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Health Technology Assessment (HTA)

HTA Report

Title	Calcitonin gene-related peptide antagonists for the prevention of migraine
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Technology	Erenumab (Aimovig®) Fremanezumab (Ajovy®)s Galcanezumab (Emgality®) Eptinezumab (Vyepti®)
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Executive Summary

Background

Calcitonin gene-related peptide (CGRP) antagonists are monoclonal antibodies indicated for the preventative treatment of migraine in adults; erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) are provisionally listed on the Spezialitätenliste until February 2024, February 2024, April 2024 and April 2024, respectively. The Spezialitätenliste listing for each drug has limitations relating to the effectiveness of treatment after 3, 6 and 12 months, and requires patients to have failed at least 2 prior prophylactic therapies.

Objective

This HTA evaluates the clinical effectiveness and safety, costs, cost-effectiveness and budget impact of CGRP antagonists (erenumab, fremanezumab, galcanezumab, eptinezumab) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with episodic and chronic migraine.

Methods

A systematic literature search was conducted from 1 January 2012 to 9 March 2022 in Medline, Embase, Cochrane Library, EconLit, INAHTA HTA database, Cost-Effectiveness Analysis Registry, and grey literature sources. Studies were prioritised for inclusion by study design using a hierarchical selection process, whereby meta-analyses were included preferentially, followed by randomised controlled trials (RCTs) and finally non-randomised studies of interventions; only the highest level of available evidence was included. Meta-analysis of RCTs was conducted using a random effects, inverse variance modelling approach. If meta-analysis could not be conducted, results were reported narratively. Risk of bias of the included RCTs was evaluated using the Cochrane Risk of Bias 2.0 tool, and the overall strength of evidence for key outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

A Markov model was developed to quantify the cost-utility of CGRP antagonists using incremental quality-adjusted life years (QALY), with univariate, scenario and probabilistic sensitivity analyses evaluating uncertainties in the model. The results have been presented as incremental cost-utility ratios (ICUR) and as a series of cost-effectiveness acceptability curves to show the probability that a given intervention can be considered cost-effective under a range of willingness-to-pay thresholds (WTPs).

Results

Overall, 27 RCTs were included:

- 8 RCTs reported data comparing erenumab to placebo and 1 RCT compared erenumab to topiramate. The median sample size was 577 (range 246–955), with 5,057 participants included across all 9 independent trials. The duration of treatment ranged from 3–6 months.
- 3 RCTs reported data comparing eptinezumab with placebo. The median sample size was 665 (range 364–1072), with 2,101 participants included across all 3 independent trials. The duration of treatment ranged from 3–9 months.
- 7 RCTs reported data comparing fremanezumab to placebo. The median sample size was 571 (range 177–1,130), with 4,245 participants included across all 7 independent trials. The duration of treatment ranged from 2–3 months.
- 7 RCTs reported data comparing galcanezumab to placebo and 1 RCT compared galcanezumab 120 mg to 240 mg doses. The median sample size was 459 (range 207–1,113), with 4,501 participants included across all 8 included trials. The duration of treatment ranged from 3–12 months.

Selected key outcomes are summarised as follows.

Almost all the included studies reported significantly fewer monthly migraine days (MMDs), significantly more patients with a response rate of >50% and significant improvements in the Migraine-Specific Quality of Life questionnaire (MSQ) for all CGRP antagonists compared to placebo, irrespective of dose. There was more RCT evidence for patients with episodic migraine than for chronic migraine, and a greater number of trials conducted for erenumab and galcanezumab compared to fremanezumab or eptinezumab. Subgroup analyses of patients with >2 prior treatment failures were reported for studies of erenumab, with one each conducted for fremanezumab and galcanezumab. While almost all trials of CGRP antagonists reported significantly fewer MMDs, the evidence was strongest for erenumab, followed by galcanezumab. Adverse events were not well reported in the included trials. Where reported, most trials showed no significant differences in adverse events between CGRP antagonists and placebo.

Costs and cost-effectiveness

CGRP antagonists are reimbursed for patients in Switzerland who have failed at least 2 prior prophylactic therapies. The clinical results from trials that specifically included this patient population, or presented subgroup analyses, were used as assumptions in the modelling. The clinical evidence section of the report refers to the comparator in key trials as the placebo arm. This

arm is also used in the economic model, but is referred to as best supportive care (BSC). Patients in both trials were generally allowed concomitant medication, which varies by migraine frequency.

The cost-effectiveness of CGRP antagonists versus BSC ranged from Swiss francs (CHF)134,152 to CHF318,982 per QALY gained over an analysis period of 1 year among episodic migraine patients, and CHF53,067 to CHF84,033 per QALY gained among chronic migraine patients. CGRP antagonists appear to be more cost-effective among chronic migraine patients. Analyses were also conducted at 5 and 10 years. These results are similar to existing analyses of models submitted to the Canadian Agency for Drugs and Technologies in Health (CADTH) for reimbursement.

Univariate, probabilistic and scenario sensitivity analyses were used to explore different model assumptions. Specifically, differing doses, medicines cost, Swiss-Diagnosis-related group (DRG) cost weights for health states, structural assumptions and estimated health state utilities were included in sensitivity analyses. The analyses indicated the ICUR was most sensitive to medicines cost assumptions used in the model. Scenario analysis included the rate of MMDs experienced by those discontinuing treatment; response rates and estimated utilities were the most important assumptions driving modelling results.

A budget impact analysis was undertaken to determine the additional cost of CGRP antagonists. The cost of CGRP antagonists was estimated to be CHF19.3 million in 2021 and CHF25.5 million in 2022. Given the high uncertainties associated with uptake and the sensitivity of economic modelling results to medicines prices, a range of hypothetical uptake and price scenarios were included in the budget impact analysis. The net cost of CGRP antagonists increases to CHF79.9, CHF199.8 and CHF400.9 million by 2026 at current prices assuming 10%, 25% and 50% uptake.

Conclusions

CGRP antagonists showed significantly fewer MMDs, significantly more patients with a response rate of >50% and significant improvements in the MSQ compared to placebo, irrespective of dose and with minimal side effects. Most of the evidence was for erenumab, followed by galcanezumab.

CGRP antagonists appear to be most cost-effective among chronic migraine patients compared with episodic migraine patients. Changes in unit costs have the largest impact on estimated cost-effectiveness, so strategies to reduce prices would significantly enhance economic attractiveness and reduce the budget impact of these medicines. Trials were limited by relatively short follow-up compared to modelling horizons, along with the absence of a preventive comparator. The placebo arms of clinical trials were used as a comparator, as acute medicine use was allowed. Sensitivity analyses show that results vary when longer-term effectiveness assumptions are changed.

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Abbreviations and acronyms

AEs	Adverse events
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CGRP	Calcitonin gene-related peptide
CHF	Swiss franc
CI	Confidence interval
CUA	Cost-utility analysis
DRG	Diagnosis-related group
EF	Emotional Function
EQ-5D	EuroQol 5-dimension questionnaire
EUnetHTA	European Network of Health Technology Assessment
EUR	Euro
FMH	Foederatio Medicorum Helveticorum/Swiss Medical Association
FOPH	Federal Office of Public Health/Bundesamt für Gesundheit (BAG)
GBP	British pound
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEpro GDT	GRADEpro Guideline Development Tool
HIT-6	Headache Impact Test
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICHD	International Classification of Headache Disorders
ICUR	Incremental cost-utility ratios
IHE	Institute of Health Economics
IHS	International Headache Society
INAHTA	International Network of Agencies for Health Technology Assessment
IV	Intravenous
MCID	Minimal clinically important difference
MD	Mean difference
MHDs	Monthly headache days
MIC	Minimal important change
MIDAS	Migraine Disability Assessment
mMIDAS	Modified Migraine Disability Assessment
MMDs	Monthly migraine days

MSQ	Migraine-Specific Quality of Life questionnaire
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
OKP	Swiss mandatory health insurance (obligatorische Krankenpflegeversicherung)
OR	Odds ratio
PICO	Population, intervention, comparator, outcome
QALY	Quality-adjusted life year
QoL	Quality of life
RACS	Royal Australasian College of Surgeons
RCT	Randomised control trial
RFP	Role Function–Preventive
RFR	Role Function–Restrictive
RoB 2.0	Cochrane risk-of-bias tool, version 2
SAEs	Serious adverse events
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Health Survey
SKG	Swiss Headache Society (Schweizerische Kopfwehgesellschaft)
TRAEs	Treatment-related adverse events
UK	United Kingdom
US/USA	United States/United States of America

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

Each HTA topic entails policy and research questions. In healthcare, a **policy question** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, may address a new developing technology or an older technology for which reimbursement has been questioned.

The topic of this HTA report entails the evaluation of the migraine prevention class of drugs targeting the calcitonin gene-related peptide (CGRP) and its receptor, including the monoclonal antibodies erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®). These 4 CGRP antagonists have been approved by the Swiss Agency for Therapeutic Products (Swissmedic).[1] Erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) are provisionally listed on the Spezialitätenliste until February 2024, February 2024, April 2024 and April 2024, respectively.[2] The Spezialitätenliste listing for each drug has limitations relating to the effectiveness of treatment after 3, 6 and 12 months to continue to be reimbursed, and requires patients to have failed at least 2 prior prophylactic therapies.

The Federal Office of Public Health (FOPH) of the Swiss Confederate seeks to re-evaluate the effectiveness and safety of erenumab, fremanezumab, galcanezumab and eptinezumab to inform a decision around the continued reimbursement of these drugs on the Spezialitätenliste. The financial consequences of a positive reimbursement decision are of particular interest, provided the drugs are efficacious and safe.

2 Research question

To answer a policy question, a research question must be defined and answered first. The **research question** is an answerable inquiry into the HTA topic, which requires data collection and analysis. Research questions are specific and narrow. This HTA report addresses the following research question:

For the prevention of migraine, are CGRP antagonists clinically efficacious, safe and cost-effective compared to the current standard of care and placebo?

3 Medical background

3.1 Medical context, disease description and main symptoms

Migraine is a common neurological disorder. Considered to be one of the most debilitating conditions, it affects approximately 15% of the adult population.[3,4] Migraine headaches are often characterised by moderate to severe attacks of unilateral throbbing head pain lasting 4–72 hours, occasionally accompanied by visual, sensory, motor and speech/language disturbances.[5,6]

Migraines are defined and classified using the International Classification of Headache Disorders (ICHD) (3rd edition).[6] According to ICHD diagnostic criteria, migraine is categorised as: (1) migraine without aura; (2) migraine with aura.[6]

Migraine without aura is defined as a recurring headache disorder, with attacks lasting 4–72 hours when untreated or treated unsuccessfully.[6] Migraine without aura is characterised by at least 2 of the following headache symptoms: unilateral location, throbbing sensation, moderate to severe pain intensity, and aggravation by physical activity or consequent avoidance of such activity, as well as one of the following: nausea and/or vomiting or photophobia and/or phonophobia.[6]

Migraine with aura can further be broken down into 4 subtypes: (1) migraine with typical aura, (2) migraine with brainstem aura, (3) hemiplegic migraine and (4) retinal migraine.[6] Migraine with aura is defined as a recurring headache disorder, with aura attacks usually lasting ≤60 minutes followed by common headache and migraine symptoms.[6] Migraine with aura is characterised by at least 2 of the following reversible disturbances: visual, sensory, speech/language, motor, brainstem and/or retinal.[6] This occurs in conjunction with any or all of the following: one or more aura symptoms that spread slowly over ≥5 minutes; two or more aura symptoms occurring at the same time, each lasting 5–60 minutes; one or more aura symptoms being located unilaterally and/or developing positive phenomena (e.g. pins and needles).[6] The aura is followed by headache and migraine symptoms within 60 minutes of onset.[6] Migraine with aura may also be accompanied by a prodromal or postdromal phase, characterised by symptoms occurring hours or days before a migraine headache (prodromal) or upon resolution of a migraine headache (postdromal).[6] Prodromal symptoms may include irritability, depression, yawning, food cravings, fatigue and muscle stiffness.[7] Postdromal symptoms may include depression, euphoria, fatigue and inability to concentrate.[7]

Per the ICHD diagnostic criteria, **chronic migraine** is characterised by 15 or more headache days per month for 3 months or more, with at least 8 headache days per month having features of a migraine.[6] **Episodic migraine** is characterised by fewer than 15 headache days per month for 3 months or more,

with at least 8 headache days per month having features of a migraine.[6] As per expert advice, these definitions are consistent with those used in clinical practice in Switzerland.[8]

3.2 Burden of disease

In 2016, the Global Burden of Disease Study[4] estimated that 1.04 billion people worldwide experienced migraine, contributing to 45.1 million years of life lived with disability. In the 2019 iteration of the Global Burden of Disease Study,[9] migraine was ranked second for cause of disability and first among women younger than 50 years of age. It was estimated that migraine affects approximately 1.6 million people in Switzerland, resulting in around 70,000 years of life lived with disability in 2016.[4] In a cohort study of 4,547 people, representative of the canton of Zurich, the cumulative 30-year (1978–2008) prevalence of migraine with aura was estimated to be 3% (sex-specific cumulative prevalence: 2.1% in males; 3.9% in females), whereas the cumulative 30-year prevalence of migraine without aura was 36% (20.7% in males; 50.7% in females).[10] Migraine—both with and without aura—is 2 to 3 times more prevalent in females than males.[10,11] Globally, migraine is most prevalent in females age 20–64 years, whereas in males the prevalence is higher from age 10–19 years.[12]

In Europe, it has been estimated that the total annual cost of migraine is around EUR111 billion, with a mean per-person annual cost of migraine of EUR1,222 among adults age 18–65 years. This estimate includes direct (medicines, outpatient healthcare, hospitalisation) and indirect (reduced labour productivity) costs.[13] The review of Stovner and Andrée found that approximately 72–98% of migraine-related costs can be attributed indirectly to work productivity losses, including work absences or reduced output when working with a migraine, while around 30% are associated with direct costs such as appointments, diagnostic tests, treatments and hospital stays.[14]

3.3 Treatment strategy

There is no cure for migraine; however, it can be managed with non-pharmacological treatments, acute therapies or prophylactic treatments.

- Non-pharmacological migraine treatments are recommended by guidelines as a first-line therapy and are commonly used in combination with pharmacological agents to treat migraine. These typically involve lifestyle changes, mindfulness activities and supplementation to reduce symptoms.[8,15] They include aerobic exercise, behavioural and psychological therapies, stress management and relaxation techniques, acupuncture and massage, and supplementation (e.g. magnesium, riboflavin, coenzyme Q10).[16]
- Acute therapies are used to alleviate symptoms associated with migraine at the time of attack in order to limit disability and reduce the pain associated with migraine symptoms.[11,17] Acute

therapies include analgesics (e.g. aspirin, nonsteroidal anti-inflammatory drugs), antiemetics (e.g. metoclopramide, domperidone) and triptans (e.g. almotriptan, rizatriptan, sumatriptan, zolmitriptan)

- Prophylactic treatments, where indicated, aim to prevent and reduce the frequency, severity and duration of expected migraine attacks in those with a history of migraine.[11,17] These include beta blockers (e.g. propranolol, metoprolol), calcium antagonists (e.g. flunarizine), anticonvulsants (e.g. topiramate, valproic acid), antidepressants (e.g. amitriptyline) and CGRP antagonists (e.g. erenumab, fremanezumab, galcanezumab, eptinezumab, ubrogepant, rimegepant).[16,17] Prophylactic treatments, with the exception of CGRP antagonists, are considered to be the standard of care for migraine prevention in Switzerland.[15,18-20]

Non-pharmacological migraine treatments are recommended prior to the initiation of pharmacological treatments;[8] however, where these treatments are ineffective at limiting migraine on their own, pharmacological treatments are incorporated into the management of symptoms for these patients.[8] Through consultation with a medical professional, the decision of which drug to choose is based on: (1) level of evidence; (2) migraine subtype, frequency and disability; (3) medication side effects, comorbidities and concomitant medication; (4) patient characteristics and preference; (5) response to previous treatments; (6) contraindications/allergies; (7) cost and insurance coverage.[8,21] Typically, choice of treatment will begin with a titration phase of the most tolerable/safest treatment. Alternative treatments with greater possible side effects will be progressively initiated if the previous treatment was found to be intolerable or ineffective after 8–12 weeks (example treatment pathway: riboflavin and/or coenzyme Q10 > magnesium > beta blocker > anticonvulsant).[8,21] In cases where more than 2 standard-of-care medications (i.e. beta blocker, calcium antagonist, anticonvulsant or antidepressant) have failed, CGRP antagonists are then considered as a treatment option for those who experience attacks that last at least 4 hours on at least 8 days per month (episodic) or 15 days per month (chronic).[2,8] In Switzerland, prescription of CGRP antagonists and follow-up may only be carried out by a Foederatio Medicorum Helveticorum (FMH)/Swiss Medical Association-certified specialist in neurology.[2]

Advances in migraine research have resulted in the development of newer treatments for management of migraine.[22,23] These treatments include CGRP antagonists—erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®)—which are the only specific preventative treatments for migraine.[22,23] It is hypothesised that the CGRP receptor may be involved via its role in the vasodilation of meningeal and cerebral blood vessels and/or its role in activating trigeminal sensory nerve fibres, which results in a pain response and subsequent inflammation.[24,25] It has been demonstrated that CGRP is released and detected at higher levels during migraine attacks, with CGRP levels normalising after treatment, meaning CGRP may play a role in inducing migraine attacks.[24]

4 Technology

4.1 CGRP antagonists

Four monoclonal antibodies that target CGRP or its receptors—erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®)—are of interest in this HTA report.

Erenumab (AMG334) is a human monoclonal antibody that binds to the CGRP receptor and blocks its function.[23] Fremanezumab (TEV48125) is a fully humanised monoclonal antibody that selectively targets CGRP isoforms, preventing CGRP from binding to its receptors.[23] Galcanezumab (LY2951742) is a humanised monoclonal antibody that binds to the CGRP ligand and blocks its binding to the receptor.[23] Eptinezumab (ALD403) is also a humanised monoclonal antibody that binds to the CGRP ligand and blocks its binding to the receptor.[26] ***Table 1*** provides additional details on the characteristics of each treatment.

The selection of an appropriate CGRP antagonist (i.e. erenumab, fremanezumab, galcanezumab or eptinezumab) depends on a number of factors, including:

- patient preference (i.e. administered monthly [erenumab, fremanezumab, galcanezumab] vs quarterly [fremanezumab at a higher dose, or eptinezumab])
- contraindications
- overall effectiveness of each treatment on the biological target at an individual level (i.e. treatment that targets the CGRP receptor [erenumab] vs the ligand [fremanezumab, galcanezumab, eptinezumab]).[8,27]

As per © COGE GmbH Tarifpool © SASIS AG sales data from 2022, erenumab is the most utilised CGRP antagonist in Switzerland with the largest number of packs sold (66%), followed by galcanezumab (19%), then fremanezumab (15%), and finally eptinezumab (0.5%).[28]

4.2 Alternative technologies

4.2.1 Beta blockers

Beta blockers are also commonly prescribed for the prophylactic treatment of migraine. As per the Swiss Headache Society/Schweizerische Kopfwehgesellschaft (SKG), 2 beta blockers are approved for use in Switzerland—propranolol and metoprolol.[18] Propranolol is available in 4 formulations, while metoprolol is available in 8 formulations (***Table 1***). The exact mechanism of action of beta blockers on the prevention of migraine is still unclear; however, the inhibition of beta-1 mediated effects is considered the main mode of action.[29,30] Propranolol is administered orally via tablets at 10–320 mg dosage per day, with the recommended dosage for migraine prophylaxis being 80–160 mg per day.[1] Metoprolol is

administered orally via tablets at 25–200 mg dosage per day, with the recommended dosage for migraine prophylaxis being 100–200 mg per day.[1]

4.2.2 Calcium antagonists

For the prevention of migraine, a single calcium antagonist—flunarizine (Sibelium®, Janssen-Cilag AG)—is approved for use in Switzerland.[18] Flunarizine acts as a calcium channel blocker, which is hypothesised to counteract the narrowing of cerebral blood vessels, ultimately preventing migraine.[31] Flunarizine is administered orally via tablets at 5–10 mg dosage per day, with the recommended dosage for migraine prophylaxis being 5 mg per day.[1]

4.2.3 Anticonvulsants

Certain anticonvulsants may be prescribed for the prophylactic treatment of migraine in adults. Topiramate is currently the only anticonvulsant approved for use in Switzerland.[18] This drug is available in 3 formulations (***Table 1***). The exact mechanism of action of topiramate is unclear; however, it is thought that it prevents the action of voltage-gated sodium channels, leading to the prevention of migraine.[32] Topiramate is administered orally via tablets at 25–400 mg dosage per day, with the recommended dose for migraine prophylaxis being 100 mg per day.[1,32]

4.2.4 Antidepressants

Antidepressants are another class of medication that can be prescribed for prophylactic treatment of migraine in adults. In Switzerland, amitriptyline (Saroten®, Lundbeck [Schweiz] AG) is currently approved for use.[18] Amitriptyline is a tricyclic antidepressant that inhibits serotonin and norepinephrine uptake.[33] Amitriptyline is administered orally in tablet form. It can be administered at 10–150 mg dosage per day, although for the prophylaxis of migraine it is typically administered at lower doses (e.g. 25–75 mg per day).[1,33]

Refer to ***Table 1*** for additional details of the described alternative technologies.

Table 1 Prophylactic treatments for the prevention of migraine

***Drug:* brand name/ (manufacturer)**	**Dosage, administration and pharmaceutical form**	**Indications**	**Half life**	**Metabolism**	**Contraindications**
CGRP antagonists					
Erenumab: Aimovig® (Novartis Pharma Schweiz AG)	70 mg in 1 ml solution (70 mg/ml) monthly 140 mg in 1 ml solution (140 mg/ml) monthly † (available in a single pre-filled pen) Subcutaneous injection (pre-filled pen)	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	28 days	Degraded into peptides and amino acids by enzymatic proteolysis[34]	Hypersensitivity to active ingredient or any other ingredient in solution; latex allergy, constipation or hypertension[35]
Fremanezumab: Ajovy® (Teva Pharma AG)	225 mg in 1.5 ml solution (150 mg/ml) monthly 675 mg quarterly (3 pre-filled pens) Subcutaneous injection (pre-filled pen/syringe)	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	30 days	Degraded into peptides and amino acids by enzymatic proteolysis[34]	Hypersensitivity to active ingredient or any other ingredient in solution
Galcanezumab: Emgality® (Eli Lilly [Suisse] SA)	120 mg/ml once monthly (starting dose of 240 mg/ml, 2 pre-filled pens) Subcutaneous injection (pre-filled pen)	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	27 days	Degraded into peptides and amino acids by enzymatic proteolysis[34]	Hypersensitivity to active ingredient or any other ingredient in solution
Eptinezumab: Vyepti® (Lundbeck [Schweiz] AG	100 mg in 1 ml solution (100 mg/ml) quarterly 300 mg in 1 ml solution (300 mg/ml) quarterly IV infusion	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	27 days	Degraded into peptides and amino acids by enzymatic proteolysis[34]	Hypersensitivity to active ingredient or any other ingredient in solution
Beta blockers					
Propranolol:	Recommended dose for migraine: 80–160 mg daily Dosage range: 10–320 mg daily Oral administration	Hypertension; angina; anxiety; essential tremor; pheochromocytoma; long-term prophylaxis after myocardial infarction; portal hypertension; oesophageal varices; prophylactic treatment for migraine in adults	3–6 hours	Hepatic metabolism, into metabolites[36]	Hypersensitivity to active ingredient or any other ingredient in tablet; bronchial asthma; bronchospasm; bradycardia; hypotension; heart failure; 2nd/3rd degree AV blockage; cardiogenic shock; Prinzmetal's angina; peripheral circulatory disorders; sick sinus syndrome; pheochromocytoma; metabolic acidosis; hyperglycaemia; long-term fasting
Propranolol Helvepharm (Helvepharm AG)	Available in 10, 40 and 80 mg tablets				
Propranolol retard Helvepharm (Helvepharm AG)	Available in 160 mg capsules				
Propranolol Zentiva (Helvepharm AG)	Available in 10, 40 and 80 mg tablets				
Propranolol retard Zentiva (Helvepharm AG)	Available in 160 mg capsules				
Metoprolol:	Recommended dose for migraine: 100–200 mg daily Dosage range: 25–200 mg daily Oral administration	Hypertension; angina; chronic heart failure; cardiac arrhythmias; cardiovascular disorders with palpitations; prophylactic treatment for migraine in adults	3.5 hours	Oxidatively degraded in the liver, into 3 metabolites[37]	Hypersensitivity to active ingredient or any other ingredient in tablet; other beta blockers; bronchial asthma; bronchospasm; bradycardia; hypotension; heart failure; 2nd/3rd degree AV blockage;
Beloc Zok 25/50/100/200 (Recordati AG)	Available in 25, 50, 100 and 200 mg tablets				

Drug: brand name/ (manufacturer)	Dosage, administration and pharmaceutical form	Indications	Half life	Metabolism	Contraindications
Logimax (Recordati AG)	Available in 5/50 and 10/100 mg tablets (also containing 5 or 10 mg of felodipine)				cardiogenic shock; peripheral circulatory disorders; sick sinus syndrome; acute myocardial infarction; pheochromocytoma
Lopresor 100/retard (Daiichi Sankyo [Schweiz] AG)	Available in 100 and 200 mg tablets				
Meto Zerok (Sandoz Pharmaceuticals AG)	Available in 25, 50, 100 and 200 mg tablets				
Metoprolol Axapharm (Axapharm AG)	Available in 25, 50, 100 and 200 mg tablets				
Metoprolol Helvepharm (Helvepharm AG)	Available in 25, 50, 100 and 200 mg tablets				
Metoprolol Mepha (Mepha Pharma AG)	Available in 25, 50, 100 and 200 mg tablets				
Metropolol Spirig HC (Spirig HealthCare AG)	Available in 25, 50, 100 and 200 mg tablets				
Calcium antagonists					
Flunarizine: Sibelium® (Janssen-Cilag AG)	Recommended dose for migraine: 5 mg daily (single administration) Dosage range: 5–10 mg daily Oral administration Available in 5 mg tablets	Prophylactic treatment for migraine in adults; vestibular balance disorders	5–15 hours	Hepatic metabolism into 15 metabolites[38]	Hypersensitivity to active ingredient or any other ingredient in tablet; depression; extrapyramidal symptoms or Parkinson's disease
Anticonvulsants					
Topiramate: Topamax (Janssen-Cilag AG) Topiramat Sandoz (Sandoz Pharmaceuticals AG) Topiramat Spirig HC (Spirig HealthCare AG)	Recommended dose for migraine: 100 mg daily (50 mg divided into 2 individual administrations) Dosage range: 25–400 mg daily Oral administration Available in 25, 50, 100 and 200 mg tablets ‡	Epilepsy; prophylactic treatment for migraine in adults	21 hours	Metabolites not known to be active Characterised by reactions of glucuronidation, hydroxylation and hydrolysis Approximately 70% eliminated unchanged in the urine[32]	Hypersensitivity to active ingredient or any other ingredient in tablet; pregnancy and breastfeeding; women of childbearing age who do not use a safe contraceptive method
Antidepressants					
Amitriptyline: Amitriptyline Saroten® (Lundbeck [Schweiz] AG)	Recommended dose for migraine: 25–75 mg daily Dosage range: 10–150 mg daily Oral administration Available as 10 and 25 mg tablets	Depressive disorders; neuropathic pain, prophylactic treatment of chronic tension headaches or migraine in adults	25 hours	Metabolised by demethylation and hydroxylation, followed by glucuronidation[39]	Hypersensitivity to active ingredient or any other ingredient in tablet; recent heart attack; any degree of heart valve blockage, arrhythmia or irregularities; simultaneous use with monoamine oxidase inhibitors

Abbreviations

AV = atrioventricular, **CGRP** = calcitonin gene-related peptide, **IV** = intravenous.

