–15–19 Off TX	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
20–23 Off TX–20–23 Off TX	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
24–28 Off TX–24–28 Off TX	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000

Off TX, off treatment.

TABLE 106 Information on drug preparation, administration and recommended doses[a]

Interventions	Available preparations	Strength	Route of administration	Recommended dose	Administration
BTA 150U	200-unit powder for solution for injection vials	200 U	Subcutaneous injection	The recommended total dose is 155 units administered intramuscularly (into the muscle)	Administered by a nurse in a hospital/clinic every 12 weeks. 15-minute appointment
Eptinezumab 100 mg	Eptinezumab 100 mg/ml injection single use vial	100 mg	Intravenous infusion	Recommended dose is 100 mg every 12 weeks. Review treatment 6 months after initiation	Administered by a nurse in a hospital/clinic every 12 weeks. 15-minute appointment
Eptinezumab 300 mg	Eptinezumab 100 mg/ml injection single use vial	100 mg	Intravenous infusion	Recommended dose is 300 mg every 12 weeks. Review treatment 6 months after initiation	Administered by a nurse in a hospital/clinic every 12 weeks. 15-minute appointment
Fremanezumab – monthly	225 mg/1.5 ml solution for injection pre-filled pens/ injection	225 mg	Subcutaneous injection	Recommended dose is 225 mg once a month, review treatment within first 3 months and regularly thereafter	First dose administered by a nurse in a hospital/ clinic, a 30-minute appointment. Subsequent doses assumed 10% would not be able to self-administer
Fremanezumab – quarterly	225 mg/1.5 ml solution for injection pre-filled pens/ injection	675 mg	Subcutaneous injection	Recommended dose is 675 mg every 3 months, review treatment within first 3 months and regularly thereafter	First dose administered by a nurse in a hospital/ clinic, a 30-minute appointment. Subsequent doses assumed 10% would not be able to self-administer
Galcanezumab 120 mg	120 mg/1 ml solution for injection pre-filled pens	120 mg	Subcutaneous injection	Loading dose 240 mg for 1 dose, then maintenance 120 mg once a month. Maintenance dosing to start 1 month after loading dose	First dose administered by a nurse in a hospital/ clinic, a 30-minute appointment. Subsequent doses assumed 10% would not be able to self-administer
Topiramate	Topiramate 25 mg tablets. 60 tablets in one pack	25 mg	Tablet	Initially 25 mg once daily for 1 week, then increased in steps of 25 mg every week; usual dose 50–100 mg daily in 2 divided doses; maximum 200 mg per day	No administration required

Source: https://bnf.nice.org.uk/.[51]

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TABLE 107 Frequency of resource use for each health state (per 3 month/12 week cycle)

For all prophylactic drugs including placebo				
Health states	**GP visits**	**A&E visits**	**Hospital admissions**	**Triptan usage**
0–3 MHD	0.69	0.10	0.03	1.88
4–9 MHD	0.69	0.10	0.03	5.07
10–14 MHD	0.69	0.10	0.03	5.07
15–19 MHD	2.07	0.41	0.09	7.29
20–23 MHD	2.07	0.41	0.09	7.29
24–28 MHD	2.07	0.41	0.09	7.29
0–3 Off TX	0.69	0.10	0.03	1.88
4–9 Off TX	0.69	0.10	0.03	5.07
10–14 Off TX	0.69	0.10	0.03	5.07
15–19 Off TX	2.07	0.41	0.09	7.29
20–23 Off TX	2.07	0.41	0.09	7.29
24–28 Off TX	2.07	0.41	0.09	7.29
Source	IBMS[190]	IBMS[190]	IBMS[190]	IBMS[190]
	Placebo and topriamate	BTA	Eptinezumab, fremanezumab, galcanezumab	
Health states[a]	Consultant visit (15 minutes)	Consultant visit (30 minutes)	Nurse visits	Consultant visits
0–3 MHD	1.00	1.00	0.277	0.036
4–9 MHD	1.00	1.00	0.398	0.064
10–14 MHD	1.00	1.00	0.144	0.114
15–19 MHD	1.00	1.00	0.381	0.219
20–23 MHD	1.00	1.00	0.381	0.219
24–28 MHD	1.00	1.00	0.381	0.219
Source	182	182	179,181	179,181

Off TX, off treatment.
a There were no additional costs with the off treatment health states.

Appendix 10 Economic model results

Base-case cost-effectiveness planes

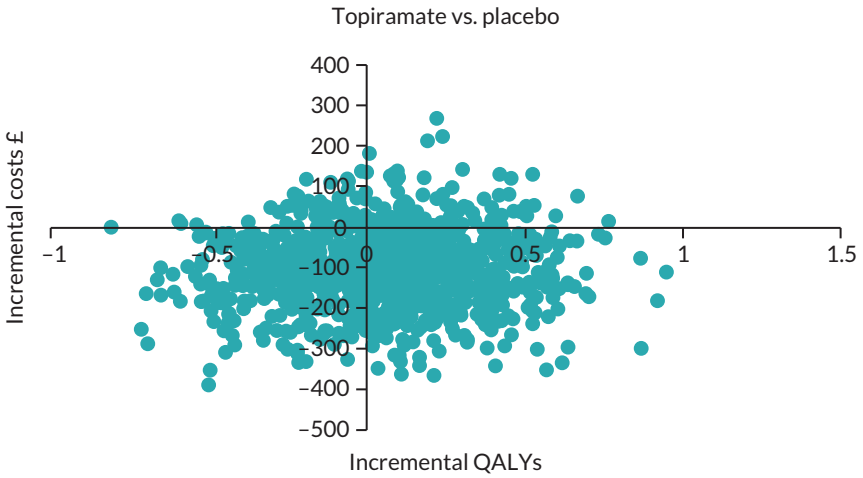

FIGURE 50 Cost-effectiveness plane – topiramate vs. placebo.