Notes

† In patients who do not experience sufficient effects from 70 mg/ml of erenumab (Aimovig®), dosage may be increased to 140 mg/ml of erenumab (Aimovig®), as long as sufficient effects can be demonstrated.

‡ Topamax (Janssen-Cilag AG) also available in 15 and 50 mg capsules.

Source

Swissmedic 2021[1] unless otherwise referenced in table.

4.3 Regulatory status / provider

In Switzerland, erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) are approved by Swissmedic.[1] Erenumab, fremanezumab, galcanezumab and eptinezumab are provisionally listed on the Spezialitätenliste[2] until February 2024, February 2024, April 2024 and April 2024, respectively. Details regarding the coverage conditions of erenumab, fremanezumab, galcanezumab and eptinezumab according to the Spezialitätenliste are reported in ***Appendix A***. The approved dosages for each CGRP antagonist are provided in the population, intervention, comparator, outcome (PICO) (***Table 3***). In Switzerland, the prescription of CGRP antagonists and follow-up may only be carried out by an FMH/Swiss Medical Association-certified specialist in neurology.[2] Reimbursement in other European countries is outlined in ***Table 2***.

Table 2 Reimbursement of CGRP antagonists for migraine prevention in European countries other than Switzerland

Country‖	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Denmark[40]	Not reimbursed	Not reimbursed	Not reimbursed	Not reimbursed
England[41]	Reimbursed	Not reimbursed	Reimbursed	Not reimbursed
France[42]	Reimbursed	Reimbursed	Reimbursed	Reimbursed
Italy[43]	Reimbursed	Not reimbursed	Not reimbursed	Not reimbursed
Netherlands[44]	Reimbursed	Reimbursed	Reimbursed	Not reimbursed
Norway[45]	Not reimbursed	Not reimbursed	Not reimbursed	Not reimbursed
Scotland[46]	Not reimbursed	Not reimbursed	Not reimbursed	Not reimbursed

Abbreviations
NR = not reported.
Notes
‖ Countries were chosen at random based on published and retrievable data via targeted searches.

5 Population, Intervention, Comparator, Outcome (PICO)

Table 3 PICO criteria

Population(s)	1. Patients diagnosed with episodic migraine (characterised by less than 15 headache days per month)[6] **Subgroup 1:** Patients diagnosed with episodic migraine (i.e. migraine attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline) 2. Patients diagnosed with chronic migraine (characterised by 15 or more headache days per month for 3 months or more, with at least 8 migraine days per month)[6] **Subgroup 2:** Patients diagnosed with chronic migraine (i.e. migraine attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline) *Exclusion: Paediatric patients (<18 years)*
Intervention(s)	• Erenumab (Aimovig®)—70 or 140 mg once monthly • Fremanezumab (Ajovy®)—225 mg once monthly or 675 mg quarterly • Galcanezumab (Emgality®)—120 mg once monthly (starting dose of 240 mg) • Eptinezumab (Vyepti®)—100 mg or 300 mg quarterly
Comparator(s)	• Placebo • Standard of care for migraine prevention o Beta blockers: propranolol, metoprolol o Calcium antagonist: flunarizine o Anticonvulsants: topiramate o Antidepressants: amitriptyline • Other CGRP antagonists (i.e. comparing each intervention to each of the others)
Outcome(s)	**Clinical outcomes:** • Monthly migraine and headache days (MMD, MHD) • Health-related and migraine-specific quality of life (HIT-6, MSQ, MIDAS, EQ-5D, SF-36) • Migraine/headache pain intensity (VAS, NRS) • Number of days per month with a migraine that needs to be treated with acute pain relievers (i.e. MMDs with acute medication use) • Response rate (defined as ≥50% reduction in the average number of days with migraine after 6 months of treatment compared to prior to treatment) • Treatment adherence • Mortality • Treatment-related AEs • Serious AEs • AEs leading to discontinuation • AEs upon discontinuation of CGRP antagonists (e.g. rebound effect) **Health-economic outcomes:** • Costs, utilities, ICER, budget impact

Abbreviations

AEs = adverse events, **CGRP** = calcitonin gene-related peptide, **EQ-5D** = EuroQol 5-dimension questionnaire, **HIT-6** = Headache Impact Test, **ICER** = incremental cost-effectiveness ratio, **MHDs** = monthly headache days, **MIDAS** = Migraine Disability Assessment, **MMDs** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NRS** = numerical rating scale, **SAEs** = serious adverse events, **SF-36** = 36-Item Short Form Health Survey, **VAS** = visual analogue scale.

Source

IHS 2018[6]

The categories forming the PICO criteria (***Table 3***) follow the International Headache Society (IHS) position statement for the development of HTAs for acute and preventative treatment of migraine.[20]

5.1 Population

There are 2 key populations of interest: patients diagnosed with chronic migraine and patients diagnosed with episodic migraine. As mentioned, chronic migraine is characterised by 15 or more headache days per month persisting for 3 months or more, with at least 8 headache days per month having features of a migraine,[6] whereas episodic migraine is characterised by fewer than 15 headache days per month.[6] Additionally, 2 subgroups will be included to reflect the Swiss context in which CGRP antagonists are used: (i) patients diagnosed with chronic migraine (i.e. attacks lasting at least 4 hours on at least 15 days per month) and (ii) patients diagnosed with episodic migraine (i.e. attacks lasting at least 4 hours on at least 8 days per month) for a duration of at least 1 year (see ***Appendix A***). Prior to starting CGRP antagonist treatment, these subgroups must have trialled and failed to respond adequately to at least 2 other migraine prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or antidepressants; ***Appendix A***).

5.2 Intervention

The following CGRP antagonists approved for use in Switzerland for a specific patient population and administered via subcutaneous injection through a pre-filled pen/syringe (***Appendix A***) will be included: 70 or 140 mg erenumab (Aimovig®) once monthly, 225 mg once monthly or 675 mg quarterly of fremanezumab (Ajovy®), and galcanezumab (Emgality®) at a starting dose of 240 mg, then 120 mg per month thereafter. Finally, 100 or 300 mg eptinezumab (Vyepti®) quarterly—administered via intravenous (IV) infusion—will also be included.

5.3 Comparator

The comparators of interest include medications that are considered the standard of care for migraine prevention. Each intervention (i.e. CGRP antagonists) will be compared to each other, where direct evidence is available, and to placebo. Standard-of-care medications for migraine prevention approved for use in Switzerland include beta blockers (i.e. propranolol and metoprolol), calcium antagonists (i.e. flunarizine), anticonvulsants (i.e. topiramate) and antidepressants (i.e. amitriptyline). All standard-of-care drugs are oral formulations taken daily. Placebo will include any inactive substance designed to have no therapeutic value, per the description provided in each trial.

5.4 Outcome

5.4.1 Clinical outcomes

Monthly migraine days (MMDs) and **monthly headache days (MHDs)** are critical outcomes. A migraine day is often defined as any calendar day (usually recorded in a headache diary/eDiary) on which the onset, continuation or recurrence of migraine or probable migraine occurs, with features meeting ICHD criteria.[47-49] Additionally, any calendar day on which acute migraine-specific medication (e.g. triptans, ergots, gepants) are used to treat a headache is also considered a migraine day.[47-49] A headache day is defined as any calendar day (usually recorded in a headache diary/eDiary) on which a migraine, probable migraine or non-migraine headache occurred.[50] **Response rate** is also a critical outcome, directly related to MMDs and MHDs. Response rate is defined as a reduction of the average number of days with migraines after receiving treatment for a specified duration (e.g. 3 months, 6 months) compared to prior to treatment beginning (i.e. baseline).[20] Rates commonly include 30%, 50%, 75% and 100%, although 50% is the only response rate recommended for use as a primary endpoint.[47] A reduction in MMDs, MHDs and response rate compared to baseline will be assessed.[20]

The **number of days per month with a migraine that needs to be treated with acute pain relievers** is an important outcome. The use of acute pain relievers, especially migraine-specific medication (e.g. triptans, ergots, gepants), is commonly recorded and reported across clinical studies. A reduction in the number of calendar days on which acute medications are used is important for assessing the effectiveness of an intervention, and also to reduce medication overuse, a common issue among migraine patients.[47]

Migraine/headache pain intensity is an important outcome. Migraine pain intensity is a self-reported measure and most commonly categorised on a 4-point scale as either no pain or mild, moderate or severe pain.[47,51] Clinical studies will often require participants to rate the severity of MMD and/or MHD in order to gather as much information as possible about the event. Other clinical studies also implement the use of an 11-point numerical rating scale to measure pain intensity (0 meaning ‘no headache at all’ and 10 meaning ‘the worst possible headache’).[51,52] The 11-point numerical rating scale may be further grouped into categories with ratings from 1–3 considered mild, 4–6 as moderate and 7–10 as severe.[52]

The effects of migraine on **health-related and migraine-specific quality of life** is a critical outcome. Health-related quality of life is a patient-reported outcome of overall health status measured via the assessment of domains that focus on physical, mental, emotional and social functioning. Instruments commonly used to measure health-related quality of life include the EuroQoL 5-dimensions questionnaire (EQ-5D) and the 36-item Short Form Health Survey (SF-36). Additionally, other patient-reported outcome measures exist to assess the specific impact of migraine on quality of life (QoL),

functional and emotional burden, and the progression and overall effectiveness in patients who initiate preventative treatment.[53] Several valid and reliable instruments commonly used to measure migraine-specific QoL include the migraine-specific QoL questionnaire (MSQ), the Headache Impact Test (HIT-6), and the Migraine Disability Assessment (MIDAS). Where findings are available for these outcome measures, a description of each instrument will be briefly described in ***Section 7***.

Treatment adherence is an important outcome. Treatment adherence refers to whether patients take their medication as prescribed, present for their subcutaneous injection or IV infusion, and continue/follow the treatment regimen as advised by a medical professional.[54] Treatment adherence is measured over the study period and reported as a percentage to provide behavioural information.[54]

Mortality and serious adverse events (SAEs) are critical safety outcomes. An SAE is defined as *"an adverse event (AE) that results in death, is life-threatening, leads to hospitalisation (or prolonged existing hospitalisation), results in persistent or significant disability, a birth defect, or any other important medical event that may jeopardise the patient or require medical intervention to prevent any of the outcomes listed above"*.[55] AEs will be deemed serious by the study investigators of each trial.

AEs and treatment-related adverse events (TRAEs) are important outcomes. Irrespective of severity, AEs are defined as any unanticipated medical incident in a patient that has been administered a pharmaceutical product, which does not have to be causally related to the treatment administered.[55] AEs or TRAEs identified and deemed relevant by the study investigators of each trial will be considered appropriate to the analysis.

AEs leading to withdrawal/discontinuation is an important outcome. Both serious adverse events and AEs may lead to withdrawal of a participant from a clinical trial (by the study investigator or participants themselves) or discontinuation of an investigational product. The incidence of AEs that lead to discontinuation of a treatment are considered to reflect the tolerability of preventative treatments.[47] AEs leading to withdrawal/discontinuation as assessed and reported by the study investigators of each trial will be considered relevant to the analysis.

AEs upon discontinuation of CGRP antagonists (e.g. rebound effect) is an important safety outcome. This outcome will seek to determine whether patients experience AEs after ceasing CGRP antagonist treatment, which will reflect whether stopping treatment (expectedly or unexpectedly) could jeopardise a patient's health.[56]

A **minimal clinically important difference (MCID)** is the smallest difference in a specific outcome measure that would warrant a change in patient management as a result of patient-perceived improvement. Other metrics used to determine the smallest change in outcome measurement that translates to a patient feeling better, as well as changes in function, include the minimally important

difference, minimally important change, and minimal clinically important improvement.[57-59] MCIDs for outcomes described above are detailed in ***Appendix E***.

5.4.2 Health-economic outcomes

Health-economic outcomes are described in ***Section 8.2.1.8***.

6 HTA key questions

For evaluation of the technology, the following key questions covering central HTA domains as designated by the European Network of Health Technology Assessment (EUnetHTA) Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact), are addressed:

1. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate] antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with episodic migraine?
    a. Subgroup 1: Are CGRP antagonists for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with episodic migraine (attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
2. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with chronic migraine?
    a. Subgroup 2: Are CGRP antagonists for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with chronic migraine (attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention

therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

3. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with episodic migraine?
    a. Subgroup 1: Are CGRP antagonists for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with episodic migraine (attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
4. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with chronic migraine?
    a. Subgroup 2: Are CGRP antagonists for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients diagnosed with chronic migraine (attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
5. What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with episodic migraine?
    a. Subgroup 1: What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants

[topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with episodic migraine (attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

6. What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with chronic migraine?
    a. Subgroup 2: What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with chronic migraine (attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
7. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with episodic migraine?
    a. Subgroup 1: Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with episodic migraine (attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
8. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the

current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with chronic migraine?

   a. Subgroup 2: Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with chronic migraine (attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

9. What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with episodic migraine?

   a. Subgroup 1: What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with episodic migraine (attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

10. What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with chronic migraine?

   a. Subgroup 2: What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants

[topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients diagnosed with chronic migraine (attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

6.1 Additional question(s)

11. In patients diagnosed with episodic migraine, are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®] and eptinezumab [Vyepti®])?
    a. Subgroup 1: In patients diagnosed with episodic migraine (attacks that last at least 4 hours on at least 8 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline), are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®] and eptinezumab [Vyepti®])?
12. In patients diagnosed with chronic migraine, are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®] and eptinezumab [Vyepti®])?
    a. Subgroup 2: In patients diagnosed with chronic migraine (attacks that last at least 4 hours on at least 15 days per month) for at least 1 year and who did not respond or insufficiently responded to at least 2 other prevention therapies (e.g. beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline), are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®] and eptinezumab [Vyepti®])?

7 Effectiveness, efficacy and safety

Summary statement efficacy, effectiveness and safety

Almost all the included studies reported significantly fewer monthly migraine days (MMDs), significantly more patients with a response rate of >50% and significant improvements in the MSQ for all CGRP antagonists compared to placebo. There was more evidence for patients with episodic migraine than for chronic migraine and a greater number of trials conducted for erenumab and galcanezumab compared to fremanezumab or eptinezumab. Subgroup analyses of patients with more than two prior treatment failures were reported for studies of erenumab with one each conducted for fremanezumab and galcanezumab. While almost all trials of CGRP antagonists reported significantly fewer MMDs, the evidence was strongest for erenumab, followed by galcanezumab. Adverse events were not well reported in the included studies for all drug types. Where reported, the majority of trials showed no significant differences in adverse events between CGRP antagonists and placebo.

7.1 Methodology effectiveness, efficacy and safety

7.1.1 Databases and search strategy

A systematic literature search was conducted in 6 biomedical databases (Medline, Embase, Cochrane Library, EconLit, International Network of Agencies for Health Technology Assessment [INAHTA] HTA Database, Cost-Effectiveness Analysis [CEA] Registry) (***Table A1, Appendix B***). Key search terms related to the population and intervention were combined and applied to these databases. No search filters were placed on the searches; however, a date limit of 10 years was placed on randomised control trials (RCTs) and a date limit of 5 years placed on non-RCTs.

7.1.2 Study selection

Database searches were conducted up to 9 March 2022 (***Table A7*** to ***Table A11, Appendix B***). Results from the literature searches were imported into Rayyan (Rayyan Systems Inc., United States).[60] Rayyan functions similarly to EndNote but allows for easy blinding of reviewers and management of study inclusion conflicts.[60] The search results were screened by title and abstract against the predetermined inclusion and exclusion criteria (***Appendix C***) by 2 reviewers. All articles deemed potentially relevant were reviewed in full text by each reviewer independently. Conflicts between reviewers on study inclusion were settled via consensus at each stage of study selection. If consensus could not be reached, a third reviewer decided whether to include or exclude the citation.

Study selection was limited to English, French, German and Italian language studies. French, German and Italian are 3 of the 4 official languages of Switzerland. The fourth language of Romansh was not included because of the limited number of publications available.[61,62]

Studies were prioritised for inclusion by study design using a hierarchical selection process. For each intervention, RCTs meeting the predetermined inclusion and exclusion criteria (***Appendix C***) were included to assess the clinical effectiveness and safety of CGRP antagonists for the prevention of migraine. If no RCTs were identified for a particular intervention, then non-randomised comparative studies were included. If no comparative data were available, then single-arm studies reporting pre- and post-treatment outcomes related to CGRP antagonists were included.

Due to the adequate volume of RCTs identified during screening for each intervention, the authors determined there was sufficient RCT evidence available for each CGRP antagonist without needing lower levels of evidence. However, targeted screening of observational evidence was required to answer the additional questions (***Section 6.1***) regarding whether switching from one CGRP antagonist to another is effective/efficacious in those who previously experienced inadequate treatment effects using a CGRP antagonist; however, no relevant evidence was identified.

7.1.3 Other sources

Searches were conducted in ClinicalTrals.gov and the EU Clinical Trials Registry to identify ongoing clinical trials related to CGRP antagonists for the prevention of migraine (***Table A2, Appendix B***). Websites of HTA agencies that are members of INAHTA were also searched to identify relevant HTA reports that included cost-effectiveness analyses (CEA) (***Table A3, Appendix B***). Grey literature searches were conducted on specialty websites (***Table A4, Appendix B***) to highlight any relevant literature that may not have been otherwise identified.

7.1.4 Assessment of quality of evidence

The assessment of the quality of evidence was performed by one reviewer and checked by a second reviewer. Any differences were settled via consensus. If consensus could not be reached, a third reviewer was consulted. Study quality and risk of bias (RoB) was assessed using different tools depending on the trial design. RCTs were evaluated using the Cochrane risk-of-bias tool version 2 (RoB 2.0).[63] The overall quality of the evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[64,65] The GRADEpro Guideline Development Tool (GDT) was used to construct the summary of evidence tables.[66] One reviewer appraised the outcomes using GRADE, which was then checked by a second reviewer. Any differences were settled via consensus. If consensus could not be reached, a third reviewer was consulted.

7.1.5 Data extraction, analysis and synthesis of the domains of efficacy, effectiveness and safety

7.1.5.1 Data extraction

One reviewer independently extracted data (on a trial-arm level) into a standardised template, which was then checked against the original study record by a second reviewer. Disagreements were settled by discussion or use of a third independent reviewer. Data of interest included:

- trial information: trial arm, trial identifier, location, date, number of institutions, study design, length of follow-up, inclusion/exclusion criteria, study author
- demographic information: number of participants, age, sex, comorbidities, indication, disease history (i.e. number of years), migraine condition (type of migraine, intensity, frequency, average duration), body mass index, highest level of education, smoking status, alcohol status, caffeine intake
- intervention and comparator: drug name, dose, frequency of administration, concomitant and prior treatments/interventions (both pharmacological and non-pharmacological)
- outcomes of interest: event rates at baseline, final or change from baseline scores in any of the aforementioned outcomes (***Table 3***)
- any noteworthy features (i.e. effect modifiers), limitations or differences in the studies.

For studies that reported outcomes graphically, *WebPlotDigitizer* was used to estimate numerical values.[67]

7.1.5.2 Data analysis

Data on each CGRP antagonist was analysed separately. Similarly, data on each class of comparator was grouped separately. Only direct comparative evidence was considered. Network or indirect analyses were considered to be outside the scope of this review.

Meta-analysis was considered when at least 2 RCTs reporting the same outcome(s) in the same population, intervention and comparator group were identified. Pooling of data for meta-analysis was only conducted when methodologically sound to do so.

If meta-analysis was inappropriate, the results were reported narratively. Any meta-analyses were conducted according to the methodology described in ***Section 7.1.5.3*** of this HTA report.

7.1.5.3 Meta-analysis methods

Dichotomous outcomes were meta-analysed using Review Manager version 5.3.[68-72] The meta-analysis was performed using random-effects models with the Mantel-Haenszel statistical model. It was intended to report the pooled relative risk; however, most studies reported odds ratios (OR) with 95% confidence intervals (CI), so for consistency pooled ORs were reported.

Continuous outcomes were meta-analysed using Review Manager version 5.3.[68-72] The meta-analysis was performed using random-effects models with the inverse variance method. Continuous outcomes were reported as mean differences (MD), which were then interpreted as clinically important based on MCIDs. Where no MCID was defined for an outcome, only the statistical significance was reported and caution was recommended in the interpretation of the reported result.

7.1.5.4 Assessment of heterogeneity

Meta-analysis results were illustrated using forest plots, as they provide a visual representation of the reported effect sizes and uncertainty across the included studies. Heterogeneity and inconsistency were also assessed statistically. The statistical methods used to measure heterogeneity in meta-analyses of continuous outcomes were Tau^2 and I^2. The statistical methods used to measure heterogeneity in meta-analyses of dichotomous outcomes were the Chi^2 test ($p < 0.10$ indicated significant heterogeneity) and I^2. The significance of I^2 was dependent on the strength of the evidence for heterogeneity (i.e. Tau^2 and Chi^2) as well as direction and size of the measured effect. It was interpreted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*.[73] An I^2 of 0–40% is low (i.e. may not be important), 30–60% is moderate, 50–90% is substantial and 75–100% is considerable heterogeneity.[73]

7.1.5.5 Subgroup and sensitivity analyses

Data for each of the populations were analysed separately. For each population, CGRP antagonists were analysed separately and by dose and duration of follow up.

As per the PICO criteria (***Table 3***), a broad population of chronic and episodic migraine patients was included to ensure that all available evidence was identified to address the research question. Additional subgroups were included that sought to capture the conditions for reimbursement of CGRP antagonists in Switzerland (***Appendix A***). Where evidence was identified that met the specific population for reimbursement in Switzerland, subgroup analyses were conducted to investigate outcomes meeting the PICO criteria (see ***Table 3***).

7.1.5.6 Assessment of publication bias

Publication bias was to be assessed for meta-analyses using funnel plots; however, this method requires a minimum of 10 studies per outcome and study numbers were insufficient.[74]

7.1.5.7 Missing values

Missing standard deviations (SD) were obtained from available means, sample sizes, standard errors (SE) and 95% CIs (for samples over 100 participants) using formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*.[73]

$$SD = \sqrt{N}\ x\ (upper\ limit - lower\ limit)/3.92$$

Where continuous values needed to be combined, formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)* were used:[73]

$$Sample\ size = N_1 + N_2$$

$$Mean = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2\ 2M_2 M_2)}{N_1 + N_2 - 1}}$$

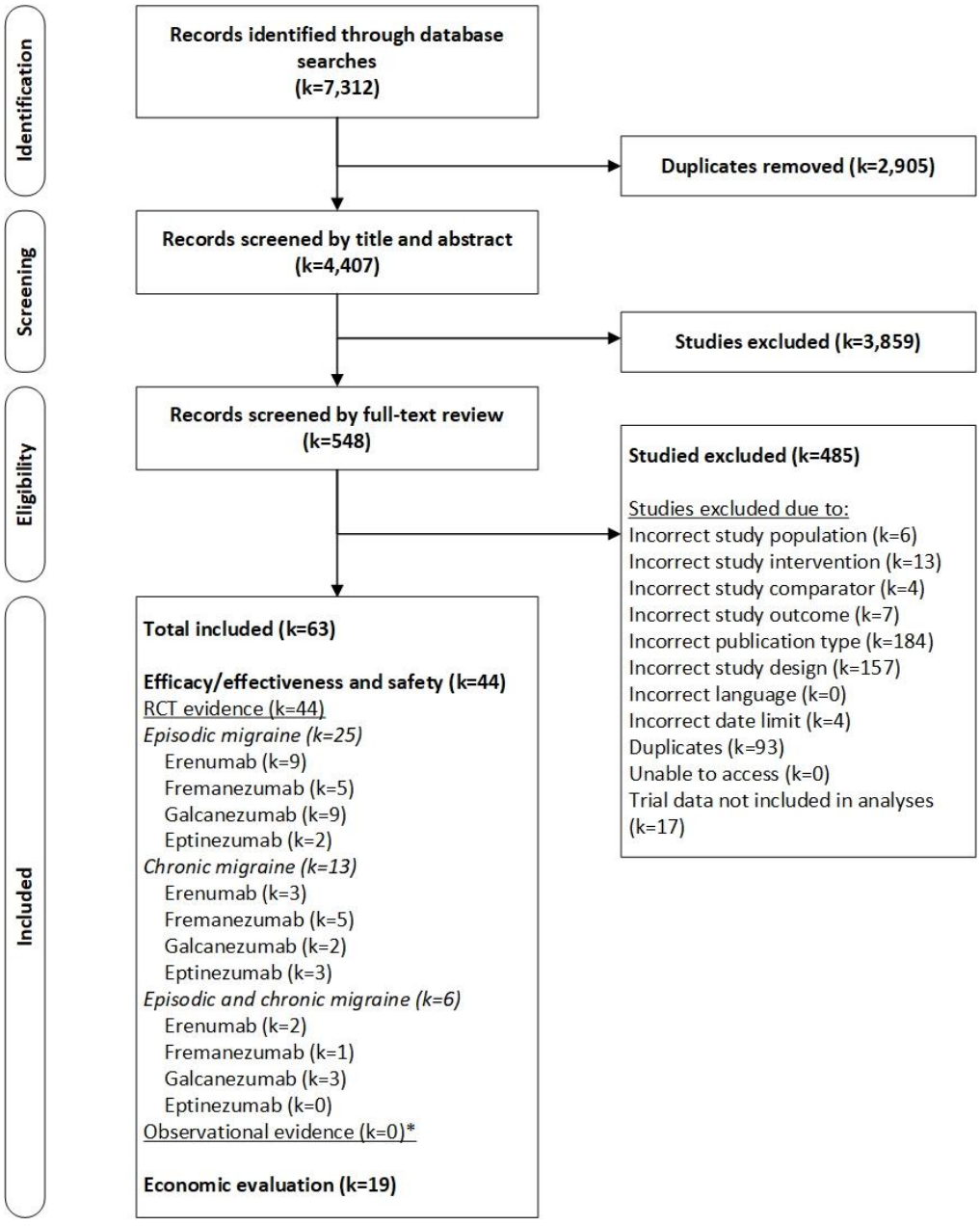
For studies that reported outcomes graphically, *WebPlotDigitizer* was used to convert graph points into numerical values.[67]

7.2 Results effectiveness, efficacy and safety

7.2.1 PRISMA flow diagram

The results of the systematic literature search are summarised in ***Figure 1***. A complete list of publications excluded at full text review is available in ***Appendix D***.

Figure 1 PRISMA flow diagram



Abbreviations
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **RCT** = randomised controlled trial.
Notes
* A targeted screening of observational evidence was conducted to answer the Additional Question(s) (***Section 6.1***) regarding 'switching of CGRP antagonists', however no evidence was identified.

7.2.2 Study characteristics and quality assessment of included studies

7.2.2.1 Study characteristics

Overall, 27 RCTs were included (k = 44 publications) in the assessment of clinical effectiveness and safety. The characteristics of each included trial are briefly described below per intervention, with additional details presented in ***Table 4***.

7.2.2.1.1 Erenumab

In total, 9 RCTs[48,49,75-81] (k = 14 publications) were included in the assessment of clinical effectiveness and safety of erenumab. All included RCTs were multicentre and conducted across various countries (see ***Table 4*** for further details). Of the included trials, 6 RCTs[48,49,75-78] (k = 9 publications) were conducted solely in patients with episodic migraine, 1 RCT[79] (k = 3 publications) was conducted solely in patients with chronic migraine, and 2 RCTs[80,81] (k = 2 publications) incorporated a mixed population of both episodic and chronic migraine patients. ICHD criteria were used to define headache across all included trials, although 1 RCT[78] used ICHD-2 and 8 RCTs[48,49,75-77,79-81] used ICHD-3.

As per the dosages of interest to the PICO criteria, 3 RCTs[75,78,81] compared erenumab 70 mg to placebo, 1 RCT[49] compared erenumab 140 mg to placebo, 4 RCTs compared both erenumab 70 mg and 140 mg to placebo,[48,76,77,79] and one RCT compared erenumab 70/140 mg to topiramate 25–100 mg.[80] All dosages of erenumab and matched placebo were administered subcutaneously once per month, whereas topiramate was administered orally once (25 mg dose) or twice (50, 75, 100 mg dose) per day. It is important to note that other doses of erenumab were also administered in some of the included studies; however, these doses were not extracted or analysed as they are not reimbursed in Switzerland.

The median sample size was 577 (range 246–955), with 5,057 participants included across all 9 independent trials. The duration of treatment ranged from 3 to 6 months. Participants were most commonly female, with a reported mean age ranging between 37.1 and 45 years. For clinical effectiveness, the most frequently studied outcomes included MMDs, acute medication use, response rate (50%), MSQ and HIT-6. For safety, the most reported outcomes included AEs, SAEs and AEs leading to discontinuation. Treatment adherence, mortality and AEs upon discontinuation were not reported for erenumab.

Additional study characteristics on the use of concomitant preventative migraine medication and the inclusion/exclusion of participants based on previous migraine preventive treatment failure across each included trial are shown in ***Table A20, Appendix F***.

7.2.2.1.2 Eptinezumab

In total, 3 RCTs[82-84] (k = 5 publications) were included in the assessment of clinical effectiveness and safety of eptinezumab. All included RCTs were multicentre and conducted across various countries (see ***Table 4*** for further details). Of the included trials, 1 RCT[82] (k = 2 publications) was conducted solely in patients with episodic migraine and 2 RCTs[83,84] (k = 3 publications) were conducted solely in patients with chronic migraine. ICHD criteria were used to define headache across all included trials, although 1 RCT[82] used ICHD-2 and 2 RCTs[83,84] used ICHD-3.

As per the dosages of interest to the PICO criteria, all 3 RCTs[82-84] compared eptinezumab 100 mg and 300 mg to placebo. All dosages of eptinezumab and matched placebo were administered IV every 3 months[82,84] or as a single nonrecurring dose[83] at the start of the trial. It is important to note that other doses of eptinezumab were also administered in some of the included studies; however, these doses were not extracted or analysed as they are not reimbursed in Switzerland.

The median sample size was 665 (range 364–1072), with 2,101 participants included across all 3 independent trials. The duration of treatment ranged from 3 to 9 months. Participants were most commonly female, with a reported mean age ranging between 36.7 and 41 years. For clinical effectiveness, the most frequently studied outcomes included MMDs, MHDs, response rate (50%, 75%) and HIT-6. For safety, the most commonly reported outcomes included SAEs and AEs leading to discontinuation. MSQ, MIDAS, migraine/headache pain intensity, treatment adherence, mortality, AEs, TRAEs and AEs upon discontinuation were not reported for eptinezumab.

Additional study characteristics on the use of concomitant preventative migraine medication and the inclusion/exclusion of participants based on previous migraine preventative treatment failure across each included trial are shown in ***Appendix F***.

7.2.2.1.3 Fremanezumab

In total, 7 RCTs[85-91] (k = 11 publications) were included in the assessment of clinical effectiveness and safety of fremanezumab. All included RCTs were multicentre and conducted across various countries (see ***Table 4*** for further details). Of the included trials, 3 RCTs[85-87] (k = 4 publications) were conducted solely in patients with episodic migraine, 3 RCTs[88-90] (k = 5 publications) were conducted solely in patients with chronic migraine, and 1 RCT[91] (k = 2 publications) incorporated a mixed population of both episodic and chronic migraine patients. ICHD-3 criteria were used to define headache across all included trials.

As per the dosages of interest to the PICO criteria, 1 RCT[88] compared 675/225 mg fremanezumab (i.e. 675 mg administered as a loading dose) to placebo and 6 RCTs[85-87,89-91] compared both 225 mg and 675 mg to placebo. All dosages of fremanezumab and matched placebo were administered

subcutaneously, with 1 RCT[85] administering fremanezumab 225 mg and 675 mg monthly, and 5 RCTs[86-90] administering fremanezumab 225 mg monthly and fremanezumab 675 mg quarterly. One[88] of these 5 RCTs administered a loading dose of 675 mg fremanezumab to those randomised to the 225 mg monthly intervention group. One further RCT[91] administered 675 mg fremanezumab quarterly and 225 mg fremanezumab monthly; however, those who were classified as having chronic migraine received a loading dose of 675 mg, whereas those with episodic migraine did not. It is important to note that other doses of fremanezumab were also administered in some of the included studies; however, these doses were not extracted or analysed as they are not reimbursed in Switzerland.

The median sample size was 571 (range 177–1,130), with 4,245 participants included across all 7 independent trials. The duration of treatment ranged from 2 to 3 months. Participants were most commonly female, with a reported mean age ranging between 40 and 46.8 years. For clinical effectiveness, the most frequently studied outcomes included MMDs, MHDs, acute medication use, response rate (50%), MIDAS and HIT-6. For safety, the most reported outcomes included TRAEs, SAEs and AEs leading to discontinuation. MSQ, migraine/headache pain intensity, treatment adherence, mortality and AEs upon discontinuation were not reported for fremanezumab.

Additional study characteristics on the use of concomitant preventative migraine medication and the inclusion/exclusion of participants based on previous migraine preventative treatment failure across each included trial are shown in ***Appendix F***.

7.2.2.1.4 Galcanezumab

In total, 8 RCTs[50,92-98] (k = 14 publications) were included in the assessment of clinical effectiveness and safety of galcanezumab. All included RCTs were multicentre and conducted across various countries (see ***Table 4*** for further details). Of the included RCTs, one independent trial[97] was initiated as open label to assess the safety of galcanezumab in both episodic and chronic migraine patients. Five RCTs[92-96] (k = 9 publications) were conducted solely in patients with episodic migraine, 1 RCT[50] (k = 2 publications) was conducted solely in patients with chronic migraine, and 2 RCTs[97,98] (k = 3 publications) incorporated a mixed population of both episodic and chronic migraine patients. ICHD criteria were used to define headache across all included trials, although 1 RCT[96] used ICHD-2 and 7 RCTs[50,92-95,97,98] used ICHD-3.

As per the dosages of interest to the PICO criteria, 4 RCTs compared galcanezumab 120 mg and galcanezumab 240 mg to placebo, 2 RCTs[95,98] compared galcanezumab 120 mg to placebo, 1 open label RCT[97] compared galcanezumab 120 mg to galcanezumab 240 mg, and 1 RCT compared galcanezumab 150 mg to placebo.[96] All dosages of galcanezumab and matched placebo were administered subcutaneously once per month. It is important to note that other doses of galcanezumab

were also administered in some of the included studies; however, these doses were not extracted or analysed as they are not reimbursed in Switzerland.

The median sample size was 459 (range 207–1,113), with 4,501 participants included across all 7 included trials. The duration of treatment ranged from 3 to 12 months. Participants were most commonly female, with a reported mean age ranging between 39.1 and 46.3 years. For clinical effectiveness, the most frequently studied outcomes included MMDs, MHDs, acute medication use, response rate (50%, 75%, 100%), MSQ and MIDAS. For safety, the most reported outcomes included SAEs and AEs leading to discontinuation. Migraine/headache pain intensity, treatment adherence, mortality and AEs upon discontinuation were not reported for galcanezumab.

Additional study characteristics on the use of concomitant preventative migraine medication and the inclusion/exclusion of participants based on previous migraine preventative treatment failure across each included trial are shown in ***Appendix F***.

7.2.2.2 Evidence table

Table 4 Characteristics of included RCTs assessing clinical effectiveness and safety

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
Erenumab											
ARISE 2018[75] NCT02483585[99]	RCT; Phase 3; 69 sites; North America, Europe	Episodic	Erenumab 70 mg	Once a month	3 months	3 months	286	42 (11.0)	245 (85.7)	Amgen Inc.	MMDs APR RR (50%) MSQ HIT-6 MIDAS AEs SAEs discAEs
			Placebo	Once a month	3 months	3 months	291	42 (12.0)	247 (84.9)		
EMPOwER 2021[76] NCT03333109	RCT; Phase 3; 83 sites; 11 countries in Asia, Middle East, Latin America	Episodic	Erenumab 70 mg	Once a month	3 months	6 months	338	37.3 (10.0)	272 (80.5)	Novartis Pharma	MMDs APR RR (50%, 75%, 100%) HIT-6 MIDAS EQ-5D-5L AEs TRAEs SAEs discAEs
			Erenumab 140 mg	Once a month	3 months	6 months	224	37.1 (9.6)	184 (82.1)		
			Placebo	Once a month	3 months	6 months	338	38.0 (10.1)	281 (83.1)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
LIBERTY 2018[49] NCT03096834[100]	RCT; Phase 3b; 59 sites; 16 countries *	Episodic	Erenumab 140 mg	Once a month	12 weeks	184 weeks (+ 2-week screening phase)	121	44.6 (10.5)	97 (80.0)	Novartis Pharma	MMDs APR RR (50%, 75%, 100%) HIT-6 SAEs discAEs
			Placebo	Once a month	12 weeks	184 weeks (+ 2-week screening phase)	125	44.2 (10.6)	103 (82.0)		
Sakai et al 2019[77] NCT02630459	RCT; Phase 2; 43 sites; Japan	Episodic	Erenumab 70 mg	Once a month	6 months	119–124 months	135	43.8 (9.0)	115 (85.2)	Amgen Inc.	MMDs APR RR (50%) HIT-6 AEs SAEs discAEs
			Erenumab 140 mg	Once a month	6 months	119–124 months	137	45.0 (8.3)	112 (81.8)		
			Placebo	Once a month	6 months	119–124 months	136	43.7 (9.1)	118 (86.8)		
STRIVE 2017[48] NCT02456740[101, 102]	RCT; Phase 3; 121 sites; 13 countries †	Episodic	Erenumab 70 mg	Once a month	24 weeks	24 weeks	317	41.1 (11.3) Range: 18–63	268 (84.5)	Amgen Inc. and Novartis Pharma	MMDs APR RR (50%, 75%) MSQ HIT-6 MIDAS AEs SAEs discAEs
			Erenumab 140 mg	Once a month	24 weeks	24 weeks	319	40.4 (11.1) Range: 19–65	272 (85.3)		
			Placebo	Once a month	24 weeks	24 weeks	319	41.3 (11.2) Range 18–65	274 (85.9)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
Sun et al 2016[78] NCT01952574	RCT; Phase 2; 59 centres; 8 countries ‡	Episodic ‖	Erenumab 70 mg	Once a month	12 weeks	12 weeks	107	42.6 (9.9)	82 (77.0)	Amgen Inc.	MMDs MHDs APR RR (50%) MSQ HIT-6 MIDAS MPI AEs SAEs discAEs
			Placebo	Once a month	12 weeks	12 weeks	160	41.4 (10.0)	132 (83.0)		
Tepper et al 2017[79] NCT02066415[103, 104]	RCT; Phase 2; 69 centres; 10 countries §	Chronic	Erenumab 70 mg	Once a month	12 weeks	12 weeks (DBTP)	191	41.4 (11.3)	166 (87.0)	Amgen Inc.	MMDs APR RR (50%, 75%) MSQ HIT-6 MIDAS AEs SAEs discAEs
			Erenumab 140 mg	Once a month	12 weeks	12 weeks (DBTP)	190	42.9 (11.1)	160 (84.0)		
			Placebo	Once a month	12 weeks	12 weeks (DBTP)	286	42.1 (11.3)	226 (79.0)		
HER-MES 2022[80] NCT03828539[105]	RCT; Phase 4; 82 sites; Germany	•4–7 MMDs = 94 (24.2) •Episodic (8–14 MMDs) = 248 (63.9)	Erenumab 70 or 140 mg	Once a month	24 weeks	28 weeks	388	40.8 (12.4)	331 (85.3)	Novartis Pharma	MMDs RR (50%) HIT-6 SF-36

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
		•Chronic (≥15 MMDs) = 43 (11.1) •4–7 MMDs = 92 (23.7) •Episodic (8–14 MMDs) = 254 (65.5) •Chronic (≥15 MMDs) = 42 (10.8)	Topiramate 25–100 mg	•For 25mg dose: one tablet daily (night) •For 50, 75, 100 mg dose: 2 tablets daily (morning and night)	24 weeks	28 weeks	388	40.7(12.4)	335 (86.3)		TRAEs SAEs discAEs
Takeshima et al 2021[81] NCT03812224[106]	RCT; Phase 3; 41 sites; Japan	Episodic: 79 (60.8) Chronic: 51 (39.2)	Erenumab 70 mg	Once a month	24 weeks	24 weeks	130	44.2 (8.5)	111 (85.4)	Amgen Inc.	MMDs MHDs APR RR (50%) SAEs discAEs
		Episodic: 80 (61.1) Chronic: 51 (38.9)	Placebo	Once a month	24 weeks	24 weeks	131	44.6 (9.3)	116 (88.5)		
Eptinezumab											
PROMISE-1 2020[82] NCT02559895[107, 108]	RCT; Phase 3; 84 sites; USA, Republic of Georgia	Episodic ‖ ‖	Eptinezumab 100 mg	Every 3 months	36 weeks	56 weeks	221	40.0 (10.7)	179 (80.3)	H. Lundbeck A/S, Copenhagen, Denmark.	MMDs MHDs APR RR (50%, 75%, 100%) SF-36 SAEs discAEs
			Eptinezumab 300 mg	Every 3 months	36 weeks	56 weeks	222	40.2 (11.7)	199 (88.8)		
			Placebo	Every 3 months	36 weeks	56 weeks	222	39.9 (11.7)	186 (83.8)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
Dodick et al 2019[83] NCT02275117	RCT; Phase 2b; 92 sites; USA, Australia, New Zealand, Republic of Georgia	Chronic	Eptinezumab 300 mg	Once	12 weeks	12 weeks	121	37.2 (10.0)	98 (81.0)	Alder BioPharmaceuticals	MMDs MHDs RR (50%, 75%) HIT-6 SAEs
			Eptinezumab 100 mg	Once	12 weeks	12 weeks	122	36.7 (9.4)	104 (85.0)		
			Placebo	Once	12 weeks	12 weeks	121	37.2 (9.2)	109 (90.0)		
PROMISE-2 2020[84] NCT02974153[109, 110]	RCT; Phase 3; 128 sites; 13 countries ‖	Chronic	Eptinezumab 100 mg	Every 3 months	12 weeks	32 weeks	356	41.0 (11.7)	307 (86.2)	H. Lundbeck A/S, Copenhagen, Denmark.	MMDs MHDs APR RR (50%, 75%, 100%) HIT-6 SAEs discAEs
			Eptinezumab 300 mg	Every 3 months	12 weeks	32 weeks	350	41.0 (10.4)	314 (89.7)		
			Placebo	Every 3 months	12 weeks	32 weeks	366	39.6 (11.3)	325 (88.8)		
Fremanezumab											
Bigal et al 2015b[85] NCT02025556	RCT; Phase 2b; 62 sites; USA	Episodic	Fremanezumab 225 mg	Once a month	3 months	3 months	96	40.8 (12.4)	87 (91.0)	Teva Pharma	MMDs MHDs APR RR (50%, 75%) MIDAS TRAEs SAEs
			Fremanezumab 675 mg	Once a month	3 months	3 months	97	40.7 (12.6)	82 (85.0)		
			Placebo	Once a month	3 months	3 months	104	42.0 (11.6)	92 (88.0)		
HALO EM 2018[86] NCT02629861[111, 112]	RCT; Phase 3; 123 sites; 9 countries ¶	Episodic	Fremanezumab 225 mg	Once a month	8 weeks	12 weeks	290	42.9 (12.7)	244 (84.1)	Teva Pharma	MMDs APR RR (50%)
			Fremanezumab 675 mg	Quarterly (+ PL monthly)	8 weeks	12 weeks	291	41.1 (11.4)	251 (86.3)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
			Placebo	Once a month	8 weeks	12 weeks	294	41.3 (12.0)	247 (84.0)		MIDAS AEs TRAEs SAEs discAEs
Sakai et al 2021b[87] NCT03303092	RCT; Phase 2b/3; 67 sites; Japan, Korea	Episodic	Fremanezumab 225 mg	Once a month	12 weeks	12 weeks	121	44.4 (9.5)	101 (83.5)	Otsuka Pharmaceutical Co., Ltd.	MMDs APR RR (50%) MIDAS SAEs discAEs
			Fremanezumab 675 mg	Quarterly	12 weeks	12 weeks	119	41.9 (10.1)	101 (84.9)		
			Placebo	Once a month	12 weeks	12 weeks	117	44.2 (10.7)	100 (85.5)		
Bigal et al 2015a[88] NCT02021773[113]	RCT; Phase 2b; 62 sites; USA	Chronic	Fremanezumab 675/225 mg	Once a month	3 months	3 months	88	40.0 (11.6)	76 (86.0)	Teva Pharma	MMDs MHDs APR RR (50%) TRAEs SAEs
			Placebo	Once a month	3 months	3 months	89	40.7 (11.5)	76 (85.0)		
HALO CM 2017[89] NCT02621931[114, 115]	RCT; Phase 3; 132 sites; 9 countries #	Chronic	Fremanezumab 225 mg	Once monthly	8 weeks	12 weeks	379	40.6 (12.0)	330 (87.0)	Teva Pharma	MMDs MHDs APR RR (50%) MSQ HIT-6 EQ-5D-5L AEs
			Fremanezumab 675 mg	Quarterly (+ PL monthly)	8 weeks	12 weeks	376	42.0 (12.4)	331 (88.0)		
			Placebo	Once monthly	8 weeks	12 weeks	375	41.4 (12.0)	330 (88.0)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
											SAEs discAEs
Sakai et al 2021a[90] NCT03303079	RCT; Phase 3; 67 sites; Japan, Korea	Chronic	Fremanezumab 225 mg	Once a month	12 weeks	12 weeks	189	42.7 (10.2)	163 (86.2)	Otsuka Pharmaceutical Co., Ltd.	MMDs MHDs APR RR (50%) HIT-6 SAEs discAEs
			Fremanezumab 675 mg	Quarterly	12 weeks	12 weeks	191	43.5 (10.2)	165 (86.4)		
			Placebo	Once a month	12 weeks	12 weeks	191	42.1 (10.2)	163 (85.3)		
FOCUS 2019[91] NCT03308968[116]	RCT; Phase 3b; 104 sites; 14 countries **	Episodic: 107 (39) Chronic: 169 (61)	Fremanezumab quarterly (675 mg)	675 mg as a first dose, followed by matched monthly placebo for 2 months.	3 months	3 months	276	45.8 (11.0)	229 (83.0)	Teva Pharma	MMDs MHDs APR RR (50%, 75%, 100%) MSQ HIT-6 MIDAS EQ-5D AEs TRAEs SAEs discAEs
		Episodic: 110 (39) Chronic: 173 (61)	Fremanezumab monthly (Episodic: 225 mg monthly, Chronic: 675 mg loading + 225 mg monthly)	*Episodic*-225 mg + 2 matching placebo injections as a first dose, followed by monthly 225 mg for 2 months. *Chronic*-subcutaneous	3 months	3 months	283	45.9 (11.1)	238 (84.0)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
				675 mg first dose followed by 225 mg monthly.							
		Episodic: 112 (40) Chronic: 167 (60)	Placebo	Once a month	3 months	3 months	279	46.8 (11.1)	233 (84.0)		
Galcanezumab											
Dodick et al 2014a[96] NCT01625988	RCT; Phase 2; 35 centres; USA	Episodic ‖ ‖	Galcanezumab 150 mg	Once every 2 weeks	12 weeks	24 weeks	107	40.9 (11.4)	88 (82.0)	Arteaus Therapeutics	MHDs RR (50%, 75%, 100%) AEs SAEs discAEs
			Placebo	Once every 2 weeks	12 weeks	24 weeks	110	41.9 (11.7)	96 (87.0)		
EVOLVE-1 2018[92] NCT02614183	RCT; Phase 3; 90 sites, North America	Episodic	Galcanezumab 120 mg	Once a month	6 months	10 months	213	40.9 (11.9)	181 (85.0)	Eli Lilly and Co.	MMDs APR RR (50%, 75%, 100%) MSQ MIDAS TRAEs SAEs discAEs
			Galcanezumab 240 mg	Once a month	6 months	10 months	212	39.1 (11.5)	175 (82.6)		
			Placebo	Once a month	6 months	10 months	433	41.3 (11.4)	362 (83.6)		
EVOLVE-2 2018[93] NCT02614196	RCT; Phase 3; 109 sites; 11 countries ††	Episodic	Galcanezumab 120 mg	Once a month	6 months	6 months	231	40.9 (11.2)	197 (85.3)	Eli Lilly and Co.	MMDs APR RR (50%, 75%, 100%)
			Galcanezumab 240 mg	Once a month	6 months	6 months	223	41.9 (10.8)	191 (85.7)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
			Placebo	Once a month	6 months	6 months	461	42.3 (11.3)	393 (85.3)		MSQ MIDAS SAEs discAEs
Sakai et al 2020a[94] NCT02959177[117, 118]	RCT; Phase 2; 40 sites; Japan	Episodic	Galcanezumab 120 mg	Once a month	6 months	10 months	115	43.2 (10.0)	95 (82.6)	Eli Lilly and Co.	MMDs APR RR (50%, 75%, 100%) MSQ MIDAS SAEs discAEs
			Galcanezumab 240 mg	Once a month	6 months	10 months	114	44.8 (10.2)	96 (84.2)		
			Placebo	Once a month	6 months	10 months	230	44.2 (10.0)	196 (85.2)		
Skljarevski et al 2018[95] NCT02163993[119-121]	RCT; Phase 2b; 37 centres; USA	Episodic	Galcanezumab 120 mg	Once a month	3 months	6 months	70	39.54 (12.10)	59 (79.6)	Eli Lilly and Co.	MMDs MHDs RR (50%) MSQ HIT-6 SAEs discAEs
			Placebo	Once a month	3 months	6 months	137	40.57 (10.92)	109 (84.3)		
REGAIN 2018[50] NCT02614261[122, 123]	RCT; Phase 3; 116 centres; 12 countries ‡	Chronic	Galcanezumab 120 mg	Once a month	3 months	16 months	278	39.7 (11.9)	237 (85.0)	Eli Lilly and Co.	MMDs MHDs APR RR (50%, 75%, 100%) MSQ MIDAS
			Galcanezumab 240 mg	Once a month	3 months	16 months	277	41.1 (12.4)	226 (82.0)		
			Placebo	Once a month	3 months	16 months	558	41.6 (12.1)	483 (87.0)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow-up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
											SAEs
CGAJ 2018[97] NCT02614287	OL RCT; Phase 3; 28 sites; USA, Canada, Hungary, Belgium, France	Episodic: NR (80.7) Chronic: NR (19.3)	Galcanezumab 120 mg	Once a month	12 months	16 months	135	40.2 (11.7)	110 (81.5)	Eli Lilly and Co.	MMDs MHDs APR RR (50%, 75%, 100%) MSQ MIDAS SAEs discAEs
		Episodic: NR (77.0) Chronic: NR (23.0)	Galcanezumab 240 mg	Once a month	12 months	16 months	135	43.7 (11.0)	113 (83.7)		
CONQUER 2020[98] NCT03559257[124]	RCT; Phase 3b; 64 sites; 12 countries §§	Episodic	Galcanezumab 120 mg	Once a month	3 months	3 months	137	45.9 (11.2)	112 (82.0)	Eli Lilly and Co.	MMDs APR MSQ MIDAS SAEs discAEs
			Placebo	Once a month	3 months	3 months	132	46.3 (11.8)	117 (89.0)		
		Chronic	Galcanezumab 120 mg	Once a month	3 months	3 months	95	45.8 (11.6)	83 (87.0)		
			Placebo	Once a month	3 months	3 months	98	44.8 (13.1)	85 (87.0)		

Abbreviations

AEs = adverse events, **APR** = treatment with acute pain reliever, **DBTP** = double-blind treatment phase, **discAEs** = adverse events leading to discontinuation, **EQ-5D** = EuroQol 5-dimension questionnaire, **HIT-6** = Headache Impact Test-6, **ICHD** = International Classification of Headache Disorders, **ID** = identification, **MHDs** = monthly headache days, **MIDAS** = Migraine Disability Assessment, **MMDs** = monthly migraine days, **MPI** = migraine pain intensity, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number, **NCT** = National Clinical Trial, **OL** = open label, **PL** = placebo, **RCT** = randomised controlled trial, **RR** = response rate, **SAEs** = serious adverse events, **SD** = standard deviation, **SF-36** = 36-Item Short Form Health Survey, **TRAEs** = treatment-related adverse events, **UK** = United Kingdom, **USA** = United States of America.

Notes

* Countries: Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, the Netherlands, Spain, Sweden, Switzerland, UK.

† Countries: North America (Canada, USA), Europe (Austria, Belgium, Czech Republic, Finland, Germany, the Netherlands, Poland, Slovakia, Sweden, UK) and Turkey.
‡ Countries: North America (Canada, USA) and Europe (Denmark, Finland, Germany, Norway, Sweden, Portugal).
§ Countries: North America (Canada, USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, UK).
‖ Countries: USA, Spain, Ukraine, Russian Federation, UK, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark and Belgium.
¶ Countries: Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain and USA.
# Countries: Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain and USA.
** Countries: Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, UK and USA.
†† Countries: USA, UK, the Netherlands, Spain, Czech Republic, Germany, Argentina, Israel, Korea, Taiwan and Mexico.
‡‡ Countries: Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, UK and USA.
§§ Countries: Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, UK and USA.
‖ ‖ Chronic and episodic migraine conforming to ICHD-2 criteria.

7.2.2.3 Risk of bias

The quality of RCTs was evaluated using the Cochrane Risk of Bias 2.0. RoB was assessed for all clinical effectiveness and safety outcomes combined. The RoB graph and summary are reported in ***Figure 2*** and ***Figure 3***, respectively.