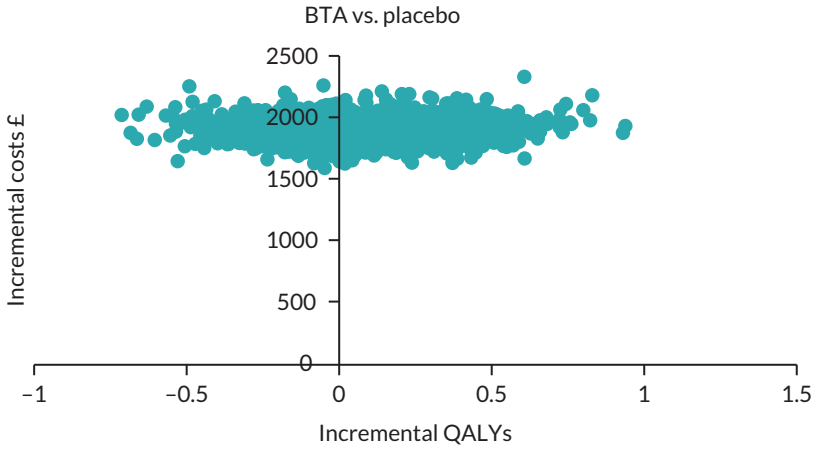

FIGURE 51 Cost-effectiveness plane – BTA vs. placebo.

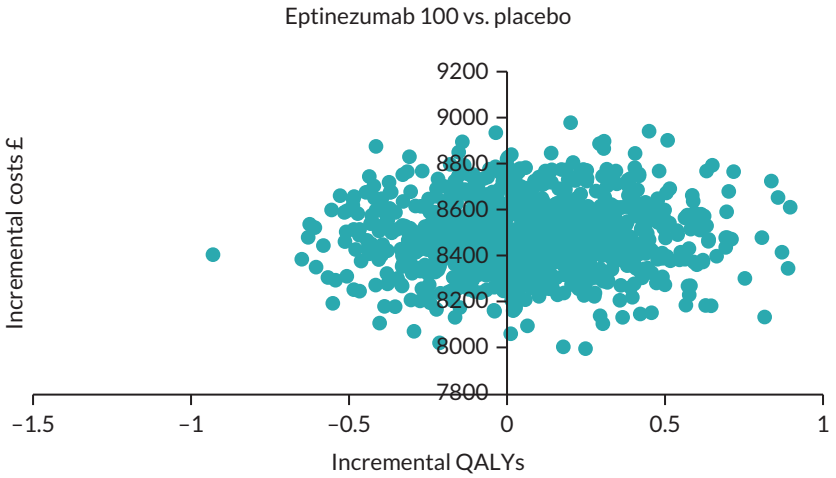

FIGURE 52 Cost-effectiveness plane – eptinezumab 100 mg vs. placebo.

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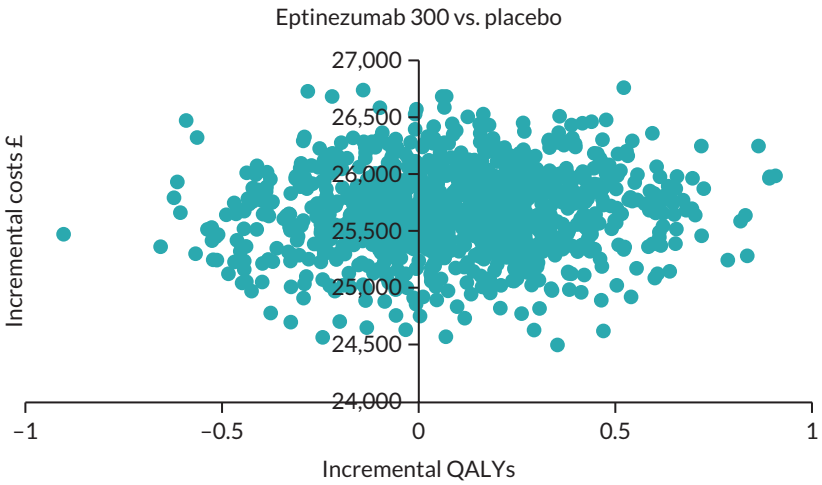

FIGURE 53 Cost-effectiveness plane – eptinezumab 300 mg vs. placebo.

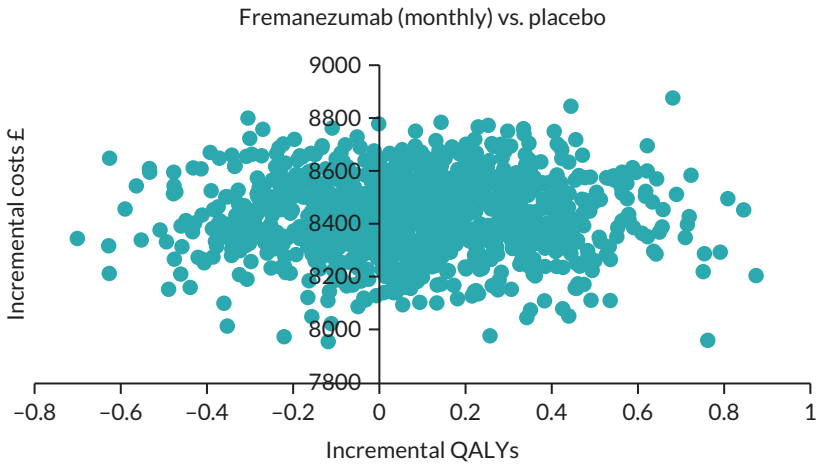

FIGURE 54 Cost-effectiveness plane – fremanezumab monthly vs. placebo.

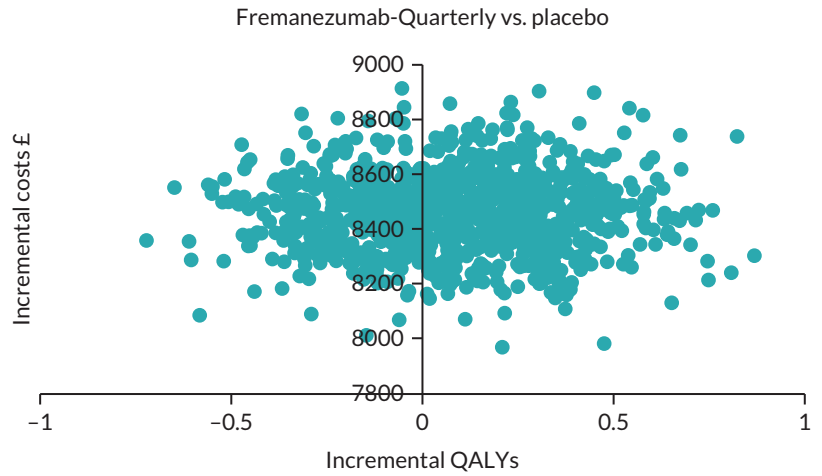

FIGURE 55 Cost-effectiveness plane – fremanezumab quarterly vs. placebo.