7.2.2.3.1 Randomisation process

All but one RCT provided adequate details and posed a low RoB for randomisation, allocation and baseline differences. Randomisation was typically assigned and concealed using a computer-generated randomisation sequence by means of an interactive web or voice response system. Drug allocation was concealed using identical packages, labelling, schedules of administration, appearance, taste and odour. Baseline differences between treatment groups appeared to be mostly balanced. One RCT (reportedly open label) did not conceal allocation and had an imbalance between treatment groups in number of MMDs at baseline.[97]

7.2.2.3.2 Deviation from intended interventions

Most studies adequately reported and posed a low RoB for blinding of participants/personnel. Participants/personnel of a single RCT, which was reported to be open label, were not blinded.[97] Two additional RCTs posed some concerns, as patients who discontinued were excluded from the analysis, though this was further assessed to not substantially impact the results.[76,83]

7.2.2.3.3 Missing outcome data

Most studies utilised intent-to-treat or modified intent-to-treat analyses for primary outcomes, with some studies using per protocol analysis methods for secondary or exploratory outcomes. Most studies that used a modified intent-to-treat analysis required participants to have received at least one dose of the study drug and provide at least one post-baseline measurement for the outcome of interest. RCTs were classified as being high RoB when missing data were ≥5% across treatment arms.[73] Two RCTs posed a high risk for missing outcome data. The first RCT[97] was reported to be open label, with intent-to-treat analysis conducted for the primary outcome and per-protocol analysis conducted for the secondary outcomes, with no methods implemented to correct for missing outcome data. As this study was reported to be open label, if discontinuation occurred due to the study drug this may have impacted the results. The second RCT[76] also scored a high RoB due to missing outcome data, with no details provided to account for differences in the total number of participants analysed across outcomes. This may have impacted the results.

7.2.2.3.4 Measurement of the outcome

All but one RCT posed a low RoB in measurement of the outcome. The majority of the outcomes in this review were reported using patient headache diaries, which can be subjective and may be biased. However, details on how data were collected, measured and analysed were well-reported across the included RCTs, therefore it was determined that ascertainment of the outcome would likely not differ between intervention groups. The single RCT[97] assessed to be of high RoB was open label and therefore not blinded.

7.2.2.3.5 Selective reporting

The majority of included RCTs had a published protocol with adequate evidence that all outcomes and assessment timepoints were defined *a priori*. Where a published protocol was unavailable, all RCTs were registered with a clinical trials database, making it easy to confirm the published results. Two RCTs posed a high RoB for selective reporting. In the first RCT,[86] the numerical results reported for multiple outcomes differed between the primary publication and the clinical trials database record, indicating that the outcome was likely measured in multiple ways. In the second RCT,[82] outcomes were not fully reported at the pre-specified timepoints and the timepoints reported may have been selected based on the results.

Figure 2 Risk of bias graph for RCTs assessing clinical effectiveness and safety outcomes combined

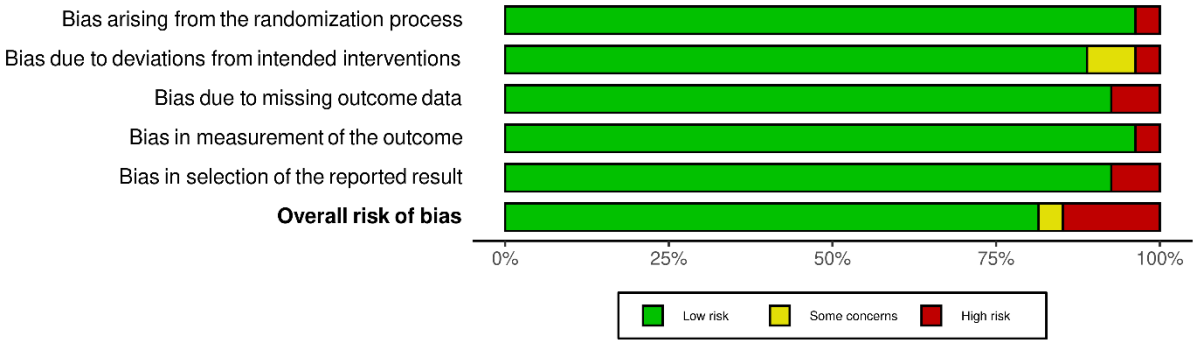
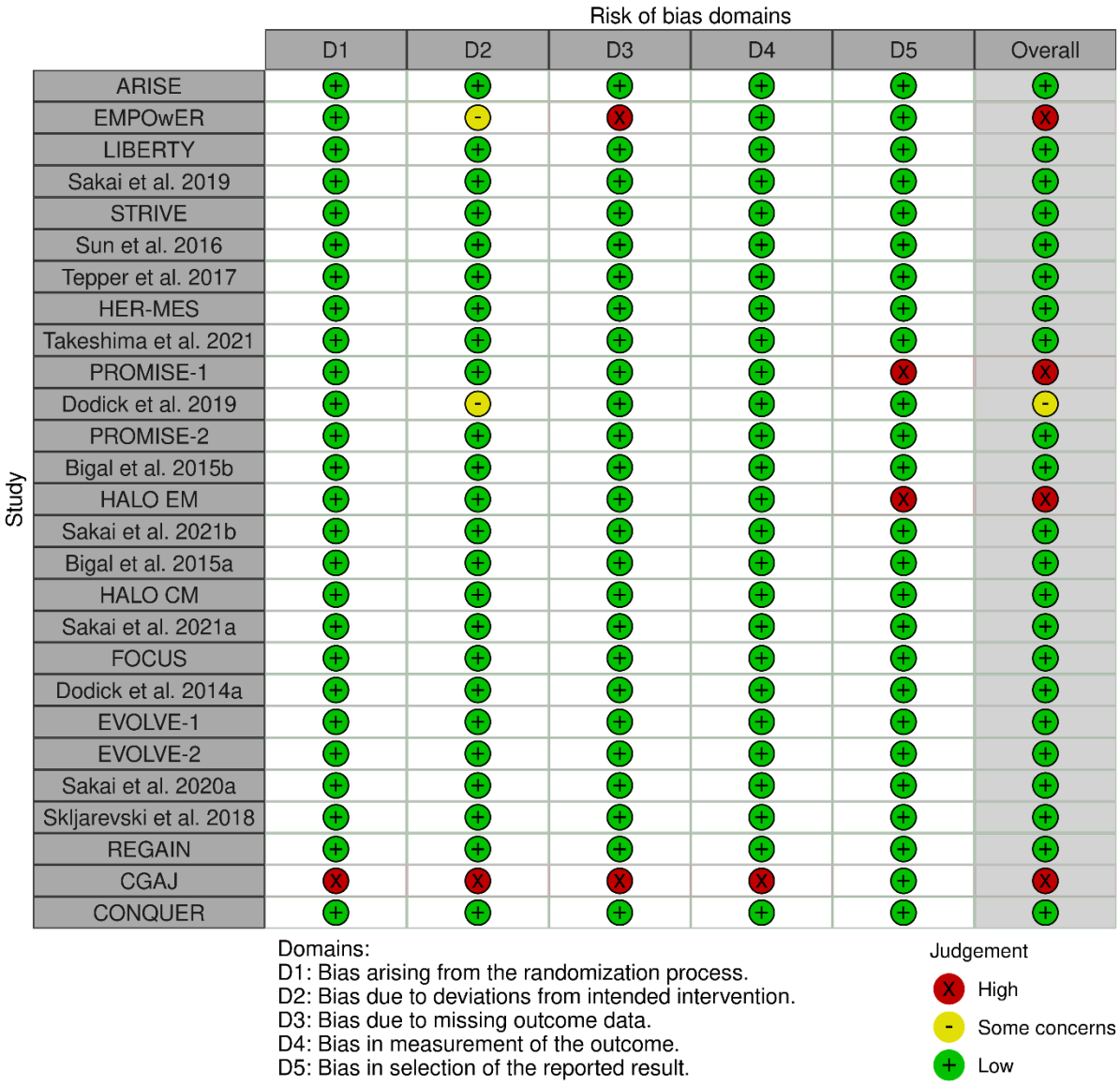


Figure 3 Risk of bias summary for clinical effectiveness and safety outcomes in the RCTs



7.2.2.4 Applicability of evidence to Switzerland

Applicability refers to the generalisability of the included clinical trials to the Swiss context. This involves comparing patient demographics and clinical characteristics of the RCTs to what occurs in Swiss practice. An overview of available information on demographics and clinical characteristics of the 2 populations of interest associated with CGRP antagonists and the other relevant comparators in Switzerland is shown in ***Table 5***.

Table 5 Swiss demographics and clinical characteristics of the populations of interest associated with CGRP antagonists and other comparators

Parameter	Characteristics
Demographics	*Episodic and chronic migraine* *Global:* • In 2016, 1.04 billion individuals were estimated to have migraine.[4] • The lifetime prevalence of migraine was estimated at 17.5% (11.6% in males; 21% in females), with a global prevalence of 14.5%.[12] • In 2016, migraine caused 45.1 million years of life lived with disability.[4] • Each day, 15.8% of the global population had headache.[12] *Europe:* • Migraine is 2–3 times more prevalent in females than males.[11] • The incidence of migraine continued to increase until 50 years of age in females; the incidence in males levelled off at 35 years of age.[10] • Migraine attacks affect an average of 8.3 days per month (100.7 days per year).[11] *Switzerland:* • In 2016, 1.6 million individuals were estimated to have migraine.[4] • In 2016, migraine caused 70,000 years of life lived with disability.[4] • The 3-month prevalence of migraine was estimated at 20% (13% in males; 24% in females).[125] • Around 59% of headache patients had a family history of headache.[125] • Female headache patients tend to be younger (18–35 years of age) compared to male headache patients (36–50 years of age).[125] • Only 27% of headache patients had seen a physician.[125] • Only 4% of males and 2% of females had used prophylactic headache medication.[125] • Individuals with headache lost 10.2 workdays per year.[125] *Episodic migraine* *Switzerland:* • The cumulative 30-year prevalence (1978–2008) of migraine with aura was estimated to be 3% (2.1% in males; 3.9% in females).[10] • The cumulative 30-year prevalence (1978–2008) of migraine without aura was 36% (20.7% in males; 50.7% in females).[10] • Females experience migraine both with and without aura at a higher rate.[10] • Parental history of migraine with and without aura was reported in 94% and 75% of patients, respectively.[10] *Chronic migraine* *Switzerland:* • Around 20% of people with migraine develop a chronic disease life course.[10]
Intervention	• Erenumab (Aimovig®)—70 or 140 mg once monthly (see ***Table 1***) • Fremanezumab (Ajovy®)—225 mg once monthly or 675 mg quarterly (see ***Table 1***) • Galcanezumab (Emgality®)—120 mg once monthly (starting dose of 240 mg) (see ***Table 1***) • Eptinezumab (Vyepti®)—100 mg or 300 mg quarterly (see ***Table 1***)
Comparator	• Standard of care for migraine prevention (see ***Table 1***): o Beta blockers: propranolol, metoprolol o Calcium antagonist: flunarizine o Anticonvulsants: topiramate o Antidepressants: amitriptyline
Clinical characteristics	Limited to: **CGRP antagonists:**

Parameter	Characteristics
	• Erenumab (Aimovig®): see ***Appendix A*** • Fremanezumab (Ajovy®): see ***Appendix A*** • Galcanezumab (Emgality®): see ***Appendix A*** • Eptinezumab (Vyepti®): see ***Appendix A*** **Beta blockers:** • Propranolol: Nil • Metoprolol: Lopresor retard (Daiichi Sankyo [Schweiz] AG) – For patients already on this drug only **Calcium antagonists:** • Flunarizine: Sibelium (Janssen-Cilag AG) – For migraine prophylaxis **Anticonvulsants:** • Topiramate: Nil **Antidepressants:** • Amitriptyline: Nil
Settings	Primary care setting or hospital General practitioner, headache specialist, neurologist

Abbreviations
CGRP = calcitonin gene-related peptide.

There was limited literature regarding the demographics of Swiss patients with episodic and chronic migraine. Evidence in a European patient population was sought to assess the applicability of evidence, although the generalisability to the Swiss context is still somewhat uncertain.

In general, the patient population receiving CGRP antagonists for migraine across the included trials appeared similar to the general Swiss and European population of migraine patients. For example, sex, ethnicity/race, age and disease course were similar. However, it is important to note that 4 trials were conducted solely in Asia,[81,87,90,94] and another in Asia, the Middle East, South America and North America.[76] These trials may be less representative of the Swiss population, as the prevalence of migraine has been reported to be lower in Asian populations.[126,127] Seven of the included trials were predominantly[82,83] or solely[85,88,92,95,96] conducted in participants of Caucasian American descent; however, this population appears to be comparable to migraine patients of European/Swiss descent.

In Swiss clinical practice, for CGRP antagonists to be reimbursed in those with episodic migraine, patients must demonstrate that they experience at least 8 migraine days per month. In the majority of the included RCTs episodic migraine was defined as 4–14 migraine days. The generalisability to the Swiss context is relatively uncertain. Furthermore, in Swiss clinical practice, migraine preventative treatment failures and the effectiveness of treatment after 3, 6 and 12 months are all considered to meet the criteria for reimbursement. These conditions are less clear or not specifically met in the included RCTs and therefore may make the included trials less representative of the Swiss context. Further details on migraine preventative treatment failures in the included trials are shown in ***Appendix F***.

It is important to note that several of the included RCTs allowed the use of 1 or 2 concomitant preventative migraine medications in both the intervention and comparator treatment arms. These concomitant preventative medications were often listed as 'standard of care' medications included as comparators in this HTA report. Refer to ***Appendix F*** for information on the concomitant medications allowed across the included trials.

7.2.2.4.1 Erenumab

Of the included 9 RCTs, 6 had centres in Europe, 5 had centres in North America, 3 had centres in Asia, 2 had centres in the Middle East, and 1 each had a centre in Oceania and South America. No study was fully conducted in Switzerland; however, 2 trials had centres located in Switzerland (i.e. ARISE [6 centres] and LIBERTY [3 centres]). These centres were in Bad Zurzach (n = 2 trials), Biel, Geneve, Lausanne, Lugano, St. Gallen and Zollikon (n = 2 trials). The location of other study centres across Europe included Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, the Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden and the United Kingdom (UK). These countries are likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. broadly following European Headache Federation guidelines)[128] and healthcare systems.

The included studies were mostly consistent with Swiss practice. The dose, administration technique, administration frequency and brand (when specified) of erenumab were the same as those listed on the Spezialitätenliste. Overall, 4 RCTs[48,75,77,81] allowed for the continued use of one concomitant preventive migraine medication throughout the duration of the trial if the dosing was stable for >2 months prior to the baseline phase and throughout the study (see ***Appendix F***). As per Swiss clinical practice, it is possible for both episodic and chronic migraine patients to continue treatment with a standard-of-care drug once commencing treatment with erenumab.[8] Therefore, this does not pose a concern if effective randomisation techniques were implemented (see ***Section 7.2.2.3***) during these trials. Furthermore, for erenumab to be reimbursed in Swiss clinical practice, patients will have needed to either have responded insufficiently or had a contraindication to 2 prior prophylactic therapies (see ***Appendix A***). In the included RCTs, 7 trials excluded participants who had shown no therapeutic response to 2–4 prior preventative treatments. Only 2 trials[49,80] included those who had had prior preventative treatment failures. A further 3 RCTs[48,79,81] included >2 treatment failures as an additional subgroup. The trials that excluded those with treatment failures are less representative of the Swiss clinical context.

7.2.2.4.2 Eptinezumab

Of the included 3 RCTs, 3 had centres in North America, 3 had centres in Asia/Europe (i.e. the Republic of Georgia) and 1 each had a centre in Europe and Oceania. None of the included trials had centres in

Switzerland. The location of study centres across Europe included Belgium, Czech Republic, Denmark, Germany, Hungary, Italy, Russia, Slovakia, Spain, the UK and Ukraine. These countries are likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. broadly following European Headache Federation guidelines)[128] and healthcare systems.

The included studies were mostly consistent with Swiss practice. The dose, administration technique, administration frequency and brand (when specified) of eptinezumab were the same as those listed on the Spezialitätenliste. One RCT[84] allowed for the continued use of one concomitant preventive migraine medication throughout the duration of the trial if the dosing was stable for at least 3 months prior to the screening phase and through to week 24 of the study (see ***Appendix F***). As per Swiss clinical practice, it is possible for both episodic and chronic migraine patients to continue treatment with a standard-of-care drug once commencing treatment with eptinezumab.[8] Therefore, this does not pose a concern if effective randomisation techniques were implemented (see ***Section 7.2.2.3***) during these trials. No information was available on whether participants were included/excluded from these trials based on therapeutic response to prior preventative treatments.

7.2.2.4.3 Fremanezumab

Of the included 7 RCTs, 5 had centres in North America, 3 had centres in Europe, 3 had centres in Asia and 2 had centres in the Middle East. No study was fully conducted in Switzerland; however, one trial had centres located in Switzerland (i.e. FOCUS [3 centres]). These centres were in Bad Zurzach, Bern and Lugano. The location of other study centres across Europe included Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Russia, Spain, Sweden and the UK. These countries are likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. broadly following European Headache Federation guidelines)[128] and healthcare systems.

The included studies were somewhat consistent with Swiss practice. The administration technique, administration frequency and brand (when specified) of fremanezumab were the same as those listed on the Spezialitätenliste. Generally, the dose of fremanezumab was comparable to Swiss practice; however, one RCT[85] administered a dose of 675 mg once per month, when this dosage is typically administered quarterly in clinical practice. It is important to note that this difference in dose and frequency was reported in a phase II trial that sought to evaluate optimal dosage and safety of fremanezumab.[85] Overall, 5 RCTs[85-87,89,90] allowed for the continued use of one concomitant preventive migraine medication in 30% of trial participants throughout the duration of the trial if the dosing was stable for >2 months prior to the baseline phase (see ***Appendix F***). One additional trial[88] allowed for the continued use of ≤2 concomitant preventive migraine medications in all trial participants throughout the duration of the trial if the dosing was stable for >2 months prior to the baseline phase. As per Swiss clinical practice, it is possible for both episodic and chronic migraine patients to continue treatment with a standard-of-

care drug once commencing treatment with fremanzumab.[8] Therefore, this does not pose a concern if effective randomisation techniques were implemented (see ***Section 7.2.2.3***) during these trials. Furthermore, for fremanezumab to be reimbursed in Swiss clinical practice, patients will have needed to either have responded insufficiently or had a contraindication to 2 prior prophylactic therapies (see ***Appendix A***). In the included RCTs, 6 trials excluded participants who had no therapeutic response to 2–4 prior preventative treatments. Only one trial[91] included those who had shown prior preventative treatment failures (no further subgroup analyses were conducted). The trials that excluded those with treatment failures are less representative of the Swiss clinical context.

7.2.2.4.4 Galcanezumab

Of the included 7 RCTs, 7 had centres in North America, 4 had centres in Europe, 4 had centres in Asia, 2 had centres in South America and 2 had centres in the Middle East. None of the included trials had centres in Switzerland. The location of study centres across Europe included Belgium, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Spain and the UK. These countries are likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. broadly following European Headache Federation guidelines)[128] and healthcare systems.

The included studies were somewhat consistent with Swiss practice. The dose, administration technique and brand (when specified) of galcanezumab were the same as those listed on the Spezialitätenliste. However, it is important to note that all included RCTs that administered a dose of 240 mg of galcanezumab[50,92-94,97] administered the dose at a monthly frequency, whereas in Swiss clinical practice this dosage is only administered as a one-off loading dose upon commencement of treatment. One RCT[50] allowed for the continued use of one concomitant preventive migraine medication (i.e. topiramate or propranolol only) throughout the duration of the trial if the dosing was stable for >2 months prior to the baseline phase and throughout the study (see ***Appendix F***). As per Swiss clinical practice, it is possible for both episodic and chronic migraine patients to continue treatment with a standard-of-care drug once commencing treatment with galcanezumab.[8] Therefore, this does not pose a concern if effective randomisation techniques were implemented (see ***Section 7.2.2.3***) during these trials. Furthermore, for galcanezumab to be reimbursed in Swiss clinical practice, patients will have needed to either have responded insufficiently or had a contraindication to 2 prior prophylactic therapies (see ***Appendix A***). In the included RCTs, 7 trials excluded participants who had shown no therapeutic response to >2 or ≥3 prior preventative treatments. Only one trial included those who had prior preventative treatment failures.[98] One RCT included >2 treatment failures as an additional subgroup.[50] The trials that excluded those with treatment failures are less representative of the Swiss clinical context.

A single trial[95] identified that licensed physicians with specialties in neurology, psychiatry, internal medicine and primary care were involved in patient assessment and care.

7.2.3 Findings: effectiveness

In this section, results are presented by drug type, then by population type. RoB was assessed using the Cochrane RoB 2.0 tool; the score shown in the following effectiveness sections is the overall score assigned to each study. Further details about RoB are reported in ***Section 7.2.2.3***. The following points apply to data reported in the effectiveness section:

- Where a single timepoint is reported (e.g. 3 months) this indicates that the outcome was recorded at this timepoint only. Where timepoints for outcomes are reported in ranges (e.g. 1–12 weeks) this indicates that the outcome was derived from averaging the scores or counts for the outcomes over each week or month.
- Blue text reported in data tables indicates comparisons calculated by the Royal Australasian College of Surgeons (RACS). These analyses were added to provide a complete data set.
- One trial reporting galcanezumab 150 mg was included and assumed to be similar to galcanezumab 120 mg. This has been reported in the text as such.[96]
- No evidence was identified to answer the research questions relating to whether switching from one CGRP antagonist to another is effective/efficacious in those who previously experienced inadequate treatment effects using a different CGRP antagonist.
- GRADE summary of findings tables for MMDs, 50% response rate and MSQ can be found in ***Section 7.2.5*** (***Table 146*** to ***Table 148***).
- Data extraction tables for all effectiveness and safety outcomes can be found in ***Table A22*** to ***Table A76, Appendix G***.

7.2.3.1 Summary of findings – effectiveness

Summary of findings tables are reported in ***Section 7.2.5***. Almost all of the included studies reported significantly fewer MMDs, significantly fewer MHDs, significantly fewer days with acute medication use, significantly more patients with a response rate of >50% and 75%, and significant improvements in QoL measures for all CGRP antagonists compared to placebo. Very few studies reported migraine pain intensity. There was more evidence for patients with episodic migraine than for chronic migraine, and a greater number of trials conducted for erenumab and galcanezumab compared to fremanezumab or eptinezumab. Subgroup analyses of patients with >2 prior treatment failures were reported for studies of erenumab, with one each conducted for fremanezumab and galcanezumab. While almost all trials of CGRP antagonists reported significantly fewer MMDs, the evidence was strongest for erenumab, followed by galcanezumab.

7.2.3.2 Monthly migraine days (MMDs)

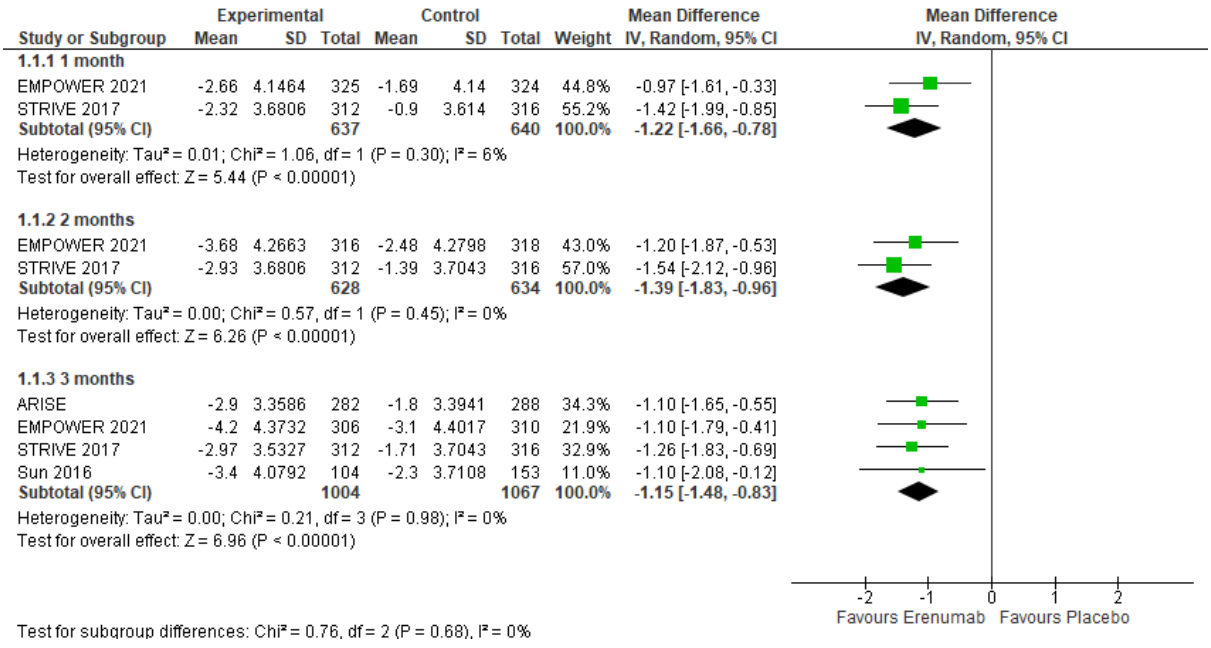
7.2.3.2.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting MMDs for erenumab 70 mg compared to placebo were available for 5 RCTs: 4 were at low RoB,[48,75,77,78] while one was at high RoB.[76] Four RCTs were suitable for combining in a meta-analysis, where MMDs were reported to be significantly less frequent in patients randomised to erenumab 70 mg at 1 month, 2 months and 3 months (***Figure 4***).[48,75,76,78] There was no heterogeneity identified at any timepoint. Sensitivity analyses excluding the single RCT at high RoB did not alter results (***Appendix H Figure A1***). One additional RCT (reporting average MMDs across study periods) reported similar results with significantly fewer MMDs among erenumab patients (***Table 6***).[77]

Figure 4 MMDs, erenumab in episodic migraine patients receiving 70 mg



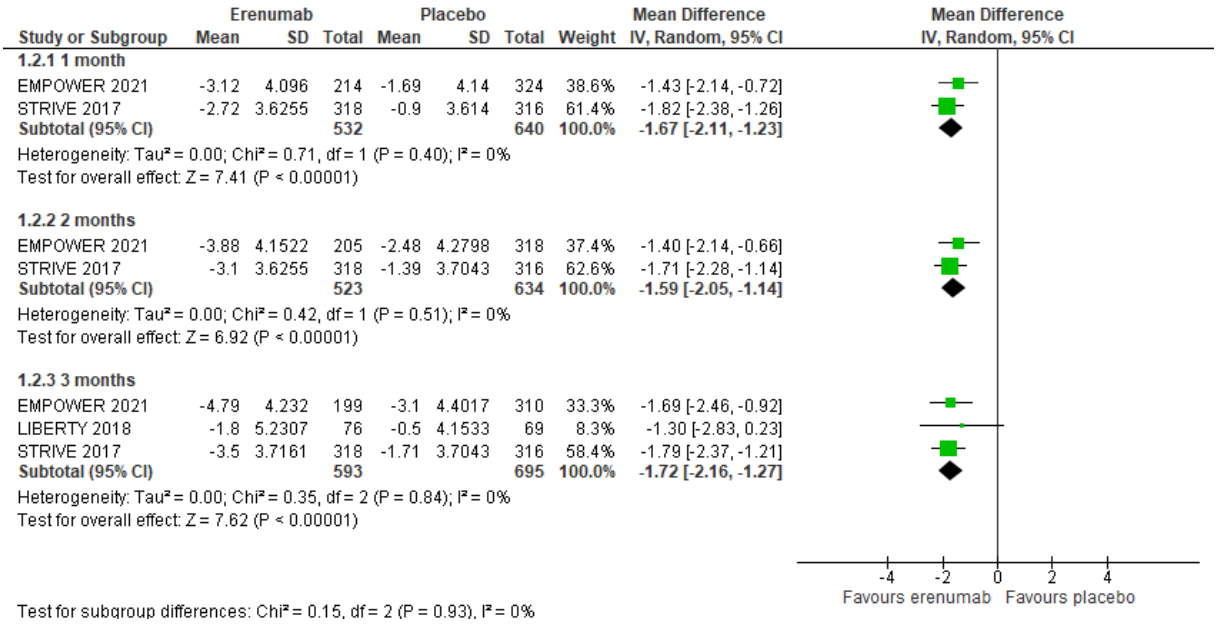
Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Erenumab 140 mg

Data reporting MMDs for erenumab 140 mg compared to placebo were available in 4 RCTs.[48,49,76,77] Three RCTs were suitable for combining in a meta-analysis, where MMDs were significantly less frequent in patients randomised to erenumab 140 mg at 1 month, 2 months and 3 months (***Figure 5***).[48,49,76] Sensitivity analyses excluding the single RCT at high RoB did not alter results (***Appendix H, Figure A2***). There was no heterogeneity identified at any timepoint. One additional RCT (reporting

average MMDs across study periods) reported similar results with significantly fewer MMDs among erenumab patients (***Table 6***).[77]

Figure 5 MMDs, erenumab in episodic migraine patients receiving 140 mg



Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 6 MMDs, erenumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Sakai et al 2019[77]	Low	4–6 months	ERU 70 mg	135	-2.25 (95% CI: -2.78, -1.73)	MD -2.31 (95% CI: -3.00, -1.62), p<0.001
			ERU 140 mg	136	-1.83 (95% CI: -2.35, -1.31)	MD -1.89 (95% CI: -2.58, -1.20), p<0.001
			Placebo	136	0.06 (95% CI: -0.46, 0.58)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias.

Chronic migraine

MMDs for erenumab among patients with chronic migraine was reported in one RCT, assessed to be at low RoB.[79] MMDs were significantly less frequent among patients randomised to erenumab 70 mg or erenumab 140 mg compared to placebo at 3 months (***Table 7***).

Table 7 MMDs, erenumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Tepper et al 2017[79]	Low	3 months	ERU 70 mg	188	-6.6 (SE 0.4)	MD -2.5 (95% CI: -3.5, -1.4), p<0.0001
			ERU 140 mg	187	-6.6 (SE 0.4)	MD -2.5 (95% CI: -3.5, -1.4), p<0.0001
			Placebo	281	-4.2 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

Two RCTs reported data for populations with both episodic and chronic migraine patients. Both studies were at low RoB (***Table 8***).[80,81,106] The trials were not suitable for combining in a meta-analysis because the comparators were different. MMDs were significantly less frequent in patients randomised to erenumab 70 mg or erenumab 140 mg compared to topiramate when MMDs were averaged across a 4–6 month time period.[80] MMDs were significantly less frequent in patients randomised to erenumab 70 mg compared to placebo when MMDs were averaged across a 4–6 month time period.[81,106]

Table 8 MMDs, erenumab in episodic and chronic patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
HER-MES[80]*	Low	4–6 months	ERU 70 or 140 mg	383	-5.86 (SE 0.24)	MD -1.84 (95% CI: -2.43, -1.25), p<0.001
			Topiramate 25–100 mg	385	-4.02 (SE 0.24)	
Takeshima et al 2021[81,106]**	Low	4–6 months	ERU 70 mg	129	-3.60 (SE 0.38)	MD -1.62 (95% CI: -2.52, -0.73), p<0.001
			Placebo	128	-1.98 (SE 0.38)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
* In HER-MES, the following numbers of patients were included: 4–7 MMDs = 94 (24.2%), Episodic (8–14 MMDs) = 248 (63.9%), Chronic (≥15 MMDs) = 43 (11.1%)
**Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine

Episodic migraine with ≥2 prior treatment failures

Three RCTs reported MMDs among episodic migraine patients with ≥2 prior treatment failures. All were at low RoB (***Table 9***).[49,81,102] None of the RCTs were suitable for combining in a meta-analysis: one trial did not report SDs or any other measure of variance[102] and the remaining 2 trials reported differing time periods—one reported MMDs averaged across 4–6 months of the study period[81] and the other reported data at 3 months.[49] All 3 trials reported significantly fewer MMDs among patients receiving erenumab: at 3 months among patients receiving erenumab 140 mg,[49] at 4–6 months among patients receiving erenumab 70 mg and those receiving erenumab 140 mg,[102] and at 4–6 months among patients receiving erenumab 70 mg.[81]

Table 9 MMDs, erenumab episodic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
LIBERTY[49]	Low	3 months	ERU 140 mg	76	-1.8 (SE 0.6)	MD -1.3 (95% CI: -2.7, 0.1), p=0.07
			Placebo	69	-0.5 (SE 0.5)	
STRIVE[102]	Low	1 month	ERU 70 mg	49	-1.6 (SD NR)	NR*
			ERU 140 mg	58	-2.5 (SD NR)	NR
			Placebo	54	-0.3 (SD NR)	NR
		2 months	ERU 70 mg	49	-1.8 (SD NR)	NR
			ERU 140 mg	58	-3 (SD NR)	NR
			Placebo	54	-0.4 (SD NR)	NR
		3 months	ERU 70 mg	49	-1.8 (SD NR)	NR
			ERU 140 mg	58	-3.5 (SD NR)	NR
			Placebo	54	-0.9 (SD NR)	NR
		4 months	ERU 70 mg	49	-2 (SD NR)	NR
			ERU 140 mg	58	-2.7 (SD NR)	NR
			Placebo	54	0 (SD NR)	NR
		5 months	ERU 70 mg	49	-1.4 (SD NR)	NR
			ERU 140 mg	58	-3 (SD NR)	NR
			Placebo	54	-0.7 (SD NR)	NR
		6 months	ERU 70 mg	49	-1.2 (SD NR)	NR
			ERU 140 mg	58	-3.1 (SD NR)	NR
			Placebo	54	-0.1 (SD NR)	NR
		4–6 months	ERU 70 mg	49	Range from 4–6 mo	MD -1.3 (95% CI: -2.6, 0.0), p<0.05
			ERU 140 mg	58	Range from 4–6 mo	MD -2.7 (95% CI: -4.0, -1.4), p<0.001
			Placebo	54	Range from 4–6 mo	NA
Takeshima et al 2021[81**]	Low	4–6 months	ERU 70 mg	78	-2.92 (SE NR)	MD -1.67 (95% CI: -2.56, -0.78), p<0.001
			Placebo	81	-1.25 (SE NR)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **mo** = months, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SD** = standard deviation, **SE** = standard error.
Notes
* Differences between erenumab and placebo were unable to be calculated for the STRIVE trial because no measure of variance was reported.
**Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine

Chronic migraine with ≥2 prior treatment failures

Two RCTs reported MMDs among chronic migraine patients with ≥2 prior treatment failures. Both were at low RoB (***Table 10***).[81,103] The RCTs were not suitable for combining in a meta-analysis because they reported differing time periods: one trial reported MMDs averaged across 4–6 months of the study period[81] and the other reported data at 3 months.[103] The Tepper et al 2017 trial reported significantly fewer MMDs among patients receiving erenumab 70 mg and erenumab 140 mg at 3 months,[103] while the second trial reported no significant differences between erenumab 70 mg and placebo at 4–6 months.[81]

Table 10 MMDs, erenumab chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Takeshima et al 2021[81]*	Low	4–6 months	ERU 70 mg	50	-5.11 (SE NR)	MD -1.57 (95% CI: -3.39, 0.24), p=0.089
			Placebo	52	-3.54 (SE NR)	
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	93	-5.4 (SE NR)	MD -2.7 (95% CI: -4.2, -1.2), p<0.001
			ERU 140 mg	92	-7.0 (SE NR)	MD -4.3 (95% CI: -5.8, -2.8), p<0.001
			Placebo	142	-2.7 (SE NR)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.

7.2.3.2.2 Eptinezumab

Episodic migraine

One RCT reported MMDs averaged across 1–12 weeks and 13–24 weeks among patients with episodic migraine who were randomised to eptinezumab (***Table 11***).[82,107] There were significantly fewer MMDs among patients receiving eptinezumab 100 mg and eptinezumab 300 mg compared to placebo at 1–12 weeks and 13–24 weeks.

Table 11 MMDs, eptinezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
PROMISE-1[82,107]	High	1–12 weeks	EPT 100 mg	221	-3.9 (95% CI: -4.28, -3.47)	MD -0.69 (95% CI: -1.25, -0.12), p=0.0182
			EPT 300 mg	222	-4.3 (95% CI: -4.70, -3.90)	MD -1.11 (95% CI: -1.68, -0.54), p=0.0001
			Placebo	222	-3.2 (95% CI: -3.60, -2.79)	NA
		13–24 weeks	EPT 100 mg	221	-4.5 (NR)	MD -0.76 (95% CI: -1.40, -0.11), p=NR*
			EPT 300 mg	222	-4.8 (NR)	MD -1.02 (95% CI: -1.66, -0.37), p=NR*
			Placebo	222	-3.8 (NR)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias.
Notes
* p values could not be calculated for 13–24-week results because no measure of variance was reported; however, 95% CI indicates these results are statistically significant.

Chronic migraine

Two RCTs reported MMDs among patients with chronic migraine. One trial was assessed to have some methodological concerns,[83] while the second was at low RoB.[84,109,110] MMDs were significantly less frequent in patients randomised to eptinezumab, either 100 mg or 300 mg, compared to placebo at 3 months in one trial[83] or in patients who were randomised to eptinezumab 100 mg and eptinezumab 300 mg compared to placebo between 1–12 weeks and between 13–24 weeks (***Table 12***).[84,109,110]

Table 12 MMDs, eptinezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Dodick et al 2019[83]	Some concerns	3 months	EPT 100 mg	118	-7.7 (SD 6.9)	MD -2.1 (95% CI: -3.8, -0.4), p=0.0178
		3 months	EPT 300 mg	114	-8.2 (SD 7.0)	MD -2.7 (95% CI: -4.4, -0.9), p=0.0034
		3 months	Placebo	116	-5.6 (SD 6.6)	NA
PROMISE -2[84,109,110]	Low	1–12 weeks	EPT 100 mg	356	-7.7 (Range -22, 10), p<0.0001	MD -2.0 (95% CI: -2.9, -1.2), p<0.0001
		1–12 weeks	EPT 300 mg	350	-8.2 (Range -23, 11), p<0.0001	MD -2.6 (95% CI: -3.4, -1.7), p<0.0001
		1–12 weeks	Placebo	366	-5.6 (Range -25, 9)	NA
		13–24 weeks	EPT 100 mg	356	-8.3 (SD 7.03)	MD -1.98 (95% CI: -2.94, -1.01), p=0.0003
		13–24 weeks	EPT 300 mg	350	-9.0 (SD 6.72)	MD -2.65 (95% CI: -3.62, -1.68), p<0.00001
		13–24 weeks	Placebo	366	-6.4 (SD 7.16)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic migraine patients combined, or subgroups of patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.2.3 Fremanezumab

Episodic migraine

Three RCTs reported MMDs among patients with episodic migraine. Two trials were at low RoB[85,87] and one trial was at high RoB.[86] None of the RCTs were suitable for combining in a meta-analysis because data were reported at different time periods. MMDs were significantly less frequent in patients randomised to fremanezumab 225 mg and fremanezumab 675 mg compared to placebo at 1– 4 weeks, 5–8 weeks and 9–12 weeks;[85] at 4 weeks and 12 weeks;[86] and at 1–12 weeks (***Table 13***).[87]

Table 13 MMDs, fremanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment**	Intervention and dose	n	Change from baseline	Difference between treatments
Bigal et al 2015b[85]	Low	1–4 weeks	FRE 225 mg	96	NR	MD -2.13 (-3.36, -0.90), p=0.0007
			FRE 675 mg	97	NR	MD -2.42 (-3.65, -1.19), p=0.0001
			Placebo	104	NR	NA
		5–8 weeks	FRE 225 mg	96	NR	MD -2.49 (-3.78, -1.20), p=0.0002
			FRE 675 mg	97	NR	MD -2.66 (-3.95, -1.36), p<0.0001
			Placebo	104	NR	NA
		9–12 weeks	FRE 225 mg	96	NR	MD -2.81 (-4.07, -1.55), p<0.0001
			FRE 675 mg	97	NR	MD -2.64 (-3.90, -1.38), p<0.0001
			Placebo	104	NR	NA
HALO EM[86]	High	4 weeks	FRE 225 mg	287	-3.5 (95% CI: -4.05, -2.93)	MD -1.8 (95% CI: -2.43, -1.18), p<0.001
			FRE 675 mg	288	-3.3 (95% CI: -3.85, -2.71)	MD -1.6 (95% CI: -2.22, -0.97), p<0.001
			Placebo	290	-1.7 (95% CI: -2.24, -1.13)	NA
		12 weeks	FRE 225 mg	287	-3.7 (95% CI: -4.15, -3.18)	MD -1.5 (95% CI: -2.01, -0.93), p<0.001
			FRE 675 mg	288	-3.4 (95% CI: -3.94, -2.96)	MD -1.3 (95% CI: -1.79, -0.72), p<0.001
			Placebo	290	-2.2 (95% CI: -2.68, -1.71)	NA
Sakai et al 2021b[87]	Low	1–12 weeks	FRE 225 mg	121	-4.0 (SE 0.4)	MD -3.0 (95% CI: -3.74, -2.23), p<0.0001
			FRE 675 mg	117	-4.0 (SE 0.4)	MD -3.0 (95% CI: -3.76, -2.24), p<0.0001
			Placebo	116	-1.0 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SD** = standard deviation, **SE** = standard error.

Chronic migraine

Three trials reported MMDs among patients with chronic migraine. All 3 trials were at low RoB.[88-90] None of the RCTs were suitable for combining in a meta-analysis because data were reported at different time periods (***Table 14***). One trial reported that MMDs were significantly less frequent in patients randomised to fremanezumab 225 mg/675 mg compared to placebo at 1–4 weeks; no differences were reported at 5–8 weeks or 9–12 weeks.[88] Two RCTs reported that MMDs were significantly less frequent in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 3 months[89] or across 1–12 weeks.[90]

Table 14 MMDs, fremanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Bigal et al 2015a[88]	Low	1–4 weeks	FRE 675/225 mg*	88	NR	MD -2.07 (95% CI: -3.7, -0.5), p=0.012
			Placebo	89	NR	
		5–8 weeks	FRE 675/225 mg	88	NR	MD -1.64 (95% CI: -3.4, 0.13), p=0.069
			Placebo	89	NR	
		9–12 weeks	FRE 675/225 mg	88	NR	MD -1.72 (95% CI: -3.7, 0.2), p=0.08
			Placebo	89	NR	
HALO CM[89]	Low	3 months	FRE 225 mg	375	-5.0 (SE 0.4)	MD -1.8 (SE 0.4), p<0.001
			FRE 675 mg	375	-4.9 (SE 0.4)	MD -1.7 (SE 0.4), p<0.001
			Placebo	371	-3.2 (SE 0.4)	NA
Sakai et al 2021a[90]	Low	1–12 weeks	FRE 225 mg	187	-4.9 (SE 0.5)	MD -2.1 (95% CI: -3.10, -1.12), p<0.001
			FRE 675 mg	189	-4.1 (SE 0.5)	MD -1.3 (95% CI: -2.27, -0.29), p=0.011
			Placebo	190	-2.8 (SE 0.5)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.
Notes
* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.

Episodic and chronic migraine

One RCT reporting data for a population with both episodic and chronic migraine patients was at low RoB.[91] MMDs were significantly less frequent in patients randomised to fremanezumab quarterly or monthly compared to placebo at 1 and 3 months (***Table 15***).

Table 15 MMDs, fremanezumab in episodic and chronic patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
FOCUS[91]*	Low	1 month	FRE quarterly	276	-4.1 (SE 0.4)	MD -3.6 (95% CI: -4.3, -2.8), p<0.0001
			FRE monthly	283	-4.1 (SE 0.4)	MD -3.5 (95% CI: -4.2, -2.8), p<0.0001
			Placebo	279	-0.6 (SE 0.4)	NA
		3 months	FRE quarterly	276	-3.7 (SE 0.3)	MD -3.1 (95% CI: -3.8, -2.4), p<0.0001
			FRE monthly	283	-4.1 (SE 0.3)	MD -3.5 (95% CI: -4.2, -2.8), p<0.0001
			Placebo	278	-0.6 (SE 0.3)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Episodic and chronic migraine patients with ≥2 prior treatment failures

One RCT reported data (in both episodic and chronic migraine patients) from a subgroup of patients with ≥2 prior treatment failures.[91] MMDs were significantly less frequent in patients randomised to fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 16***).

Table 16 MMDs, fremanezumab episodic and chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
FOCUS[91] *	Low	3 months	FRE quarterly	50	-3.6 (SE 0.7)	MD -3.4 (95% CI: -5.0, -1.8), p<0.0001
			FRE monthly	60	-4.6 (SE 0.7)	MD -4.4 (95% CI: -6.0, -2.8), p<0.0001
			Placebo	54	-0.2 (SE 0.7)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for episodic or chronic subgroups of patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.2.4 Galcanezumab

Episodic migraine

Galcanezumab 120 mg

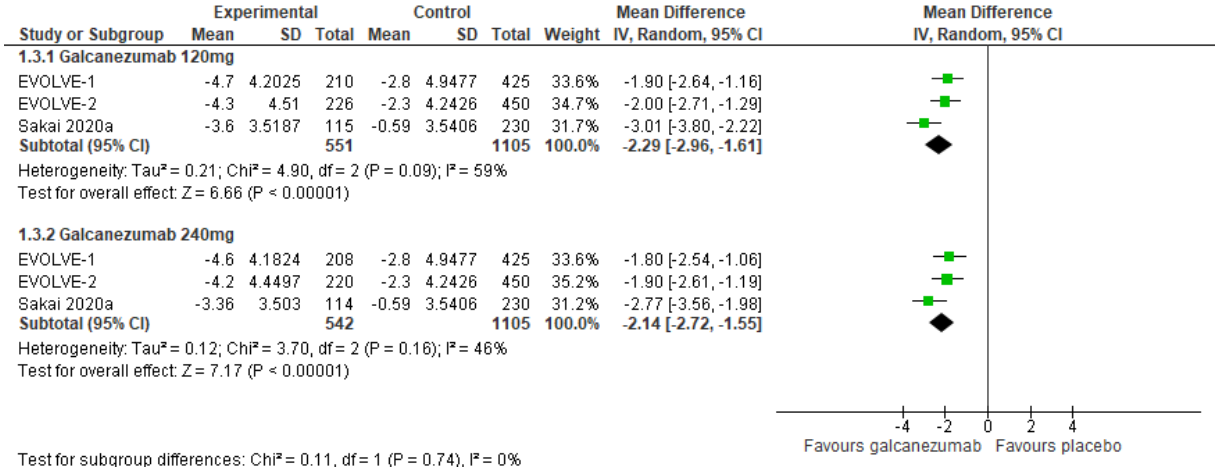
Data reporting MMDs for galcanezumab 120 mg compared to placebo were available in 5 RCTs.[92-95,98] Three RCTs at low RoB and reporting the same timepoints (data averaged across 1–6 months) were suitable for combining in a meta-analysis.[92-94] MMDs were reported to be significantly less frequent in patients randomised to galcanezumab 120 mg compared to placebo. A moderate amount of heterogeneity was reported (***Figure 6***).[92-94] Two additional RCTs, both at low RoB, reported similar results with significantly fewer MMDs among galcanezumab patients[a] (***Table 17***).[95,98]

[a] Although p values were not calculated for the Skljarevski et al 2018 trial, 95% CI values indicate these results are statistically significant.

Galcanezumab 240 mg

Data reporting MMDs for galcanezumab 240 mg compared to placebo were available in 3 RCTs. All were at low RoB and suitable for combining in a meta-analysis.[92-94] MMDs were reported to be significantly less frequent in patients randomised to galcanezumab 240 mg compared to placebo. A moderate amount of heterogeneity was reported (***Figure 6***).

Figure 6 MMDs, galcanezumab in episodic migraine patients across 1–6 months



Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 17 MMDs, galcanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
CONQUER[98]	Low	3 months	GAL120 mg	137	-2.9 (SE 0.3)	MD -2.6 (95% CI: -3.4, -1.7), p<0.001
			Placebo	132	-0.3 (SE 0.3)	
Skljarevski et al 2018[95]	Low	1–12 weeks	GAL 120 mg	69	-4.80 (SE 0.37)	MD -1.14 (95% CI: -2.02, -0.29), p=0.01
			Placebo	134	-3.66 (SE 0.28)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Two RCTs reported MMDs among patients with chronic migraine. Both were at low RoB.[50,98] They were not suitable for combining in a meta-analysis because data were reported at different time periods (***Table 18***). MMDs were significantly less frequent in patients randomised to galcanezumab 120 mg compared to placebo at 3 months[98] and in patients randomised to galcanezumab 120 mg or galcanezumab 240 mg,[50] and in patients randomised to galcanezumab 120 mg or galcanezumab 240 mg.[50]

Table 18 MMDs, galcanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
CONQUER[98]	Low	3 months	GAL 120 mg	95	-6.0 (SE 0.7)	MD -3.7 (95% CI: -5.2, -2.2), p<0.001
			Placebo	98	-2.2 (SE 0.6)	
REGAIN[50]	Low	1–3 months	GAL 120 mg	273	-4.8 (SE 0.4)	MD -2.1 (95% CI: -2.9, -1.3), p<0.001
			GAL 240 mg	274	-4.6 (SE 0.4)	MD -1.9 (95% CI: -2.7, -1.1), p<0.001
			Placebo	538	-2.7 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

One RCT reporting data for a population with both episodic and chronic migraine patients was at high RoB.[97] Patients were randomised to galcanezumab 120 mg or 240 mg. No significant differences were reported between groups (***Table 19***).

Table 19 MMDs, galcanezumab in episodic and chronic patients (combined)

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
CGAJ[97]*	High	12 months	GAL 120 mg	135	-5.6 (SE 0.34)	MD 0.90 (95% CI: -0.03, 1.83), p=0.06
			GAL 240 mg	135	-6.5 (SE 0.33)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

Chronic migraine patients with ≥2 prior treatment failures

One RCT reported data from a subgroup of patients with chronic migraine who had ≥2 prior treatment failures.[122] MMDs were significantly less frequent in patients randomised to galcanezumab 120 mg or 240 mg compared to placebo across 1–3 months (***Table 20***).

Table 20 MMDs, galcanezumab chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
REGAIN[122]	Low	1–3 months	GAL 120 mg	72	-5.35 (SE 0.71)	MD -4.35 (SE 0.07), p<0.001
			GAL 240 mg	104	-2.77 (SE 0.66)	MD 1.77 (SE 0.63), p<0.01
			Placebo	174	-1.01 (SE 0.54)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

No RCTs were identified that reported data for subgroups of episodic patients with ≥2 prior treatment failures or among subgroups of both episodic and chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.3 Monthly headache days (MHDs)

7.2.3.3.1 Erenumab

Episodic migraine

Data reporting MHDs for erenumab 70 mg compared to placebo were available in one trial assessed to be at low RoB.[78] MHDs were reported to be significantly less frequent among patients randomised to erenumab at 12 weeks (***Table 21***).

Table 21 MHDs, erenumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Sun et al 2016[78]	Low	12 weeks	ERU 70 mg	104	-3.5 (SE 0.4)	MD -1.2 (95% CI: -2.1, -0.2), p=0.022
		12 weeks	Placebo	153	-2.4 (SE 0.3)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

Data reporting MHDs for erenumab 70 mg compared to placebo were available in one trial assessed to be at low RoB.[81] MHDs were reported to be significantly less frequent among patients randomised across an average of 4–6 months (***Table 22***).

Table 22 MHDs, erenumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Takeshima et al 2021[81]*	Low	4–6 months	ERU 70 mg	130	-3.85 (SE 0.41)	MD -1.28 (95% CI: -2.22, -0.33), p=0.008
		4–6 months	Placebo	131	-2.57 (SE 0.41)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
* Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine

No RCTs were identified that reported data for chronic patients, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.3.2 Eptinezumab

Episodic migraine

One RCT reported MHDs averaged across 1–12 weeks among patients with episodic migraine randomised to eptinezumab.[82] There were significantly fewer MHDs among patients receiving eptinezumab 100 mg and eptinezumab 300 mg compared to placebo at 1–12 weeks (***Table 23***).

Table 23 MHDs, eptinezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
PROMISE-1[82]	High	1–12 weeks	EPT 100 mg	221	-4.0 (SD 3.30)	MD -0.70 (95% CI: -1.33, -0.07), p=0.03
			EPT 300 mg	222	-4.5 (SD 3.96)	MD -1.20 (95% CI: -1.90, -0.50), p=0.0007
			Placebo	222	-3.3 (SD 3.51)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Two RCTs reported MHDs among patients with chronic migraine. One trial was assessed to have some methodological concerns,[83] while the second was at low RoB.[84,109] In the former, MHDs were significantly less frequent in patients randomised to eptinezumab 100 mg or 300 mg compared to placebo at 3 months.[83] In the latter, MHDs were significantly less frequent in patients randomised to eptinezumab 100 mg or 300 mg compared to placebo at 1–12 weeks and 13–24 weeks (***Table 24***).[84,109]

Table 24 MHDs, eptinezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Dodick et al 2019[83]	Some concerns	3 months	EPT 300 mg	114	-9.6 (6.9)	MD -2.8 (95% CI: -4.5, -1.0), p=0.0022
			EPT 100 mg	118	-8.9 (6.8)	MD -2.0 (95% CI: -3.7, -0.3), p= 0.0224
			Placebo	116	-6.9 (6.4)	NA
PROMISE-2[84,109]	Low	1–12 weeks	EPT 100 mg	356	-8.2 (SD 5.78)	MD -1.7 (95% CI: -2.6, -0.9), p<0.0001
			EPT 300 mg	350	-8.8 (SD 6.1)	MD -2.3 (95% CI: -3.2, -1.4), p<0.00001
			Placebo	366	-6.4 (SD 5.99)	NA
		13–24 weeks	EPT 100 mg	356	-9.6 (SD 6.62)	-1.5 (95% CI: -2.44, -0.47), p=0.003
			EPT 300 mg	350	-10.6 (SD 6.83)	-2.4 (95% CI: -3.43, -1.42), p<0.00001
			Placebo	366	-8.1 (SD 6.90)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic patients combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.3.3 Fremanezumab

Episodic migraine

One RCT reported MHDs among patients with episodic migraine. The study was at low RoB.[85,87] MHDs were significantly less frequent in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 1–4 weeks, 5–8 weeks and 9–12 weeks (***Table 25***).[85]

Table 25 MHDs, fremanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Bigal et al 2015b[85,87]	Low	Weeks 1–4	FRE 225 mg	96	NR	-2.14 (95% CI: -3.33, -0.95), p=0.0005
			FRE 675 mg	97	NR	-2.05 (95% CI: -3.23, -0.86), p=0.0008
			Placebo	104	NR	NA
		Weeks 5–8	FRE 225 mg	96	NR	-2.62 (95% CI: -3.88, -1.36), p<0.0001
			FRE 675 mg	97	NR	-2.39 (95% CI: -3.65, -1.13), p=0.0002
			Placebo	104	NR	NA
		Weeks 9–12	FRE 225 mg	96	NR	-2.63 (95% CI: -3.91, -1.34), p<0.0001
			FRE 675 mg	97	NR	-2.58 (95% CI: -3.87, -1.30), p<0.0001
			Placebo	104	NR	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias.