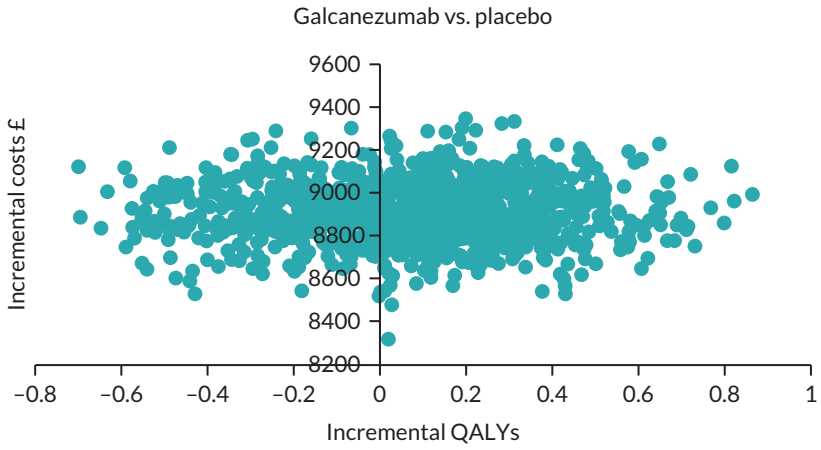

FIGURE 56 Cost-effectiveness plane – galcanezumab vs. placebo.

Base-case cost-effectiveness acceptability curves

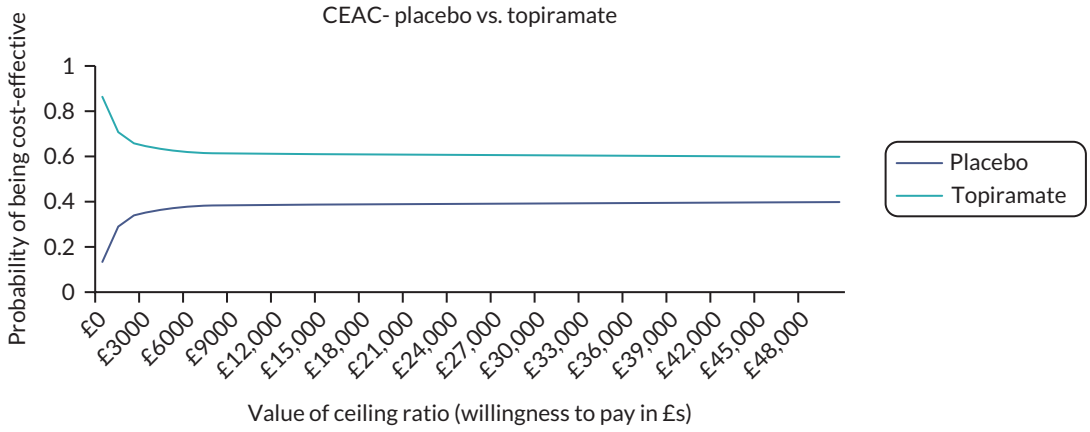

FIGURE 57 Cost-effectiveness acceptability curve – placebo vs. topiramate.

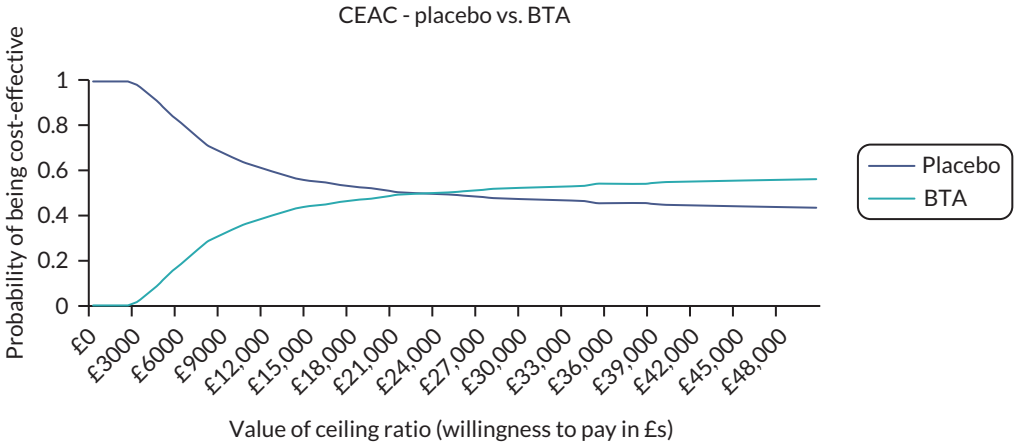

FIGURE 58 Cost-effectiveness acceptability curve – placebo vs. BTA.

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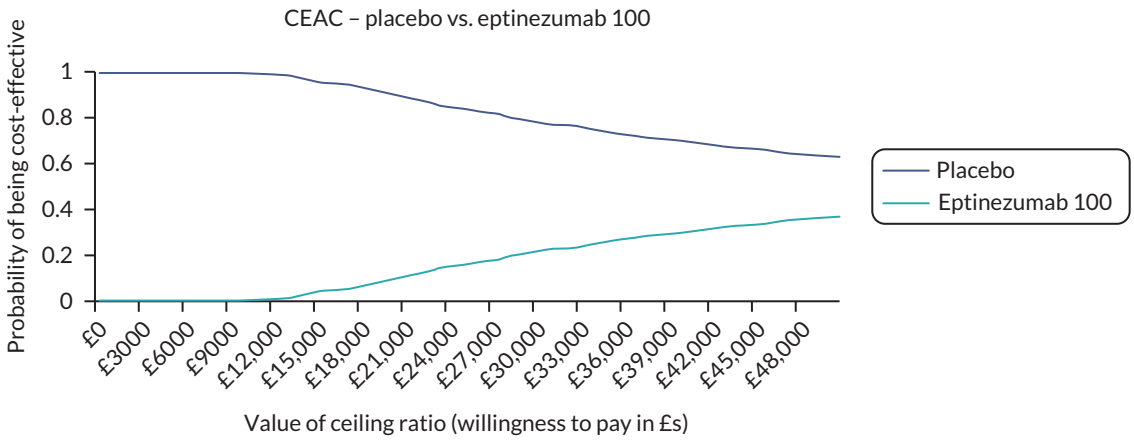

FIGURE 59 Cost-effectiveness acceptability curve – placebo vs. eptinezumab 100 mg.