Chronic migraine

Three trials reported MHDs among patients with chronic migraine. All 3 were at low RoB.[88-90] None of the RCTs were suitable for combining in a meta-analysis because data were reported over different time periods (***Table 26***). One trial reported that MHDs were significantly less frequent in patients randomised to fremanezumab 225 mg/675 mg compared to placebo at 1–4 weeks; no differences were reported at 5–8 weeks or 9–12 weeks.[88] Two RCTs reported that MHDs were significantly less frequent in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 4 or 12 weeks,[89] or across 1–12 weeks.[90]

Table 26 MHDs, fremanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Bigal et al 2015a[88]	Low	Weeks 1–4	FRE 675/225 mg*	88	NR	-2.13 (95% CI: -3.8, -0.5), p=0.012
			Placebo	89	NR	
		Weeks 5–8	FRE 675/225 mg	88	NR	-1.31 (95% CI: -3.1, 0.5), p=0.151
			Placebo	89	NR	
		Weeks 9–12	FRE 675/225 mg	88	NR	-1.74 (95% CI: -3.6, 0.1), p=0.069
			Placebo	89	NR	
HALO CM[89]	Low	4 weeks	FRE 225 mg	375	-4.5 (SE 0.3)	-2.4 (95% CI: -3.23, -1.57), p<0.00001
			FRE 675 mg	375	-4.4 (SE 0.3)	-2.3 (95% CI: -3.13, -1.47), p<0.00001
			Placebo	371	-2.1 (SE 0.3)	NA
		12 weeks	FRE 225 mg	375	-4.6 (SE 0.3)	-2.1 (95% CI: -2.93, -1.27), p<0.00001
			FRE 675 mg	375	-4.3 (SE 0.3)	-1.8 (95% CI: -2.63, -0.97), p<0.0001
			Placebo	371	-2.5 (SE 0.3)	NA
Sakai et al 2021a[90]	Low	weeks 1–12	FRE 225 mg	187	-4.1 (SE 0.4)	-1.7 (95% CI: -2.54, -0.80), p<0.001
			FRE 675 mg	189	-4.1 (SE 0.4)	-1.7 (95% CI: -2.55, -0.82), p<0.001
			Placebo	190	-2.4 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.
* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles

Episodic and chronic migraine

One RCT reporting data for a population with both episodic and chronic migraine patients was at low RoB.[91] MHDs were significantly less frequent in patients randomised to fremanezumab quarterly or monthly compared to placebo at 1 and 3 months (***Table 27***).

Table 27 MHDs, fremanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
FOCUS[91]*	Low	1 month	FRE quarterly	276	-4.2 (SE 0.4)	MD -3.7 (95% CI: -4.4, -3.0), p<0.0001
			FRE monthly	283	-4.5 (SE 0.3)	MD -3.9 (95% CI: -4.6, -3.2), p<0.0001
			Placebo	279	-0.5 (SE 0.3)	NA
		3 months	FRE quarterly	276	-3.9 (SE 0.3)	MD -3.2 (95% CI: -3.9, -2.5), p<0.0001
			FRE monthly	283	-4.2 (SE 0.3)	MD -3.6 (95% CI: -4.3, -2.9), p<0.0001
			Placebo	279	-0.6 (SE 0.3)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Episodic and chronic migraine patients with ≥2 prior treatment failures

One RCT reported data (both episodic and chronic migraine patients) for subgroups of patients with 2, 3 or 4 prior treatment failures.[116] MHDs were significantly less frequent in patients randomised to fremanezumab quarterly or monthly compared to placebo at all timepoints (***Table 28***).

Table 28 MMDs, fremanezumab episodic and chronic patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
FOCUS[116]*	Low	1 month 2 Tx failures	FRE quarterly	140	-4.1 (0.43)	MD -3.2 (95% CI: -4.09, -2.21), p<0.0001
			FRE monthly	133	-4.7 (0.43)	MD -3.8 (95% CI: -4.71, -2.80), p<0.0001
			Placebo	141	-1.0 (0.43)	NA
		1 month 3 Tx failures	FRE quarterly	85	-4.1 (0.58)	MD -4.0 (95% CI: -5.34, -2.60), p<0.0001
			FRE monthly	98	-4.0 (0.58)	MD -3.8 (95% CI: -5.11, -2.49), p<0.0001
			Placebo	82	-0.2 (0.56)	NA
		1 month 4 Tx failures	FRE quarterly	49	-5.3 (1.03)	MD -6.0 (95% CI: -8.30, -3.78), p<0.0001
			FRE monthly	50	-5.2 (0.90)	MD -5.9 (95% CI: -8.02, -3.81), p<0.0001
			Placebo	54	0.7 (1.03)	NA
		3 months 2 Tx failures	FRE quarterly	140	-3.9 (0.42)	MD -2.7 (95% CI: -3.64, -1.86), p<0.0001
			FRE monthly	133	-4.8 (0.42)	MD -3.6 (95% CI: -4.47, -2.65), p<0.0001
			Placebo	141	-1.2 (0.42)	NA
		3 months 3 Tx failures	FRE quarterly	85	-3.9 (0.59)	MD -3.6 (95% CI: -4.96, -2.21), p<0.0001
			FRE monthly	98	-3.5 (0.59)	MD -3.2 (95% CI: -4.56, -1.93), p<0.0001
			Placebo	82	-0.3 (0.57)	NA
		3 months 4 Tx failures	FRE quarterly	49	-4.7 (1.01)	MD -5.2 (95% CI: -7.42, -3.07), p<0.0001
			FRE monthly	50	-4.9 (0.88)	MD -5.4 (95% CI: -7.47, -3.42), p<0.0001
			Placebo	54	0.6 (1.02)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error, **Tx** = treatment.

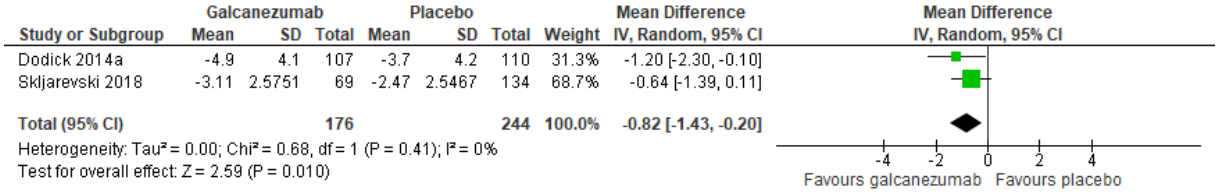
No RCTs were identified that reported data for subgroups of episodic or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.3.4 Galcanezumab

Episodic migraine

Data reporting MHDs for galcanezumab 120 mg compared to placebo were available in 2 RCTs.[96,119] Both were at low RoB and reported the same timepoints, making them suitable for combining in a meta-analysis. MHDs were reported to be significantly less frequent in patients randomised to galcanezumab 120 mg/150 mg compared to placebo. No heterogeneity was reported (***Figure 7***).

Figure 7 MHDs, galcanezumab in episodic migraine patients



Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Chronic migraine

One trial reporting MHDs among patients with chronic migraine was assessed to be at low RoB.[50] MHDs were significantly less frequent in patients randomised to galcanezumab 120 mg or 240 mg compared to placebo (***Table 29***).[50]

Table 29 MHDs, galcanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
REGAIN[50]	Low	Average across 1–9 months	GAL 120 mg	273	-4.8 (SE 0.4)	MD -1.8 (95% CI: -2.7, -1.0), p<0.001
			GAL 240 mg	274	-4.6 (SE 0.4)	MD -1.6 (95% CI: -2.4, -0.8), p<0.001
			Placebo	538	-3.0 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients and was at high RoB.[97] Patients were randomised to galcanezumab 120 mg or 240 mg and no significant differences were reported between groups (***Table 30***).

Table 30 MHDs, galcanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
CGAJ[97]*	High	12 months	GAL 120 mg	135	-2.2 (SE 0.3)	MD -0.10 (95% CI: -0.93, 0.73), p=0.81
			GAL 240 mg	135	-2.1 (SE 0.3)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.4 Number of days per month with migraine that needs to be treated with acute pain relievers

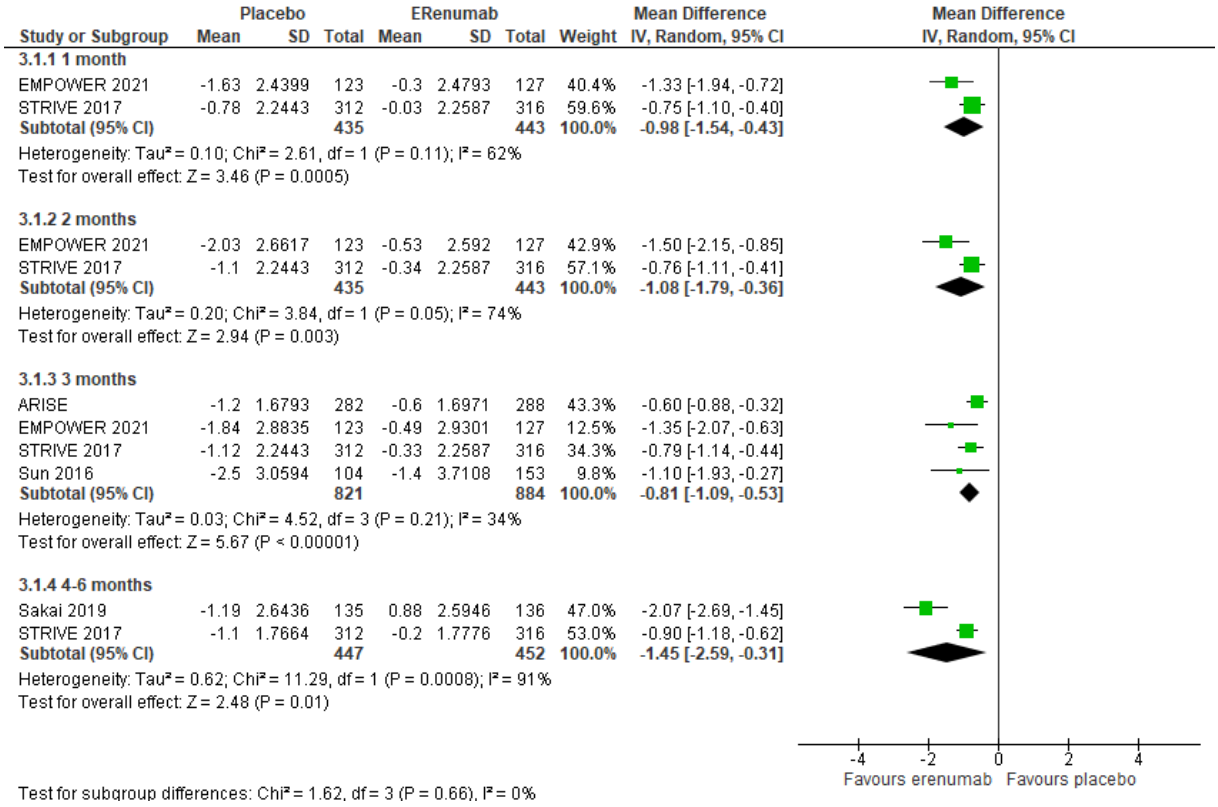
7.2.3.4.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting MHDs with acute medication use for erenumab 70 mg compared to placebo were available in 5 RCTs. Four were at low RoB[48,75,77,78] while one was at high RoB.[76] All 5 were suitable for combining in a meta-analysis. MHDs with acute medication use were reported to be significantly less frequent in patients randomised to erenumab 70 mg at 1 month, 2 months and 3 months (***Figure 8***).[48,75,76,78] There was moderate heterogeneity at 1 month and 2 months, and significant heterogeneity at 4–6 months. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A3***). One RCT reported significantly fewer MHDs with acute medication use at additional timepoints of 4, 5 and 6 months (***Table 31***).[48]

Figure 8 MHDs with acute medication use, erenumab in episodic migraine patients receiving 70 mg



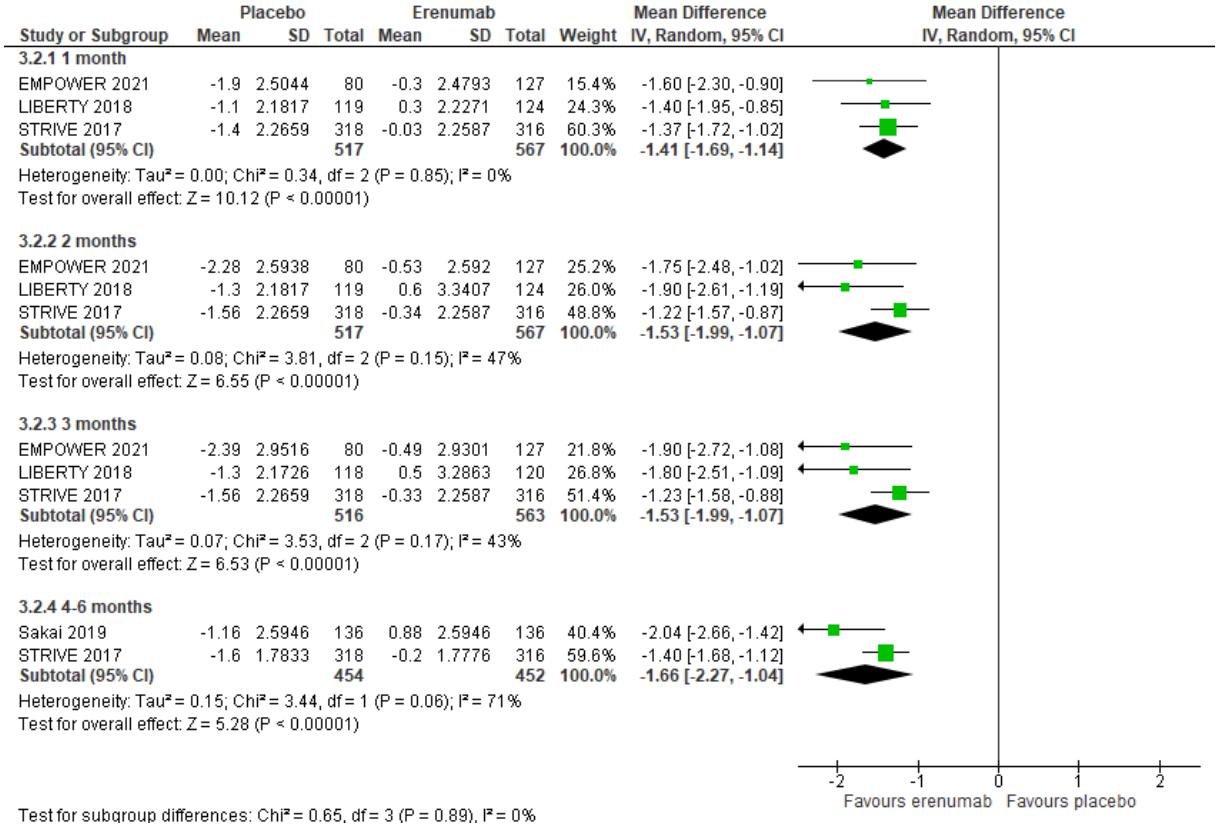
Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Erenumab 140 mg

Data reporting MHDs with acute medication use for erenumab 140 mg compared to placebo were available in 4 RCTs. Three were assessed to be at low RoB[48,49,77] and one was at high RoB.[76] All 4 were suitable for combining in a meta-analysis. MHDs with acute medication use were significantly less frequent in patients randomised to erenumab 140 mg at 1 month, 2 months, 3 months and across an average of 4–6 months (***Figure 9***).[48,49,76,77] There was moderate heterogeneity identified at 2 months, 3 months and across an average of 4–6 months. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A4***). One RCT reported significantly fewer MHDs with acute medication use at additional timepoints of 4, 5 and 6 months (***Table 31***).[48]

Figure 9 MHDs with acute medication use, erenumab in episodic migraine patients receiving 140 mg



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 31 MHDs with acute mediation use, erenumab in episodic migraine patients receiving 70 mg and 140 mg

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
STRIVE[48]	Low	4 months	ERU 70 mg	312	-1.08 (95% CI: -1.33, -0.82)	MD -0.89 (95% CI: -1.25, -0.53), p<0.0001
			ERU 140 mg	318	-1.56 (95% CI: -1.81, -1.31)	MD -1.37 (95% CI: -1.73, -1.01), p<0.0001
			Placebo	316	-0.19 (95% CI: -0.45, 0.06)	NA
		5 months	ERU 70 mg	312	-1.17 (95% CI: -1.43, -0.92)	MD -1.20 (95% CI: 0.84, 1.56), p<0.0001
			ERU 140 mg	318	-1.61 (95% CI: -1.87, -1.36)	MD 0.44 (95% CI: 0.07, 0.81), p=0.02
			Placebo	316	--0.40 (95% CI: -0.66, -0.14)	NA
		6 months	ERU 70 mg	312	-1.14 (95% CI: -1.40, -0.89)	MD -1.15 (95% CI: -1.52, -0.78), p<0.0001
			ERU 140 mg	318	-1.67 (95% CI: -1.92, -1.41)	MD -1.68 (95% CI: -2.04, -1.32), p<0.0001
			Placebo	316	0.01 (95% CI: -0.25, 0.26)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS calculated comparisons

Chronic migraine

Data reporting MHDs with acute medication use for erenumab among patients with chronic migraine was reported in one RCT, assessed to be at low RoB.[79] The number of MHDs with acute medication use was significantly less among patients randomised to erenumab 70 mg or 140 mg compared to placebo at 3 months (***Table 32***).

Table 32 MHDs with acute medication use, erenumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Tepper et al 2017[79]	Low	3 months	ERU 70 mg	188	-3.5 (SE 0.3)	MD -1.9 (95% CI: -2.6 to -1.1), p<0.0001
			ERU 140 mg	187	-4.1 (SE 0.3)	MD -2.6 (95% CI: -3.3 to -1.8), p<0.0001
			Placebo	281	-1.6 (SE 0.2)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

One RCT reporting MHDs with acute medication use for populations with both episodic and chronic migraine patients was assessed to be at low RoB.[81] The number of MHDs with acute medication use was significantly less in patients randomised to erenumab 70 mg compared to placebo across a 4–6 month period (***Table 33***).

Table 33 MHDs with acute medication use, erenumab in episodic and chronic patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Takeshima et al 2021[81] [106]	Low	4–6 months	ERU 70 mg	130	-2.57 (SE 0.32)	MD -1.47 (95% CI: -2.24, -0.71), p<0.001
			Placebo	131	-1.10 (SE 0.32)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.

Episodic migraine with ≥2 prior treatment failures

Two RCTs reported MHDs with acute medication use among episodic migraine patients with ≥2 prior treatment failures (***Table 34***). Both were at low RoB. They were not suitable for combining in a meta-analysis because one trial did not report SDs or other measures of variance.[102] The number of MHDs with acute medication use was significantly less in patients randomised to erenumab 70 mg or 140 mg compared to placebo at 12 weeks[49] and 6 months.[102] The latter trial reported the mean number of MHDs with acute medication use monthly from 1–6 months, but no statistical analyses were undertaken comparing erenumab with placebo.

Table 34 MHDs with acute medication use, erenumab episodic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
LIBERTY[49]	Low	Week 12	ERU 140 mg	76	-1.3 (SE 0.3)	MD -1.7 (95% CI: -2.6, -0.7), p<0.001
			Placebo	69	0.4 (SE 0.4)	
STRIVE[102]	Low	1 month	ERU 70 mg	49	-0.9 (SD NR)	NR
			ERU 140 mg	58	-2.2 (SD NR)	NR
			Placebo	54	-0.2 (SD NR)	NR
		2 months	ERU 70 mg	49	-1.4 (SD NR)	NR
			ERU 140 mg	58	-2.5 (SD NR)	NR
			Placebo	54	0 (SD NR)	NR
		3 months	ERU 70 mg	49	-1.1 (SD NR)	NR
			ERU 140 mg	58	-2.4 (SD NR)	NR
			Placebo	54	-1 (SD NR)	NR
		4 months	ERU 70 mg	49	-1.5 (SD NR)	NR
			ERU 140 mg	58	-2.4 (SD NR)	NR
			Placebo	54	0.3 (SD NR)	NR
		5 months	ERU 70 mg	49	-1 (SD NR)	NR
			ERU 140 mg	58	-2.2 (SD NR)	NR
			Placebo	54	-0.4 (SD NR)	NR
		6 months	ERU 70 mg	49	-0.7 (SD NR)	NR
			ERU 140 mg	58	-2.3 (SD NR)	NR
			Placebo	54	0.5 (SD NR)	NR
		4-6 months	ERU 70 mg	49	NR	MD -1.2 (95% CI: -2.2, -0.3), p=sig*
			ERU 140 mg	58	NR	MD -2.5 (95% CI: -3.4, -1.5), p=sig*
			Placebo	54	NR	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SD** = standard deviation, **SE** = standard error.
Notes
* The STRIVE study did not report mean number of MHDs from 4-6 months, therefore we could not calculate the p-value of ERU 70 mg or ERU 140 mg compared to placebo.

Chronic migraine with ≥2 prior treatment failures

One RCT reporting MHDs with acute medication use among chronic migraine patients with ≥2 prior treatment failures was at low RoB (***Table 35***). The number of MHDs with acute medication use was significantly less in patients randomised to erenumab 70 mg or 140 mg compared to placebo at 3 months.

Table 35 MHDs with acute medication use, erenumab chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	93	-4.1 (SE NR)	MD -2.8 (95% CI: -3.9, -1.7), p<0.001
			ERU 140 mg	92	-5.4 (SE NR)	MD -4.1 (95% CI: -5.3, -3.0), p<0.001
			Placebo	142	-1.3 (SE NR)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

No RCTs were identified that reported data for subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.4.2 Eptinezumab

Episodic migraine

One RCT reported MHDs with acute medication use averaged across 1–12 weeks among patients with episodic migraine randomised to eptinezumab.[82] The number of MHDs with acute medication use was significantly less in patients randomised to eptinezumab 100 mg and 300 mg compared to placebo from 1–12 weeks (***Table 36***).

Table 36 MHDs with acute medication use, eptinezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
PROMISE-1[82]	High	1–12 weeks	EPT 100 mg	221	-0.9 (SD 2.00)	MD -0.50 (95% CI: -0.81, -0.19), p=0.002
			EPT 300 mg	222	-0.8 (SD 1.77)	MD -0.40 (95% CI: -0.69, -0.11), p=0.006
			Placebo	222	-0.4 (SD 1.27)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One RCT reported MHDs with acute medication use among patients with chronic migraine and was at low RoB.[84,109] The number of MHDs with acute medication use was significantly less in patients randomised to eptinezumab 100 mg and 300 mg compared to placebo at 1–12 weeks and 13–24 weeks (***Table 37***).

Table 37 MHDs with acute medication use, eptinezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
PROMISE-2[84,109]	Low	1–12 weeks	EPT 100 mg	356	-3.3 (SD 4.89)	MD –1.2 (95% CI: -1.7, -0.6), p<0.0001
			EPT 300 mg	350	-3.5 (SD 4.62)	MD –1.4 (95% CI: -1.9, -0.9), p<0.0001
			Placebo	366	-1.9 (SD 4.18)	NA
		13–24 weeks	EPT 100 mg	356	-3.4 (SD 5.14)	MD -1.1 (95% CI: -1.86, -0.42), p=0.001
			EPT 300 mg	350	-3.9 (SD 4.96)	MD -1.7 (95% CI: -2.44, -1.01), p<0.0001
			Placebo	366	-2.2 (SD 4.73)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic migraine patients combined, or for subgroups of patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.4.3 Fremanezumab

Episodic Migraine

Three RCTs reported MHDs with acute medication use among patients with episodic migraine (***Table 38***). Two trials were at low RoB[85,87] and one was at high RoB.[86] None were suitable for combining in a meta-analysis because data were reported at different time periods. The number of MHDs with acute medication use was significantly less in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 1–4 weeks, 5–8 weeks and 9–12 weeks in one trial;[85] 4 weeks and 12 weeks in the second trial;[86] and 1–12 weeks in the third trial.[87]

Table 38 MHDs with acute medication use, fremanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Bigal et al 2015b[85]	Low	Weeks 1–4	FRE 225 mg	NR	NR	MD -2.12 (-3.15 to -1.09), p<0.0001
			FRE 675 mg	NR	NR	MD -1.98 (-3.01 to -0.94), p=0.0002
			Placebo	NR	NR	NA
		Weeks 5–8	FRE 225 mg	NR	NR	MD -2.32 (-3.44 to -1.21), p<0.0001
			FRE 675 mg	NR	NR	MD -1.86 (-2.97 to -0.74), p=0.0012
			Placebo	NR	NR	NA
		Weeks 9–12	FRE 22 5mg	NR	NR	MD -1.76 (-2.86 to -0.66), p=0.0018
			FRE 675 mg	NR	NR	MD -1.70 (-2.80 to -0.60), p=0.0026
			Placebo	NR	NR	NA
HALO EM[86] [111]	High	12 weeks	FRE 225 mg	287	-3.0 (95% CI: -3.41, -2.56)	MD -1.4 (95% CI: -1.84, -0.89), p<0.001
			FRE 675 mg	288	-2.9 (95% CI: -3.34, -2.48)	MD -1.3 (95% CI: -1.76, -0.82), p<0.001
			Placebo	290	-1.6 (95% CI: -2.04, -1.20)	NA
Sakai et al 2021b[87]	Low	weeks 1–12	FRE 225 mg	121	-3.3 (SE 0.3)	MD -2.8 (95% CI: -3.55, -2.14), p<0.0001
			FRE 675 mg	117	-3.3 (SE 0.4)	MD -2.8 (95% CI: -3.54, -2.12), p<0.0001
			Placebo	116	-0.5 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **FRE**= fremanezumab, **MD** = Mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine

Three trials reported MHDs with acute medication use among patients with chronic migraine. All 3 were at low RoB.[88-90] None of the RCTs were suitable for combining in a meta-analysis because data were reported at different times (***Table 39***). The number of MHDs with acute medication use was significantly less in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 1–4 weeks, 5–8 weeks and 9–12 weeks;[88] 12 weeks[89] or 1–12 weeks.[90]

Table 39 MHDs with acute medication use, fremanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Bigal et al 2015a[88]	Low	Weeks 1–4	FRE 675/225 mg	NR	NR	MD -1.99 (-3.6 to -0.4), p=0.016
			Placebo	NR	NR	
		Weeks 5–8	FRE 675/225 mg	NR	NR	MD -2.16 (-3.9 to -0.5), p=0.014
			Placebo	NR	NR	
		Weeks 9–12	FRE 675/225 mg	NR	NR	MD -2.15 (-4.0 to 0.3), p=0.02
			Placebo	NR	NR	
HALO CM[89]	Low	12 weeks	FRE 225 mg	375	-4.2 (SE 0.3)	MD -2.3 (95% CI: -3.13, -1.47), p<0.00001
			FRE 675 mg	375	-3.7 (SE 0.3)	MD -1.8 (95% CI: -2.63, -0.97), p<0.0001
			Placebo	371	-1.9 (SE 0.3)	NA
Sakai et al 2021a[90]	Low	weeks 1–12	FRE 225 mg	187	-3.7 (SE 0.4)	MD -1.3 (95% CI: -2.18, -0.43), p=0.003
			FRE 675 mg	189	-3.9 (SE 0.4)	MD -1.4 (95% CI: -2.30, -0.56), p=0.001
			Placebo	190	-2.4 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **FRE**= fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicated RACS-calculated comparisons.