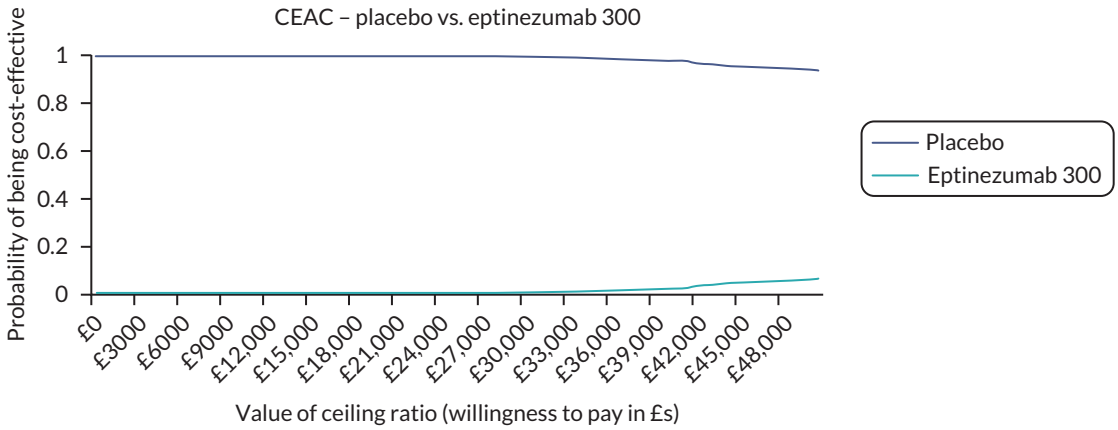

FIGURE 60 Cost-effectiveness acceptability curve – placebo vs. eptinezumab 300 mg.

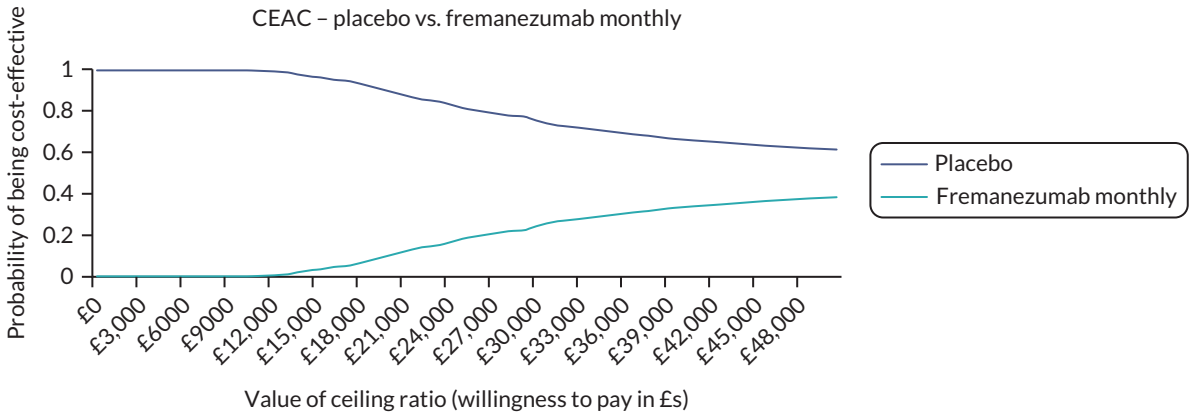

FIGURE 61 Cost-effectiveness acceptability curve – placebo vs. fremanezumab monthly.

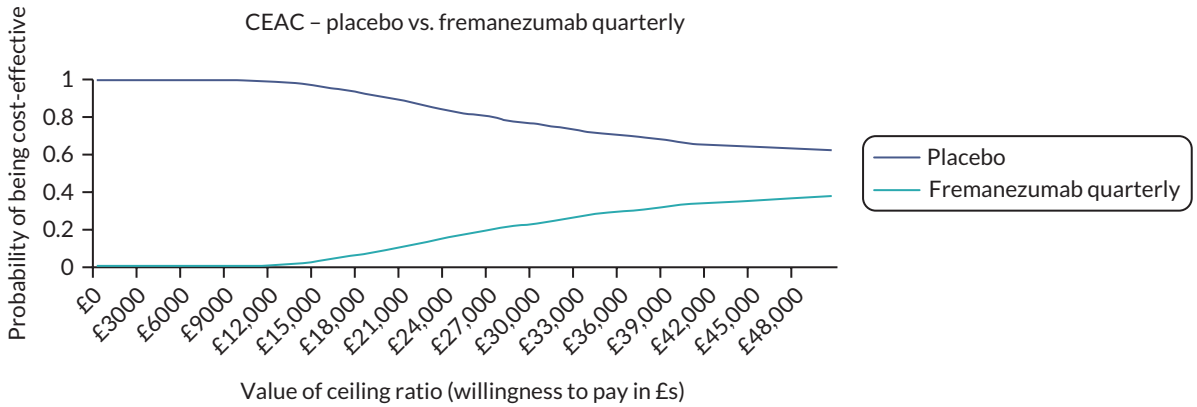

FIGURE 62 Cost-effectiveness acceptability curve – placebo vs. fremanezumab quarterly.

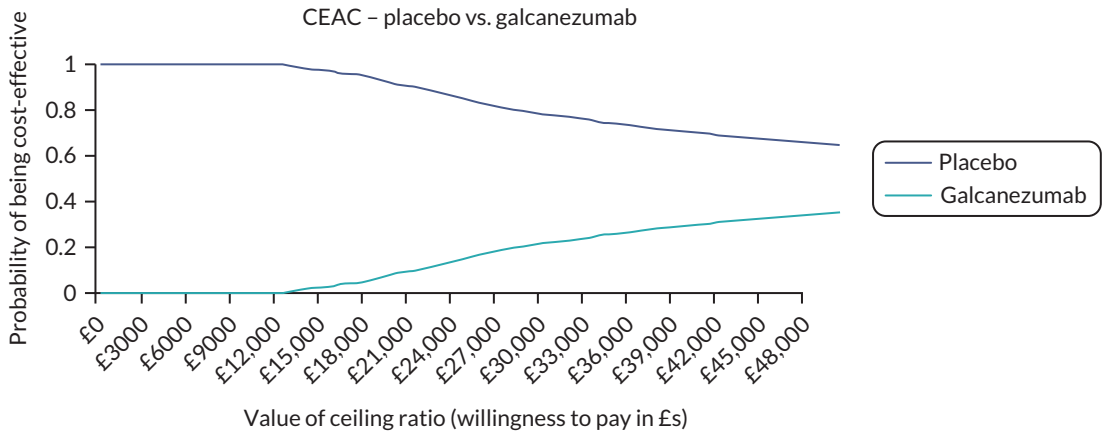

FIGURE 63 Cost-effectiveness acceptability curve – placebo vs. galcanezumab.