Episodic and chronic migraine

One RCT reported MHDs with acute medication use for a population with both episodic and chronic migraine patients and was at low RoB.[91] The number of MHDs with acute medication use was significantly less in patients randomised to fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 40***).

Table 40 MHDs with acute medication use, fremanezumab in episodic and chronic patients (combined)

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
FOCUS[91]*	Low	3 months	FRE quarterly	276	-3.7 (SE 0.3)	MD -3.1 (95% CI: -3.8 to -2.4), p<0.0001
			FRE monthly	283	-3.9 (SE 0.3)	MD -3.4 (95% CI: -4.0 to -2.7), p<0.0001
			Placebo	279	-0.6 (SE 0.3)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Episodic and chronic migraine patients with ≥2 prior treatment failures

One RCT reported MHDs with acute medication use (both episodic and chronic migraine patients) among a subgroup of patients with 2, 3 or 4 prior treatment failures.[116] The number of MHDs with acute medication use was significantly less in patients randomised to fremanezumab quarterly or monthly compared to placebo at 1 month and 3 months for 2, 3 and 4 prior treatment failures (***Table 41***).

Table 41 MHDs with acute medication use, fremanezumab episodic and chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
FOCUS[116]*	Low	1 month 2 Tx failures	FRE quarterly	140	-4.2 (0.44)	MD -3.2 (95% CI: -4.18, -2.27), p<0.0001
			FRE monthly	133	-4.4 (0.44)	MD -3.5 (95% CI: -4.42, -2.48), p<0.0001
			Placebo	141	-0.9 (0.43)	NA
		1 month 3 Tx failures	FRE quarterly	85	-4.0 (0.51)	MD -3.5 (95% CI: -4.66, -2.24), p<0.0001
			FRE monthly	98	-3.9 (0.51)	MD -3.3 (95% CI: -4.51, -2.19), p<0.0001
			Placebo	82	-0.5 (0.49)	NA
		1 month 4 Tx failures	FRE quarterly	49	-4.3 (0.91)	MD -5.4 (95% CI: -7.41, -3.41), p<0.0001
			FRE monthly	50	-4.2 (0.80)	MD -5.3 (95% CI: -7.19, -3.45), p<0.0001
			Placebo	54	1.1 (0.91)	NA
		3 months 2 Tx failures	FRE quarterly	140	-4.0 (0.44)	MD -2.9 (95% CI: -3.79, -1.94), p<0.0001
			FRE monthly	133	-4.3 (0.44)	MD -3.2 (95% CI: -4.12, -2.23), p<0.0001
			Placebo	141	-1.2 (0.43)	NA
		3 months 3 Tx failures	FRE quarterly	85	-3.7 (0.51)	MD -3.2 (95% CI: -4.44, -2.06), p<0.0001
			FRE monthly	98	-3.5 (0.51)	MD -3.0 (95% CI: -4.18, -1.89), p<0.0001
			Placebo	82	-0.4 (0.49)	NA
		3 months 4 Tx failures	FRE quarterly	49	-3.6 (0.93)	MD -4.8 (95% CI: -6.80, -2.81), p<0.0001
			FRE monthly	50	-4.0 (0.82)	MD -5.2 (95% CI: -7.05, -3.33), p<0.0001
			Placebo	54	1.2 (0.94)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error, **Tx** = treatment.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.4.4 Galcanezumab

Episodic migraine

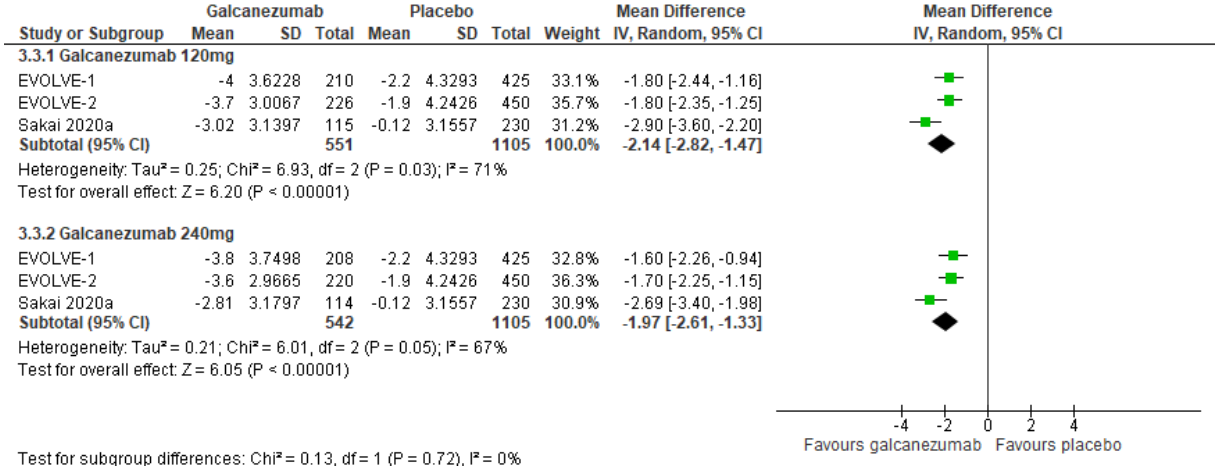
Galcanezumab 120 mg

Data reporting MHDs with acute medication use for galcanezumab 120 mg compared to placebo among patients with episodic migraine were available in 5 RCTs, all at a low RoB.[92-95,98] Three reported the same timepoints (data averaged across 1–6 months) and were suitable for combining in a meta-analysis.[92-94] The number of MHDs with acute medication use was significantly less in patients randomised to galcanezumab 120 mg compared to placebo. A moderate amount of heterogeneity was reported (***Figure 10***).[92-94] The 2 other RCTs, both at low RoB, reported similar results, with significantly fewer MMDs among galcanezumab patients (***Table 42***).[95,98]

Galcanezumab 240 mg

Data reporting MHDs with acute medication use for galcanezumab 240 mg compared to placebo among patients with episodic migraine were available in 3 RCTs. All were at low RoB and were suitable for combining in a meta-analysis.[92-94] The number of MHDs with acute medication use was significantly less in patients randomised to galcanezumab 240 mg compared to placebo. A moderate amount of heterogeneity was reported (***Figure 10***).

Figure 10 MHDs with acute medication use, galcanezumab in episodic migraine patients across 1–6 months



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 42 MHDs with acute medication use, galcanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
CONQUER[98]	Low	3 months	GAL 120 mg	137	-3.0 (SE 0.3)	MD -2.7 (95% CI: -3.5 to -1.9), p<0.0001
			Placebo	132	-0.2 (SE 0.3)	
Skljarevski et al 2018[95]	Low	1–12 weeks	GAL 120 mg	69	-3.59 (SE 0.31)	MD -1.08 (95% CI: -1.84, -0.32), p=0.005
			Placebo	134	-2.51 (SE 0.23)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Two trials reported MHDs with acute medication use among patients with chronic migraine. Both were at low RoB.[50,98] The RCTs were not suitable for combining in a meta-analysis because data were reported at different timepoints (***Table 43***). The number of MHDs with acute medication use was significantly less frequent in patients randomised to galcanezumab 120 mg compared to placebo at 3 months,[98] and for those randomised to galcanezumab 120 mg or 240 mg compared to placebo at 1–3 months.[50]

Table 43 MHDs with acute medication use, galcanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
CONQUER[98]	Low	3 months	GAL 120 mg	95	-5.4 (SE 0.6)	MD -4.0 (95% CI: -5.4 to -2.6), p<0.0001
			Placebo	98	-1.4 (SE 0.6)	
REGAIN[50]	Low	1–3 months	GAL 120 mg	273	-4.7 (SE 0.4)	MD -2.5 (95% CI: -3.3, -1.8), p<0.001
			GAL 240 mg	274	-4.3 (SE 0.4)	MD -2.0 (95% CI: -2.8, -1.3), p<0.001
			Placebo	538	-2.2 (SE 0.3)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

One RCT reporting MHDs with acute medication use for a population with both episodic and chronic migraine patients was at high RoB.[97] Patients were randomised to galcanezumab 120 mg or 240 mg and no significant differences were reported between groups (***Table 44***).

Table 44 MHDs with acute medication use, galcanezumab in episodic and chronic patients (combined)

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
CGAJ[97]*	High	12 months	GAL 120 mg	135	-5.1 (SE 0.4)	MD 0.00 (99% CI: -1.11, 1.11), p=1.00
			GAL 240 mg	135	-5.1 (SE 0.4)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group, 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

Episodic migraine patients with ≥2 prior treatment failures

One RCT reported MHDs with acute medication use among a subgroup of patients who had episodic migraine with ≥2 prior treatment failures.[124] The number of MHDs with acute medication use was significantly less in patients randomised to galcanezumab 120 mg compared to placebo at 3 months (***Table 45***).

Table 45 MHDs with acute medication use, galcanezumab episodic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
CONQUER[124]	Low	3 months	GAL 120 mg	56	-3.5 (SE 0.7)	MD -2.8 (SE 0.8), p=0.0008
			Placebo	44	-0.7 (SE 0.8)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine patients with ≥2 prior treatment failures

Two RCTs reported MHDs with acute medication use among a subgroup of patients with chronic migraine who had ≥2 prior treatment failures (***Table 46***). Both were at low RoB.[122] The number of MHDs with acute medication use was significantly less in patients randomised to galcanezumab 120 mg compared to placebo at 3 months[124] and for those randomised to galcanezumab 120 mg or 240 mg compared to placebo at 1 to 3 months.[122]

Table 46 MHDs with acute medication use, galcanezumab chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
CONQUER[124]	Low	3 months	GAL 120 mg	42	-7.0 (SE 1.1)	MD -6.2 (SE 1.8), p<0.0001
			Placebo	42	-0.8 (SE 1.0)	
REGAIN[122]	Low	1–3 months	GAL 120 mg	NR	-5.81 (SE 0.69)	MD -4.46 (SE 0.69), p<0.001
			GAL 240 mg	NR	-3.40 (SE 0.65)	MD -2.06 (SE 0.61), p<0.001
			Placebo	NR	-1.35 (SE 0.53)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHD** = monthly headache day, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

No RCTs were identified that reported data for subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.5 Response rate (>50%)

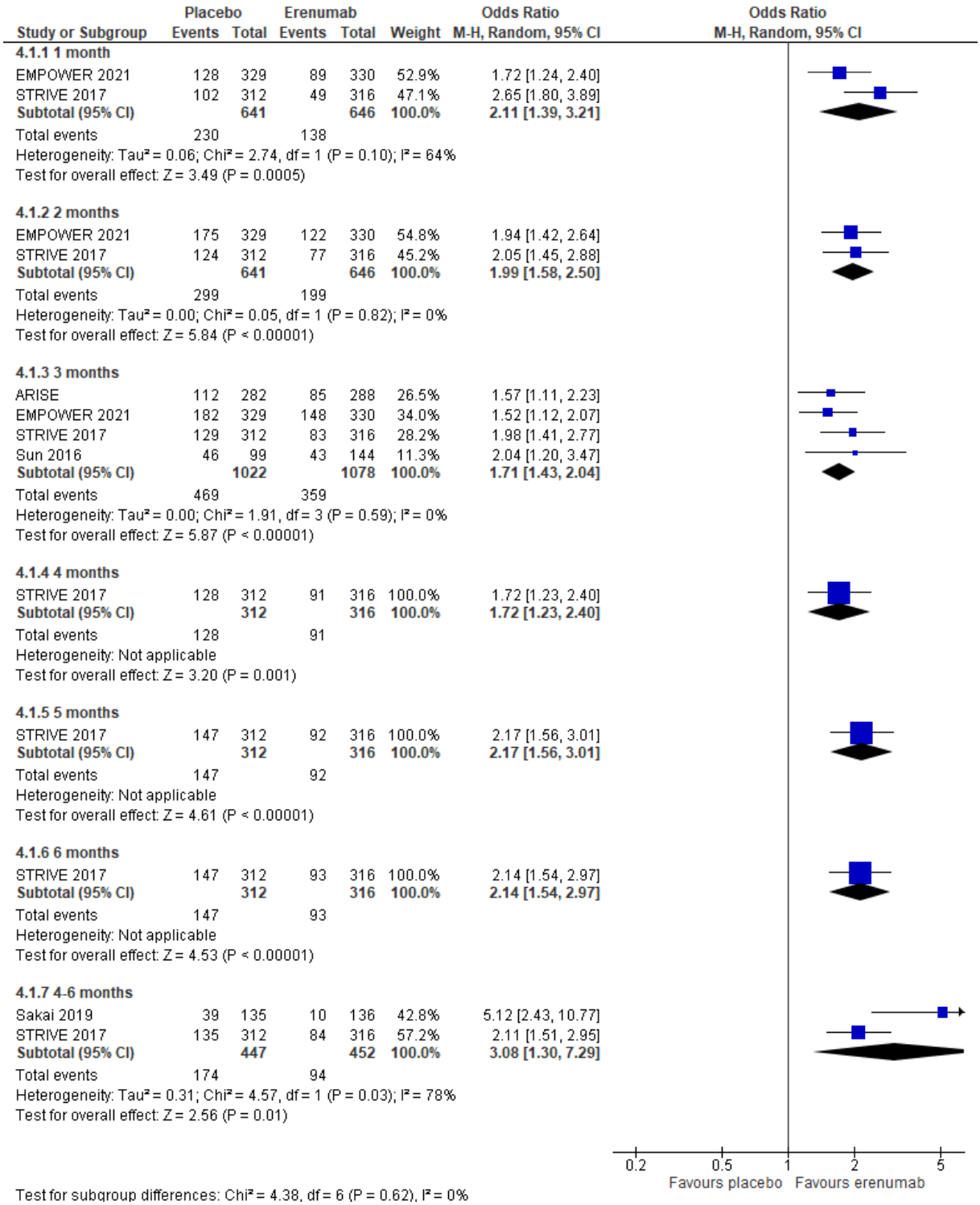
7.2.3.5.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting response rate (>50%) for erenumab 70 mg compared to placebo were available in 6 RCTs. Five were at low RoB,[48,49,75,77,78] while one was at high RoB.[76] All were suitable for combining in a meta-analysis where response rate was defined as >50% reduction in MMDs. The response rate was significantly greater in patients randomised to erenumab 70 mg at all timepoints (***Figure 11***).[48,49,75-78] Moderate heterogeneity was identified at 1 month and 4–6 months, but was not identified for the other timepoints. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A5***)

Figure 11 Response rate (>50%), erenumab in episodic migraine patients receiving 70 mg



Abbreviations

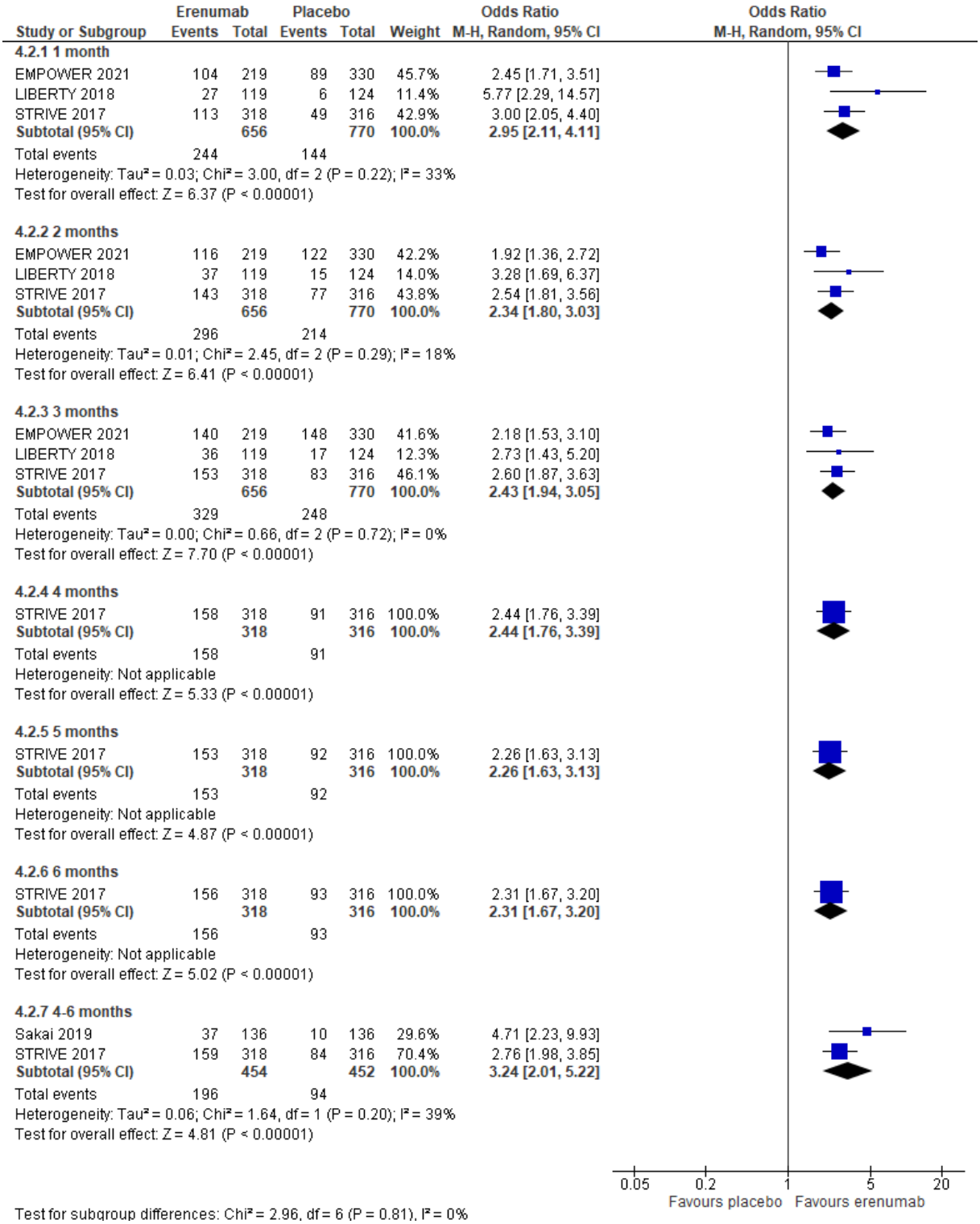
CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio

Erenumab 140 mg

Response rates (>50%) for erenumab 140 mg compared to placebo were available in 4 RCTs. Three were at low RoB,[48,49,77] while one was at high RoB.[76] All were suitable for combining in a meta-analysis.

The response rate was significantly greater in patients randomised to erenumab 140 mg at all timepoints (***Figure 12***).[76] Moderate heterogeneity was identified at 1 month, 2 months and at 4–6 months, but was not identified for other timepoints. Sensitivity analyses excluding the single RCT at high RoB did not alter the results ***(Appendix H, Figure A6).***

Figure 12 Response rate (>50%), erenumab in episodic migraine patients receiving 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine randomised to erenumab or placebo.[79] The response rate was significantly greater in patients randomised to erenumab 70 mg and 140 mg at 3 months (***Table 47***).

Table 47 Response rate (>50%), erenumab chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Tepper et al 2017[79]	Low	3 months	ERU 70 mg	188	75 (40)	OR 2.2 (95% CI: 1.5, 3.3), p=0.0001
			ERU 140 mg	187	77 (41)	OR 2.3 (95% CI: 1.6, 3.5), p<0.0001
			Placebo	281	66 (23)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.

Episodic and chronic migraine

One RCT assessed to be at low RoB reported data among patients with episodic and chronic migraine randomised to erenumab or topiramate.[80] The response rate was significantly greater in patients randomised to erenumab 70 mg or 140 mg compared to topiramate at 24 weeks (***Table 48***).

Table 48 Response rate (>50%), erenumab episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
HER-MES[80]*	Low	24 weeks	ERU 70 or 140 mg	388	215 (55.4)	OR 2.76 (95% CI: 2.06, 3.71) RR 1.78 (95% CI: 1.50, 2.11), p<0.001
			Topiramate 25–100 mg	388	121 (31.2)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **RoB** = risk of bias, **RR** = relative risk.
Notes
* In HER-MES, the following numbers of patients were included: (1) for erenumab: 4–7 MMDs = 94 (24.2%), episodic = 248 (63.9%), chronic = 43 (11.1%); (2) for topiramate: 4–7 MMDs = 92 (23.7%), episodic (8–14 MMDs) = 254 (65.5%), chronic (≥15 MMDs) = 42 (10.8%).

Episodic migraine with ≥2 prior treatment failures

Two RCTs assessed to be at low RoB reported data among a subgroup of patients with episodic migraine who had ≥2 prior treatment failures.[49,102] The trials were suitable for combining in a meta-analysis at the shared 3-month timepoint. The response rate (>50%) was significantly greater in patients randomised to erenumab 140 mg (***Figure 13***). No heterogeneity was identified. Additional data showed that the response rate was significantly greater in patients randomised to erenumab 70 mg and 140 mg compared to placebo at all timepoints (***Table 49***).

Figure 13 Response rate (>50%), erenumab episodic migraine patients with ≥2 prior treatment failures, 140 mg

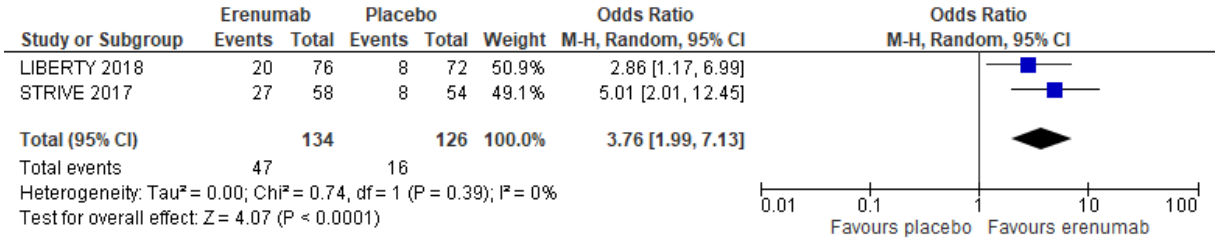


Table 49 Response rate (>50%), erenumab episodic migraine patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
LIBERTY[49]	Low	Week 12	ERU 140 mg	76	20 (26.3)	OR 2.9 (95% CI: 1.2, 7.0), p=0.019
			Placebo	72	8 (11.1)	
STRIVE[102]	Low	1 month	ERU 70 mg	49	9 (18.4)	OR 2.21 (95% CI: 0.68, 7.11), p=0.19
			ERU 140 mg	58	17 (29.3)	OR 4.06 (95% CI: 1.38, 11.97), p=0.01
			Placebo	54	5 (9.3)	NA
		2 months	ERU 70 mg	49	13 (26.5)	OR 2.08 (95% CI: 0.78, 5.55), p=0.15
			ERU 140 mg	58	24 (41.4)	OR 4.06 (95% CI: 1.63, 10.13), p=0.003
			Placebo	54	8 (14.8)	NA
		3 months	ERU 70 mg	49	13 (26.5)	OR 2.08 (95% CI: 0.78, 5.55), p=0.15
			ERU 140 mg	58	27 (46.6)	OR 5.01 (95% CI: 2.01, 12.45), p=0.0005
			Placebo	54	8 (14.8)	NA
		4–6 months	ERU 70 mg	49	13 (26.5)	OR 2.9 (95% CI: 1.0, 8.3), p=0.05
			ERU 140 mg	58	21 (36.2)	OR 4.5 (95% CI: 1.7, 12.4), p=0.003
			Placebo	54	6 (11.1)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine with ≥2 prior treatment failures

One RCT assessed to be at low RoB reported data among a subgroup of patients with chronic migraine who had ≥2 prior treatment failures.[103] The response rate was significantly greater in patients randomised to erenumab 70 mg and 140 mg compared to placebo at 3 months (***Table 50***).

Table 50 Response rate (>50%), erenumab chronic migraine patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	93	33 (35.6)	OR 3.5 (95% CI: 1.8, 6.6), p<0.001
			ERU 140 mg	92	38 (41.3)	OR 4.2 (95% CI: 2.2, 7.9), p<0.001
			Placebo	142	20 (14.2)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.

Episodic and chronic migraine with ≥2 prior treatment failures

One RCT assessed to be at low RoB reported data among a subgroup of patients with chronic migraine who had ≥2 prior treatment failures.[81] The response rate was significantly greater in patients randomised to erenumab 70 mg compared to placebo at 3 months (***Table 51***).

Table 51 Response rate (>50%), erenumab episodic and chronic migraine patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Takeshima et al 2021[81]	Low	4–6 months	ERU 70 mg	130	41 (31.5)	OR 2.33 (95% CI: 1.29, 4.23), p=0.005
			Placebo	131	22 (16.8)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **RoB** = risk of bias.

7.2.3.5.2 Eptinezumab

Episodic migraine

One RCT assessed to be at high RoB, reported response rate (>50%) averaged across 1–12 weeks, and 13–24 weeks among patients with episodic migraine randomised to eptinezumab.[82,107] The response rate was significantly greater among patients receiving eptinezumab 100 mg and 300 mg compared to placebo at 1–12 weeks and 13–24 weeks (***Table 52***).

Table 52 Response rate (>50%), eptinezumab in episodic migraine patients

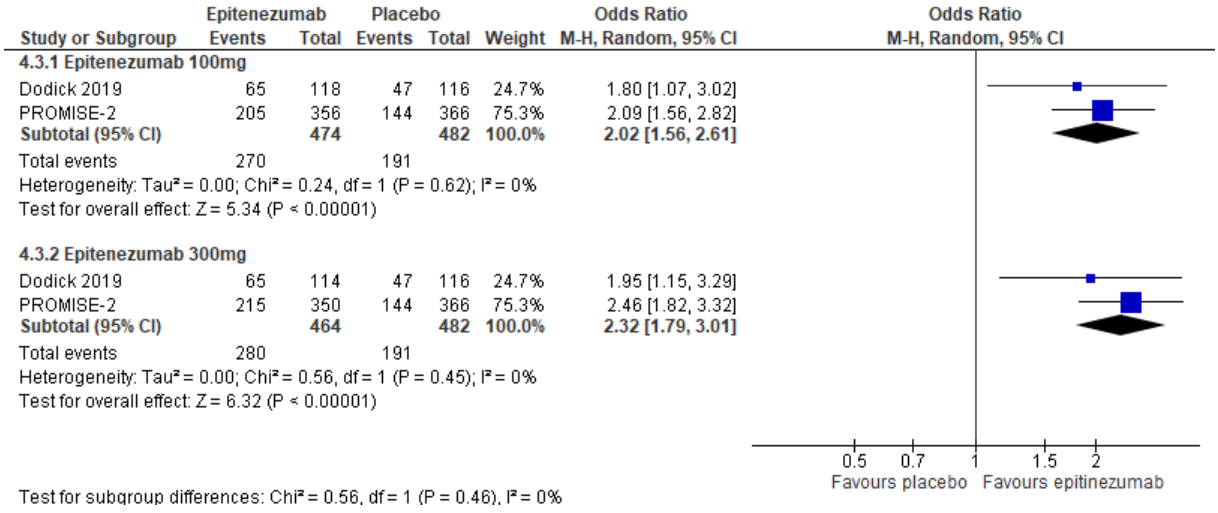
Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-1[82,107]	High	1–12 weeks	EPT 100 mg	221	110 (49.8)	OR 1.662 (95% CI NR), p=0.0085
			EPT 300 mg	222	125 (56.3)	OR 2.158 (95% CI NR), p=0.0001
			Placebo	222	83 (37.4)	NA
		13–24 weeks	EPT 100 mg	221	137 (62.0)	OR 1.55 (95% CI: 1.06, 2.26), p=0.02
			EPT 300 mg	222	145 (65.3)	OR 1.78 (95% CI: 1.22, 2.61), p=0.003
			Placebo	222	114 (51.4)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Two RCTs, one assessed to be at low RoB[84,109] and one with some concerns,[83] reported response rate (>50%) averaged across 1–12 weeks in both studies and across 13–24 weeks in one study, among patients with chronic migraine randomised to eptinezumab. The response rate (>50%) was significantly greater among patients receiving eptinezumab 100 mg and 300 mg compared to placebo at 1–12 weeks (***Figure 14***; no heterogeneity identified) and between 13–24 weeks (***Table 53***).