TABLE 108 Sensitivity analysis results – comparing each medication to placebo

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
(a) Changing time horizon – 5 years					
Deterministic results – discounted					
Placebo	3488	3.0463	–	–	–
Topiramate	3165	3.1629	−323	0.1166	Dominated
Placebo	3488	3.0463	–	–	–
BTA	6376	3.2414	2888	0.1951	14,804
Placebo	3488	3.0463	–	–	–
Fremanezu mab (monthly)	16,005	3.2398	12,517	0.1935	64,686
Placebo	3488	3.0463	–	–	–
Fremanezumab (quarterly)	16,103	3.2200	12,615	0.1737	72,640
Placebo	3488	3.0463	–	–	–

continued

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TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Eptinezumab 100	16,138	3.2237	12,651	0.1774	71,327
Placebo	3488	3.0463	–	–	–
Galcanezumab	16,545	3.2212	13,057	0.1748	74,680
Placebo	348	3.0463	–	–	–
Eptinezumab 300	42,120	3.2637	38,633	0.2164	178,540
Probabilistic results – discounted					
Placebo	3491	3.0348	–	–	–
Topiramate	3159	3.171	−333	0.1369	Dominated
Placebo	3491	3.0348	–	–	–
BTA	6383	3.2497	2892	0.2149	13,458
Placebo	3491	3.0348	–	–	–
Fremanezumab (monthly)	16,039	3.2483	12,548	0.2135	58,778
Placebo	3491	3.0348	–	–	–
Fremanezumab (quarterly)	16,120	3.2283	12,629	0.1935	65,265
Placebo	3491	3.0348	–	–	–
Eptinezumab 100	16,145	3.2163	12,654	0.1815	69,737
Placebo	3491	3.0348	–	–	–
Galcanezumab	16,577	3.2071	13,086	0.1723	75,937
Placebo	3491	3.0348	–	–	–
Eptinezumab 300	42,184	3.2573	38,693	0.2225	173,923
(b) Changing time horizon – lifetime					
Deterministic results – discounted					
Placebo	15,117	15.1901	–	–	–
Topiramate	13,324	15.7707	−1792	0.5805	Dominated
Placebo	15,117	15.1901	–	–	–
BTA	16,326	16.2092	1210	1.0190	1187
Placebo	15,117	15.1901	–	–	–
Fremanezumab (monthly)	27,364	16.1691	12,247	0.9790	12,510
Placebo	15,117	15.1901	–	–	–
Fremanezumab (quarterly)	27,741	16.0690	12,625	0.8789	14,365
Placebo	15,117	15.1901	–	–	–
Eptinezumab 100	27,736	16.0878	12,620	0.8976	14,059
Placebo	15,117	15.1901	–	–	–
Galcanezumab	28,165	16.0748	13,048	0.8847	14,749
Placebo	15,117	15.1901	–	–	–
Eptinezumab 300	57,524	16.2834	42,407	1.0932	38,790

TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Probabilistic results – discounted					
Placebo	15,138	15.1467	–	–	–
Topiramate	13,351	15.7628	−1787	0.6161	Dominated
Placebo	15,138	15.1467	–	–	–
BTA	16,381	16.2613	1243	1.1146	1115
Placebo	15,138	15.1467	–	–	–
Fremanezumab (monthly)	27,469	16.1774	12,331	1.0307	11,964
Placebo	15,138	15.1467	–	–	–
Fremanezumab (quarterly)	27,840	16.0931	12,702	0.9464	13,421
Placebo	15,138	15.1467	–	–	–
Eptinezumab 100	27,846	16.1319	12,708	0.9852	12,899
Placebo	15,138	15.1467	–	–	–
Galcanezumab	28,194	16.1418	13,056	0.9951	13,120
Placebo	15,138	15.1467	–	–	–
Eptinezumab 300	57,609	16.3428	42,471	1.1961	35,507
(c) Utility inputs – van Hout crosswalk algorithm					
Deterministic results – discounted					
Placebo	1729	1.3733	–	–	–
Topiramate	1625	1.4174	−104	0.0440	Dominated
Placebo	1729	1.3733	–	–	–
BTA	3654	1.4458	1925	0.0725	25,561
Placebo	1729	1.3733	–	–	–
Fremanezumab (monthly)	10,155	1.4470	8427	0.0737	114,365
Placebo	1729	1.3733	–	–	–
Fremanezumab (quarterly)	10,193	1.4391	8465	0.0658	128,613
Placebo	1729	1.3733	–	–	–
Eptinezumab 100	10,216	1.4406	8487	0.0673	126,158
Placebo	1729	1.3733	–	–	–
Galcanezumab	10,640	1.4396	8912	0.0663	134,439
Placebo	1729	1.3733	–	–	–
Eptinezumab 300	27,401	1.4562	25,672	0.0829	309,695
Probabilistic results – discounted					
Placebo	1723	1.3807	–	–	–
Topiramate	1627	1.4063	−96	0.0256	Dominated

continued

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TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Placebo	1723	1.3807	–	–	–
BTA	3656	1.4475	1933	0.0668	28,937
Placebo	1723	1.3807	–	–	–
Fremanezumab (monthly)	10,161	1.4608	8438	0.0801	105,328
Placebo	1723	1.3807	–	–	–
Fremanezumab (quarterly)	10,193	1.4532	8470	0.0725	116,804
Placebo	1723	1.3807	–	–	–
Eptinezumab 100	10,221	1.4346	8498	0.0539	157,699
Placebo	1723	1.3807	–	–	–
Galcanezumab	10,650	1.4436	8927	0.0629	141,848
Placebo	1723	1.3807	–	–	–
Eptinezumab 300	27,411	1.4512	25,688	0.0705	364,182
(d) Drug administration – 1% of patients can't self-administer medication					
Deterministic results – discounted					
Placebo	1729	1.3531	–	–	–
Topiramate	1625	1.3995	−104	0.0464	Dominated
Placebo	1729	1.3531	–	–	–
BTA	3654	1.4294	1925	0.0763	25,238
Placebo	1729	1.3531	–	–	–
Fremanezumab (monthly)	10,140	1.4307	8411	0.0776	108,407
Placebo	1729	1.3531	–	–	–
Fremanezumab (quarterly)	10,178	1.4224	8449	0.0693	121,905
Placebo	1729	1.3531	–	–	–
Eptinezumab 100	10,216	1.4239	8487	0.0708	119,796
Placebo	1729	1.3531	–	–	–
Galcanezumab	10,625	1.4229	8896	0.0698	127,430
Placebo	1729	1.3531	–	–	–
Eptinezumab 300	27,401	1.4403	25,672	0.0873	294,151
Probabilistic results – discounted					
Placebo	1730	1.3513	–	–	–
Topiramate	1626	1.3988	−104	0.0475	Dominated
Placebo	1730	1.3513	–	–	–
BTA	3655	1.4336	1925	0.0823	23,373
Placebo	1730	1.3513	–	–	–
Fremanezumab (monthly)	10,148	1.4218	8418	0.0768	109,651
Placebo	1730	1.3513	–	–	–
Fremanezumab (quarterly)	10,184	1.4189	8454	0.0676	125,025

TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Placebo	1730	1.3513	–	–	–
Eptinezumab 100	10,220	1.4220	8490	0.0707	120,142
Placebo	1730	1.3513	–	–	–
Galcanezumab	10,638	1.4212	8908	0.0699	127,362
Placebo	1730	1.3513	–	–	–
Eptinezumab 300	27,416	1.4392	25,686	0.0879	292,306
(e) Using MMDs instead of MHDs					
Deterministic results – discounted					
Placebo	1729	1.2257	–	–	–
Topiramate	1582	1.3212	−147	0.0955	Dominated
Placebo	1729	1.2257	–	–	–
BTA	3646	1.3606	1917	0.1348	14.216
Placebo	1729	1.2257	–	–	–
Erenumab 70	8945	1.3747	7216	0.1489	48,450
Placebo	1729	1.2257	–	–	–
Erenumab 140	8946	1.3742	7217	0.1484	48,624
Placebo	1729	1.2257	–	–	–
Fremanezumab (monthly)	10,070	1.3919	8341	0.1661	50,212
Placebo	1729	1.2257	–	–	–
Fremanezumab (quarterly)	10,133	1.3652	8404	0.1395	60,263
Placebo	1729	1.2257	–	–	–
Eptinezumab 100	10,184	1.3558	8456	0.1300	65,021
Placebo	1729	1.2257	–	–	–
Galcanezumab	10,604	1.3564	8875	0.1307	67,905
Placebo	1729	1.2257	–	–	–
Eptinezumab 300	27,377	1.3823	25,648	0.1565	163,865
Probabilistic results – discounted					
Placebo	1731	1.2245	–	–	–
Topiramate	1585	1.3220	−146	0.0975	Dominated
Placebo	1731	1.2245	–	–	–
BTA	3645	1.3566	1914	0.1321	14,493
Placebo	1731	1.2245	–	–	–
Erenumab 70	8944	1.3754	7213	0.1508	47,824
Placebo	1731	1.2245	–	–	–
Erenumab 140	8949	1.3749	7218	0.1504	48,001

continued

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TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Placebo	1730	1.2245	–	–	–
Fremanezumab (monthly)	10,072	1.3916	8341	0.1670	49,934
Placebo	1731	1.2245	–	–	–
Fremanezumab (quarterly)	10,140	1.3644	8409	0.1399	60,111
Placebo	1731	1.2245	–	–	–
Eptinezumab 100	10,188	1.3584	8457	0.1339	63,178
Placebo	1731	1.2245	–	–	–
Galcanezumab	10,610	1.3584	8879	0.1339	66,322
Placebo	1731	1.2245	–	–	–
Eptinezumab 300	27,377	1.3850	25,646	0.1605	159,779
(f) Reducing costs of MAbs by 25%					
Deterministic results – discounted					
Placebo	1729	1.3531	–	–	–
Topiramate	1625	1.3995	−104	0.0464	Dominated
Placebo	1729	1.3531	–	–	–
BTA	3654	1.4294	1925	0.0763	25,238
Placebo	1729	1.3531	–	–	–
Fremanezumab (monthly)	7996	1.4307	6267	0.0776	80,774
Placebo	1729	1.3531	–	–	–
Fremanezumab (quarterly)	8033	1.4224	6304	0.0693	90,952
Placebo	1729	1.3531	–	–	–
Eptinezumab 100	8055	1.4239	6326	0.0708	89,300
Placebo	1729	1.3531	–	–	–
Galcanezumab	8367	1.4229	6639	0.0698	95,091
Placebo	1729	1.3531	–	–	–
Eptinezumab 300	20,928	1.4403	19,199	0.0873	219,985
Probabilistic results – discounted					
Placebo	1727	1.3513	–	–	–
Topiramate	1627	1.3980	−101	0.0467	Dominated
Placebo	1727	1.3513	–	–	–
BTA	3653	1.4275	1926	0.0762	25,264
Placebo	1727	1.3513	–	–	–
Fremanezumab (monthly)	7997	1.4303	6269	0.0790	79,328
Placebo	1727	1.3513	–	–	–
Fremanezumab (quarterly)	8039	1.4225	6311	0.0712	88,656
Placebo	1727	1.3513	–	–	–

TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Eptinezumab 100	8057	1.4369	6329	0.0856	73,978
Placebo	1727	1.3513	–	–	–
Galcanezumab	8366	1.4249	6638	0.0736	90,251
Placebo	1727	1.3513	–	–	–
Eptinezumab 300	20,938	1.4533	19,211	0.1019	188,442
(g) Reducing costs of MAbs by 50%					
Deterministic results – discounted					
Placebo	1729	1.3531	–	–	–
Topiramate	1625	1.3995	−104	0.0464	Dominated
Placebo	1729	1.3531	–	–	–
BTA	3654	1.4294	1925	0.0763	25,238
Placebo	1729	1.3531	–	–	–
Fremanezumab (monthly)	5837	1.4307	4108	0.0776	52,944
Placebo	1729	1.3531	–	–	–
Fremanezumab (quarterly)	5872	1.4224	4143	0.0693	59,778
Placebo	1729	1.3531	–	–	–
Eptinezumab 100	5895	1.4239	4166	0.0708	58,804
Placebo	1729	1.3531	–	–	–
Galcanezumab	6094	1.4229	4366	0.0698	62,532
Placebo	1729	1.3531	–	–	–
Eptinezumab 300	14,455	1.4403	12,727	0.0873	145,820
Probabilistic results – discounted					
Placebo	1729	1.3415	–	–	–
Topiramate	1625	1.4078	−105	0.0663	Dominated
Placebo	1729	1.3415	–	–	–
BTA	3653	1.4218	1923	0.0803	23,965
Placebo	1729	1.3415	–	–	–
Fremanezumab (monthly)	5835	1.4395	4106	0.0980	41,902
Placebo	1729	1.3415	–	–	–
Fremanezumab (quarterly)	5869	1.4321	4140	0.0906	45,706
Placebo	1729	1.3415	–	–	–
Eptinezumab 100	5896	1.4210	4166	0.0795	52,409
Placebo	1729	1.3415	–	–	–
Galcanezumab	6097	1.4272	4367	0.0856	50,991
Placebo	1729	1.3415	–	–	–

continued

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TABLE 108 Sensitivity analysis results – comparing each medication to placebo (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)
Eptinezumab 300	14,455	1.4358	12,7276	0.0942	135,025
(h) Eptinezumab 100 vs. 300 mg					
Deterministic results – discounted					
Eptinezumab 100	10,216	1.4239	–	–	–
Eptinezuma b 300	27,401	1.4403	17,185	0.0164	1,045,846
Probabilistic results – discounted					
Eptinezumab 100	10,219	1.4247	–	–	–
Eptinezumab 300	27,415	1.4416	17,195	0.0169	1,018,261
(i) Topiramate vs. BTA					
Deterministic results – discounted					
Topiramate	1625	1.3995	–	–	–
BTA	3654	1.4294	2029	0.0298	68,002
Probabilistic results – discounted					
Topiramate	1626	1.3969	–	–	–
BTA	3655	1.4319	2030	0.0351	57,881

TABLE 109 Sensitivity analysis results – comparing all medications

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison
a) 5-year time horizon						
Deterministic results – discounted						
Topiramate	3165	3.1629	–	–	–	–
Placebo	3488	3.0463	323	−0.1166	Dominated	Placebo vs. topiramate
BTA	6376	3.2414	3211	0.0784	40,928	BTA vs. topiramate
Fremanezumab (monthly)	16,005	3.2398	9629	−0.0016	Dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	16,103	3.2200	9727	−0.0214	Dominated	Fremanezumab (quarterly) vs. BTA
Eptinezumab 100	16,138	3.2237	9763	−0.0177	Dominated	Eptinezumab 100 vs. BTA
Galcanezumab	16,545	3.2212	10,170	−0.0202	Dominated	Galcanezumab vs. BTA
Eptinezumab 300	42,120	3.2627	35,745	0.0213	1,676,779	Eptinezumab 300 vs. BTA
Probabilistic results – discounted						
Topiramate	3159	3.1717	–	–	–	–
Placebo	3491	3.0348	333	−0.1369	Dominated	Placebo vs. topiramate

TABLE 109 Sensitivity analysis results – comparing all medications (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison
BTA	6383	3.2497	3224	0.0779	41,366	BTA vs. topiramate
Fremanezumab (monthly)	16,039	3.2483	9656	−0.0014	Dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	16,120	3.2283	9737	−0.0214	Dominated	Fremanezumab (quarterly) vs. BTA
Eptinezumab 100	16,145	3.2163	9762	−0.0334	Dominated	Eptinezumab 100 vs. BTA
Galcanezumab	16,577	3.2071	10,194	−0.0425	Dominated	Galcanezumab vs. BTA
Eptinezumab 300	42,184	3.2573	35,801	0.0076	4,707,286	Eptinezumab 300 vs. BTA
b) Lifetime horizon						
Deterministic results – discounted						
Topiramate	13,324	15.7707	–	–	–	–
Placebo	15,117	15.1901	1792	−0.5805	Dominated	Placebo vs. topiramate
BTA	16,326	16.2092	3002	0.4385	6846	BTA vs. topiramate
Fremanezumab (monthly)	27,364	16.1691	11,038	−0.0400	Dominated	Fremanezumab (monthly) vs. BTA
Eptinezumab 100	27,736	16.0878	11,410	−0.1214	Dominated	Eptinezumab 100 vs. BTA
Fremanezumab (quarterly)	27,741	16.0690	11,415	−0.1402	Dominated	Fremanezumab (quarterly) vs. BTA
Galcanezumab	28,165	16.0748	11,838	−0.1344	Dominated	Galcanezumab vs. BTA
Eptinezumab 300	57,524	16.2834	41,197	0.0742	555,210	Eptinezumab 300 vs. BTA
Probabilistic results – discounted						
Topiramate	13,351	15.7628	–	–	–	–
Placebo	15,138	15.1467	1787	−0.6161	Dominated	Placebo vs. topiramate
BTA	16,381	16.2613	3030	0.4985	6077	BTA vs. topiramate
Fremanezumab (monthly)	27,469	16.1774	11,088	−0.0840	Dominated	Fremanezumab (monthly) vs. BTA
Eptinezumab 100	27,846	16.1319	11,465	−0.1294	Dominated	Fremanezumab (quarterly) vs. BTA
Fremanezumab (quarterly)	27,840	16.0931	11,459	−0.1682	Dominated	Eptinezumab 100 vs. BTA
Galcanezumab	28,194	16.1418	11,813	−0.1195	Dominated	Galcanezumab vs. BTA
Eptinezumab 300	57,609	16.3428	41,228	0.0815	505,711	Eptinezumab 300 vs. BTA
c) Utility inputs – van Hout crosswalk algorithm						
Deterministic results – discounted						
Topiramate	1625	1.4174	–	–	–	–

continued

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TABLE 109 Sensitivity analysis results – comparing all medications (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison
Placebo	1729	1.3733	104	−0.0440	Dominated	Placebo vs. topiramate
BTA	3654	1.4458	2029	0.0284	71,339	BTA vs. topiramate
Fremanezumab (monthly)	10,155	1.4470	6501	0.0012	Extendedly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,193	1.4391	38	−0.0079	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	10,216	1.4406	60	−0.0064	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	10,640	1.4396	485	−0.0074	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	27,401	1.4562	23,747	0.0104	2,280,271	Eptinezumab 300 vs. BTA
Probabilistic results – discounted						
Topiramate	1627	1.4063	–	–	–	
Placebo	1723	1.3807	96	−0.0256	Dominated	Placebo vs. topiramate
BTA	3656	1.4475	2029	0.0412	49,265	BTA vs. topiramate
Fremanezumab (monthly)	10,161	1.4608	6505	0.0133	Extendendly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,193	1.4532	32	−0.0076	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	10,221	1.4346	60	−0.0262	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	10,650	1.4436	489	−0.0172	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	27,411	1.4512	23,755	0.0037	6,353,726	Eptinezumab 300 vs. BTA
d) Drug administration – 1% of patients can't self-administer medication						
Deterministic results – discounted						
Topiramate	1625	1.3995	–	–	–	–
Placebo	1729	1.3531	104	−0.0464	Dominated	Placebo vs. topiramate
BTA	3654	1.4294	2029	0.0298	68,002	BTA vs. topiramate
Fremanezumab (monthly)	10,140	1.4307	6486	0.0013	Extendedly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,178	1.4224	38	−0.0083	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	10,216	1.4239	76	−0.0067	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	10,625	1.4229	485	−0.0078	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	27,401	1.4403	23,747	0.0110	2,160,037	Eptinezumab 300 vs. BTA

TABLE 109 Sensitivity analysis results – comparing all medications (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison
Probabilistic results – discounted						
Topiramate	1626	1.3988	–	–	–	–
Placebo	1730	1.3513	104	−0.0475	Dominated	Placebo vs. topiramate
BTA	3655	1.4336	2028	0.0349	58,183	BTA vs. topiramate
Fremanezumab (monthly)	10,148	1.4281	6493	−0.0056	Dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,184	1.4189	6529	−0.0147	Dominated	Fremanezumab (quarterly) vs. BTA
Eptinezumab 100	10,220	1.4220	6566	−0.0117	Dominated	Eptinezumab 100 vs. BTA
Galcanezumab	10,638	1.4212	6984	−0.0124	Dominated	Galcanezumab vs. BTA
Eptinezumab 300	27,416	1.4392	23,762	0.0055	4,294,946	Eptinezumab 300 vs. BTA
e) Using MMDs instead of MHDs						
Deterministic results – discounted						
Topiramate	1582	1.3212	–	–	–	–
Placebo	1729	1.2257	147	−0.0955	Dominated	Placebo vs. topiramate
BTA	3646	1.3606	2064	0.0394	52,428	BTA vs. topiramate
Erenumab 70	8945	1.3747	5299		Extendedly dominated	Erenumab 70 vs. BTA
Erenumab 140	8946	1.3742	1	0.0141		Erenumab 140 vs. erenumab 70
Fremanezumab (monthly)	10,070	1.3919	6424	−0.0005	Dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,133	1.3652	63	0.0313	205,481	Fremanezumab (quarterly) vs. fremanezumab
Eptinezumab 100	10,184	1.3558	115	−0.0267	Dominated	(monthly)
Galcanezumab	10,604	1.3564	534	−0.0361	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Eptinezumab 300	27,377	1.3828	17,307	−0.0354 −0.0096	Dominated Dominated	Galcanezumab vs. fremanezumab (monthly) eptinezumab 300 vs. fremanezumab (monthly)
Probabilistic results – discounted						
Topiramate	1585	1.3220	–	–	–	–
Placebo	1731	1.2245	146	−0.0975	Dominated	Placebo vs. topiramate
BTA	3645	1.3566	2060	0.0346	59,596	BTA vs. topiramate
Erenumab 70	8944	1.3754	5299	0.0188	Extendedly dominated	Erenumab 70 vs. BTA
Erenumab 140	8949	1.3749	5	−0.0005	Dominated	Erenumab 140 vs. erenumab 70

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TABLE 109 Sensitivity analysis results – comparing all medications (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison
Fremanezumab (monthly)	10,072	1.3916	6427	0.0350	183,732	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	10,140	1.3644	68	−0.0272	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	10,188	1.3584	116	−0.0332	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	10,610	1.3584	538	−0.0332	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	27,377	1.3850	17,305	−0.0065	Dominated	Eptinezumab 300 vs. fremanezumab (monthly)
f) Reducing costs of MAbs by 25%						
Deterministic results – discounted						
Topiramate	1625	1.3995	–	–	–	–
Placebo	1729	1.3531	104	−0.0464	Dominated	Placebo vs. topiramate
BTA	3654	1.4294	2029	0.0298	68,002	BTA vs. topiramate
Fremanezumab (monthly)	7996	1.4307	4342	0.0013	Extendedly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	8033	1.4224	37	−0.0083	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	8055	1.4239	59	−0.0067	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	8367	1.4229	371	−0.0078	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	20,928	1.4403	17,274	0.0110	1,571,264	Eptinezumab 300 vs. BTA
Probabilistic results – discounted						
Topiramate	1623	1.4026	–	–	–	–
Placebo	1730	1.3398	107	−0.0628	Dominated	Placebo vs. topiramate
BTA	3653	1.4388	2031	0.0362	56,100	BTA vs. topiramate
Fremanezumab (monthly)	7998	1.4364	4344	−0.0025	Dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	8033	1.4284	4380	−0.0104	Dominated	Fremanezumab (quarterly) vs. BTA
Eptinezumab 100	8060	1.4232	4406	−0.0157	Dominated	Eptinezumab 100 vs. BTA
Galcanezumab	8372	1.4174	4718	−0.0215	Dominated	Galcanezumab vs. BTA
Eptinezumab 300	20,928	1.4385	17,275	−0.0003	Dominated	Eptinezumab 300 vs. BTA
g) Reducing costs of MAbs by 50%						
Deterministic results – discounted						
Topiramate	1625	1.3995	–	–	–	–

TABLE 109 Sensitivity analysis results – comparing all medications (*continued*)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER: cost per QALY gained (£)	Comparison
Placebo	1729	1.3531	104	−0.0464	Dominated	Placebo vs. topiramate
BTA	3654	1.4294	2029	0.0298	68,002	BTA vs. topiramate
Fremanezumab (monthly)	5837	1.4307	2183	0.0013	Extendedly dominated	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	5872	1.4224	35	−0.0083	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	5895	1.4239	58	−0.0067	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	6094	1.4229 1.4403	258	−0.0078	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	14,455		10,801	0.0110	982,491	Eptinezumab 300 vs. BTA
Probabilistic results – discounted						
Topiramate	1625	1.4078	–	–	–	–
Placebo	1729	1.3415	105	−0.0663	Dominated	Placebo vs. topiramate
BTA	3653	1.4218	2028	0.0140	144,881	BTA vs. topiramate
Fremanezumab (monthly)	5835	1.4395	2182	0.0177	123,111	Fremanezumab (monthly) vs. BTA
Fremanezumab (quarterly)	5869	1.4321	34	−0.0074	Dominated	Fremanezumab (quarterly) vs. fremanezumab (monthly)
Eptinezumab 100	5896	1.4210	61	−0.0185	Dominated	Eptinezumab 100 vs. fremanezumab (monthly)
Galcanezumab	6097	1.4272	261	−0.0123	Dominated	Galcanezumab vs. fremanezumab (monthly)
Eptinezumab 300	14,455	1.4358	8620	−0.0037	Dominated	Eptinezumab 300 vs. fremanezumab (monthly)

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