Figure 14 Response rate (>50%), eptinezumab in chronic migraine patients: 1–12 weeks



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio.

Table 53 Response rate (>50%), eptinezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-2[84,109]	Low	13–24 weeks	EPT 100 mg	356	217 (61.0)	OR 1.99 (95% CI: 1.48, 2.67), p<0.00001
			EPT 300 mg	350	224 (64.0)	OR 2.66 (95% CI: 1.68, 3.06), p<0.00001
			Placebo	366	161 (44.0)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.5.3 Fremanezumab

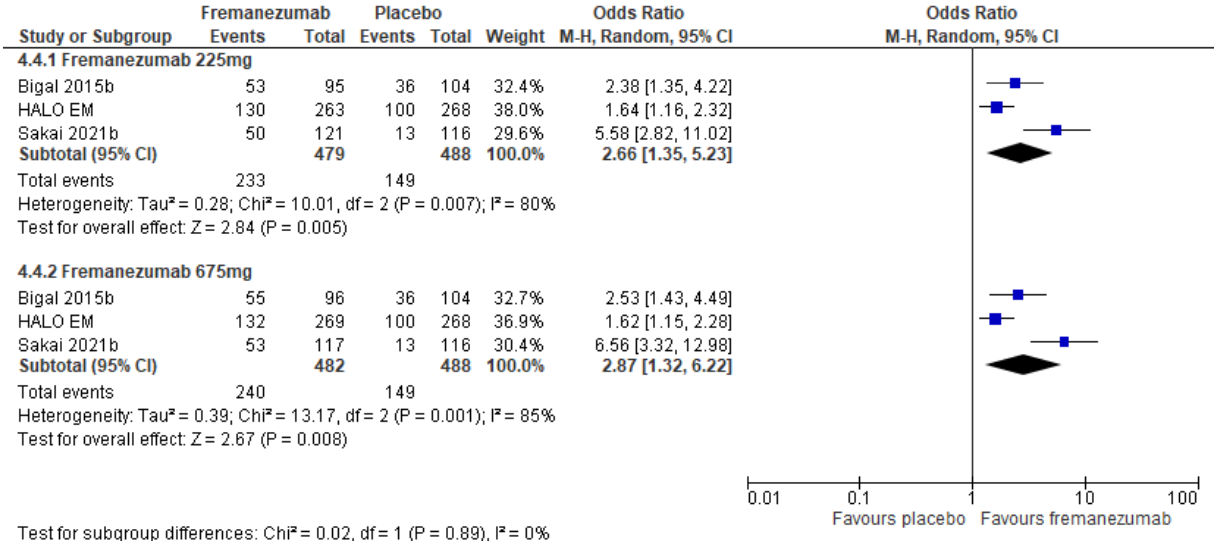
Episodic migraine

Three RCTs reported response rate (>50%) among patients with episodic migraine. Two trials were at low RoB[85,87] and one was at high RoB.[86] All 3 reported the same timepoint (12 weeks; ***Figure 15***) and were suitable for combining in a meta-analysis[b]. The response rate was significantly greater among patients receiving fremanezumab 225 mg and 675 mg compared to placebo at 12 weeks.[85-87,112] Sensitivity analyses excluding the trial at high RoB did not alter the results (***Appendix H, Figure A7***).

Additional data (***Table 54***) showed that the response rate was significantly greater among patients receiving fremanezumab 225 mg and 675 mg compared to placebo at 1–4 weeks and 5–8 weeks in one trial[85] and at 1–12 weeks in a second trial.[86]

[b] Bigal et al 2015b reported data at an average of 9–12 weeks. This was assumed to be similar enough to a 12-week timepoint to consider these data together in a meta-analysis.

Figure 15 Response rate (>50%), fremanezumab in episodic migraine patients, 12 weeks



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio.

Table 54 Response rate (>50%), fremanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Bigal et al 2015b[85]	Low	Weeks 1–4	FRE 225 mg	95	42 (44)	OR 3.33 (95% CI: 1.77, 6.27), p=0.0001
			FRE 675 mg	96	50 (52)	OR 4.57 (95% CI: 2.43, 8.58), p<0.0001
			Placebo	104	20 (19)	NA
		Weeks 5–8	FRE 225 mg	95	52 (55)	OR 2.28 (95% CI: 1.29, 4.04), p=0.0043
			FRE 675 mg	96	53 (55)	OR 2.33 (95% CI: 1.32, 4.12), p=0.0034
			Placebo	104	36 (35)	NA
		Weeks 9–12	FRE 225 mg	95	53 (56)	OR 2.38 (95% CI: 1.35, 4.22), p=0.0027
			FRE 675 mg	96	55 (57)	OR 2.53 (95% CI: 1.43, 4.49), p=0.0013
			Placebo	104	36 (35)	NA
HALO EM[86,112]	High	weeks 1–12	FRE 225 mg	287	137 (47.7)	Difference vs placebo 19.8 (95% CI: 12.0, 27.6), p<0.001
			FRE 675 mg	288	128 (44.4)	Difference vs placebo 16.5 (95% CI: 8.9, 24.1), p<0.001
			Placebo	290	81 (27.9)	NA

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.

Notes

Blue text indicates RACS-calculated comparisons.

Chronic migraine

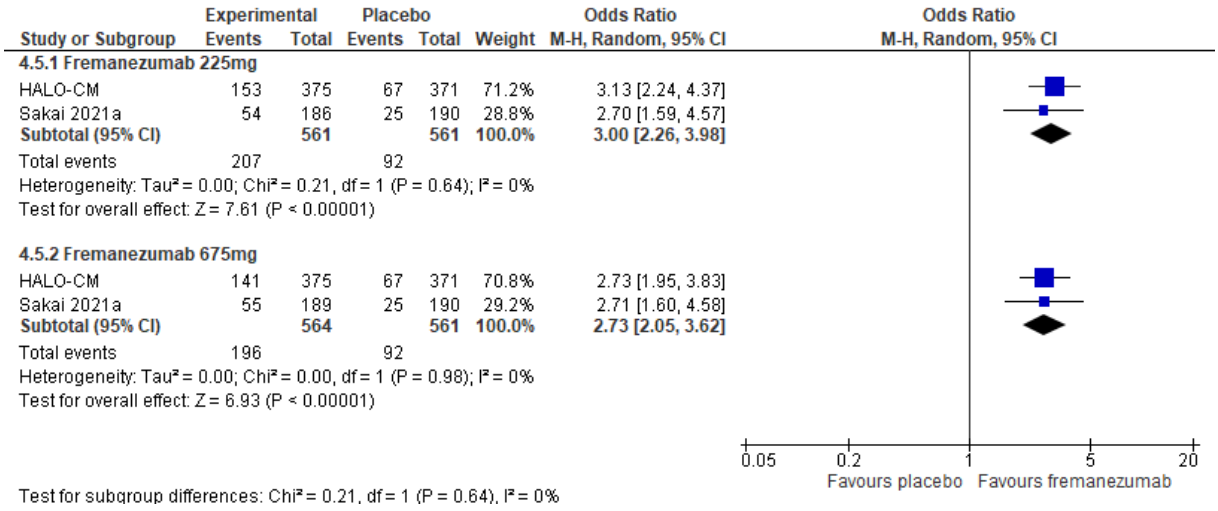
Three trials, all at low RoB, reported response rate (>50%) among patients with chronic migraine.[88-90]

Two of the RCTs reported the same timepoint and were suitable for combining in a meta-analysis. The

response rate was significantly greater among patients receiving fremanezumab 225 mg or 675 mg at 1–12 weeks (***Figure 16***).[113]

Additional data (***Table 55***) reported that the response rate was significantly greater among patients receiving fremanezumab 675 mg/225 mg compared to placebo at 1–4 weeks and 9–12 weeks (but not 5–8 weeks) in one trial,[113] and significantly greater in patients receiving fremanezumab 225 mg and fremanezumab 675 mg compared to placebo at 12 weeks in a second trial.[89,90,115]

Figure 16 Response rate (>50%), fremanezumab in chronic migraine patients, 1–12 weeks



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel, **OR** = odds ratio.

Table 55 Response rate (>50%), fremanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Bigal et al 2015a[113]	Low	Weeks 1–4	FRE 675/225 mg*	87	36 (41)	OR 2.2 (95% CI: 1.1, 4.1), p=0.019
			Placebo	89	22 (25)	
		Weeks 5–8	FRE 675/225 mg	87	42 (48)	OR 1.44 (95% CI: 0.79, 2.62), p=0.231
			Placebo	89	35 (39)	
		Weeks 9–12	FRE 675/225 mg	87	46 (53)	OR 2.44 (95% CI: 1.3, 4.5), p=0.004
			Placebo	89	28 (31)	
HALO CM[89,115]	Low	12 weeks	FRE 225 mg	345	154 (44.5)	OR 3.64 (95% CI: 2.57, 5.15), p<0.001
			FRE 675 mg	350	142 (40.5)	OR 3.08 (95% CI: 2.18, 4.37), p<0.001
			Placebo	342	62 (18.1)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
*In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.

Episodic and chronic migraine

One RCT at low RoB reported data for a population with both episodic and chronic migraine patients.[91] The response rate was significantly greater among patients receiving fremanezumab 225 mg or 675 mg compared to placebo at 1 month and 3 months (***Table 56***).

Table 56 Response rate (>50%), fremanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
FOCUS[91]*	Low	1 month	FRE quarterly	276	105 (38)	OR 5.8 (95% CI: 3.6, 9.3), p<0.0001
			FRE monthly	283	101 (36)	OR 5.3 (95% CI: 3.3, 8.4), p<0.0001
			Placebo	278 279	28 (10)	NA
		3 months	FRE quarterly	276	95 (34)	OR 5.8 (95% CI: 3.6, 9.6), p<0.0001
			FRE monthly	283	97 (34)	OR 5.8 (95% CI: 3.6, 9.5), p<0.0001
			Placebo	278 279	24 (9)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.5.4 Galcanezumab

Episodic migraine

Data reporting response rate (>50%) were available in 5 RCTs, all at low RoB.[92-96] None of the RCTs were suitable for combining in a meta-analysis because they reported either different timepoints or reported mean percentage responses rather than raw numbers. The response rate (>50%) was significantly greater among patients randomised to galcanezumab 120 mg or galcanezumab 240 mg compared to placebo at all timepoints (***Table 57***).

Table 57 Response rate (>50%), galcanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Dodick et al 2014a[96]	Low	3 months	GAL 150 mg	98	69 (70.4)	OR 2.88 (90% CI: 1.78, 4.69), p=0.0003
			Placebo	104	47 (45.2)	
EVOLVE-1[92]	Low	6 months	GAL 120 mg	210	Mean 62.3% (SE 2.4)	OR 2.63 (95% CI: 2.05, 3.37), p<0.001
			GAL 240 mg	208	Mean 60.9% (SE 2.5)	OR 2.48 (95% CI: 1.94, 3.18), p<0.001
			Placebo	425	Mean 38.6% (SE 1.7)	NA
EVOLVE-2[93]	Low	1–6 months	GAL 120 mg	226	Mean 59.3% (SE 2.4)	NR, p<0.001
			GAL 240 mg	220	Mean 56.5% (SE 2.5)	NR, p<0.001
			Placebo	450	Mean 36% (SE 1.7)	NA
Sakai et al 2020a[94]	Low	1–6 months	GAL 120 mg	115	57 (49.8)	OR 3.83 (95% CI: 2.35, 6.22), p<0.001
			GAL 240 mg	114	55 (48.2)	OR 3.63 (95% CI: 2.23, 5.91), p<0.001
			Placebo	230	47 (20.3)	NA
Skljarevski et al 2018[95]	Low	1–12 weeks	GAL 120 mg	69	53 (76.5)	OR 2.10 (95% CI: 1.09, 4.06), p=0.03
			Placebo	134	82 (60.9)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One trial reported response rate (>50%) among patients with chronic migraine and was at low RoB.[50,123] The response rate (>50%) was significantly greater among patients receiving galcanezumab 120 mg or 240 mg compared to placebo across an average of 1–3 months (***Table 58***).

Table 58 Response rate (>50%), galcanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
REGAIN[50,123]	Low	1–3 months	GAL 120 mg	273	27.6 (2.7)	OR 2.1 (95% CI: 1.6, 2.8), p<0.001
			GAL 240 mg	274	27.5 (2.6)	OR 2.1 (95% CI: 1.6, 2.8), p<0.001
			Placebo	538	15.4 (1.6)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients and was at high RoB.[97] There was no difference in the response rate (>50%) for patients receiving galcanezumab 120 mg compared to galcanezumab 240 mg at 12 months (***Table 59***).

Table 59 Response rate (>50%), galcanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
CGAJ[97]*	High	12 months	GAL 120 mg	135	89 (65.6)	OR 0.70 (95% CI: 0.42, 1.19), p=0.19
			GAL 240 mg	135	99 (73.7)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were two treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group, 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

Chronic migraine patients with ≥2 prior treatment failures

One RCT reported data among a subgroup of patients with ≥2 prior treatment failures who had chronic migraine.[122] The response rate (>50%) was significantly greater among patients receiving galcanezumab 120 mg or 240 mg compared to placebo across an average of 1–3 months (***Table 60***).

Table 60 Response rate (>50%), galcanezumab chronic patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
REGAIN[122]	Low	1–3 months	GAL 120 mg	NR	29.6 (4.7)	OR 2.22 (95% CI: 1.26, 3.92)
			GAL 240 mg	NR	18.7 (3.3)	OR 4.05 (95% CI: 2.25, 7.31)
			Placebo	NR	9.4 (1.9)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RoB** = risk of bias.

No RCTs were identified that reported data for subgroups of episodic patients with ≥2 prior treatment failures or for episodic and chronic patients combined with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.6 Response rate (>75%)

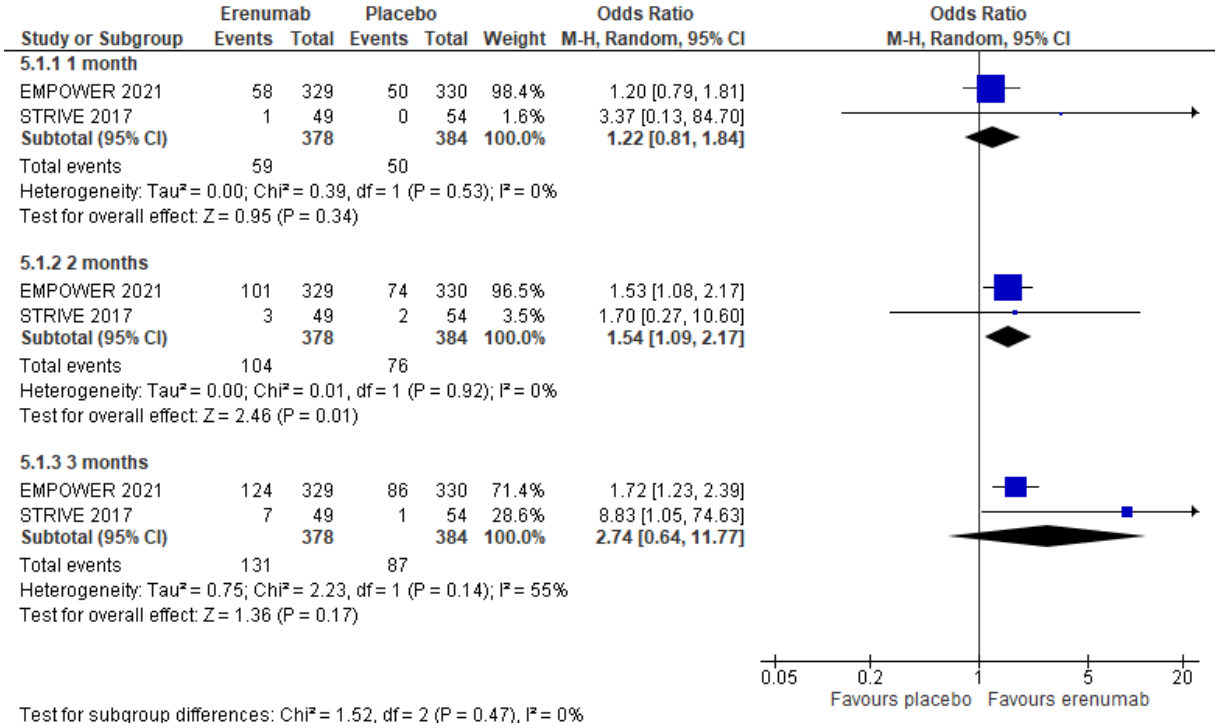
7.2.3.6.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting response rate (>75%) for erenumab 70 mg compared to placebo were available in 2 RCTs; one was at low RoB,[102] one was at high RoB.[76] Both RCTs were suitable for combining in a meta-analysis where response rate was defined as >75% reduction in the number of MMDs. The response rate was significantly greater in patients randomised to erenumab 70 mg at 2 months, but not at 1 month or 3 months (***Figure 17***). Moderate heterogeneity was identified at 1 month and at 4–6 months but not at other timepoints. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A8***)

Figure 17 Response rate (>75%), erenumab in episodic migraine patients receiving 70 mg



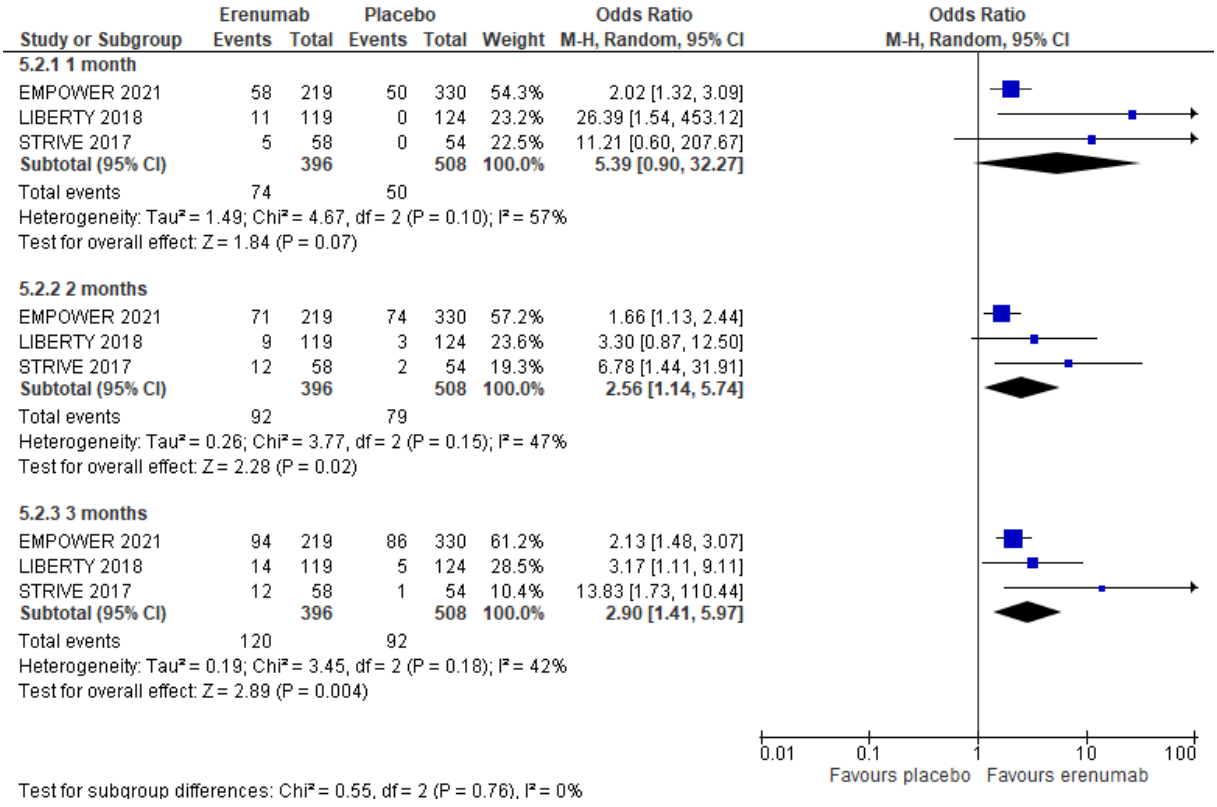
Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio.

Erenumab 140 mg

Data reporting response rate (>75%) for erenumab 140 mg compared to placebo were available in 3 RCTs; 2 were at a low RoB[49,102] while 1 was at high RoB.[76] All RCTs were suitable for combining in a meta-analysis, where the response rate was significantly greater in patients randomised to erenumab 140 mg at 2 months and at 3 months. There were no differences between groups at 1 month. (***Figure***

18).[76] Moderate heterogeneity was identified at 1 month, 2 months and 4–6 months, but not at the other timepoints. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A9***).

Figure 18 Response rate (>75%), erenumab in episodic migraine patients receiving 140 mg



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio.

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine randomised to erenumab 70 mg and erenumab 140 mg or placebo.[103] The response rate (>75%) was significantly greater in patients randomised to erenumab 70 mg and 140 mg at 3 months (***Table 61***).

Table 61 Response rate (>75%), erenumab chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	93	10 (11.1)	OR 3.6 (95% CI: 1.2, 10.9), p<0.05
			ERU 140 mg	92	25 (21.7)	OR 8.0 (95% CI: 2.8, 23.0), p<0.001
			Placebo	142	5 (3.5)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.

Episodic migraine with ≥2 prior treatment failures

One RCT assessed to be at low RoB reported data among a subgroup of patients with episodic migraine who had ≥2 prior treatment failures.[49] There was no difference in the response rate (>75%) between patients randomised to erenumab 140 mg compared to placebo at 12 weeks (***Table 62***).

Table 62 Response rate (>75%), erenumab episodic migraine patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
LIBERTY[49]	Low	Week 12	ERU 140 mg	72	3 (4.2)	OR 3.0 (95% CI: 0.8, 11.5), p=0.089
			Placebo	76	9 (11.8)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.

No RCTs were identified that reported data for episodic and chronic migraine combined or for subgroups of chronic patients with ≥2 prior treatment failures or for episodic and chronic patients combined with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.6.2 Eptinezumab

Episodic migraine

One RCT assessed to be at high RoB, reported response rate (>75%) averaged across 1–4 weeks, 1–12 weeks and 13–24 weeks among patients with episodic migraine randomised to eptinezumab.[82,107] The response rate was significantly greater among patients receiving eptinezumab 100 mg and 300 mg compared to placebo at most timepoints, except eptinezumab 100 mg across an average of 1–12 weeks, where there was no difference compared to placebo (***Table 63***).

Table 63 Response rate (>75%), eptinezumab in episodic migraine patients

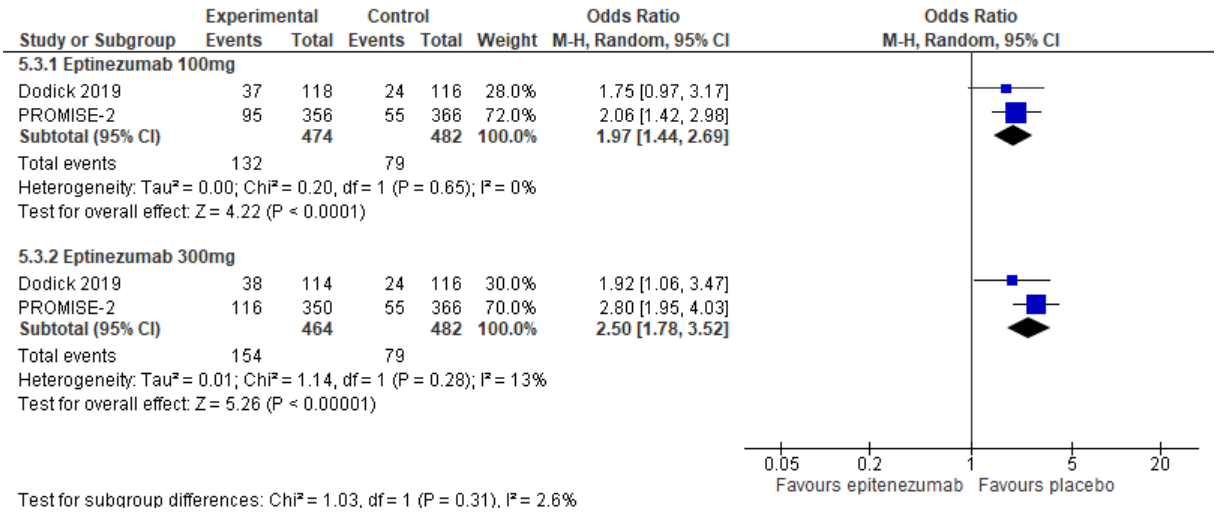
Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-1[82,107]	High	1–4 weeks	EPT 100 mg	221	68 (30.8)	OR 1.752 (95% CI NR), p=0.0112
			EPT 300 mg	222	70 (31.5)	OR 1.817 (95% CI NR), p=0.0066
			Placebo	222	45 (20.3)	NA
		1–12 weeks	EPT 100 mg	221	49 (22.2)	OR 1.47 (95% CI NR), p=0.1126
			EPT 300 mg	222	66 (29.7)	OR 2.179 (95% CI NR), p=0.0007
			Placebo	222	36 (16.2)	NA
		13–24 weeks	EPT 100 mg	221	74 (33.5)	OR 1.53 (95% CI: 1.01, 2.31), p=0.04
			EPT 300 mg	222	89 (40.1)	OR 2.03 (95% CI: 1.35, 3.05), p=0.0006
			Placebo	222	55 (24.8)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Two RCTs, 1 assessed to be at low RoB[84,109] and 1 with some concerns about study quality,[83] reported response rate (>75%) averaged across 1–12 weeks among patients with chronic migraine randomised to eptinezumab.[82,107] The response rate was significantly greater among patients receiving eptinezumab 100 mg and 300 mg compared to placebo from 1–12 weeks, with low heterogeneity reported (***Figure 19***). One trial reported additional data across an average of 1–4 weeks and 13–24 weeks. The response rate was significantly greater among patients receiving eptinezumab 100 mg and 300 mg at both timepoints compared to placebo (***Table 64***).

Figure 19 Response rate (>75%), eptinezumab in chronic migraine patients: 1–12 weeks



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio.

Table 64 Response rate (>75%), eptinezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-2[84,109]	Low	1–4 weeks	EPT 100 mg	356	110 (30.9)	OR 2.4 (95% CI: 1.7, 3.5), p<0.0001
			EPT 300 mg	350	129 (36.9)	OR 3.2 (95% CI: 2.2, 4.6), p<0.0001
			Placebo	366	57 (15.6)	NA
		13–24 weeks	EPT 100 mg	356	140 (39.3)	OR 2.08 (95% CI: 1.51, 2.87), p<0.00001
			EPT 300 mg	350	151 (43.1)	OR 2.43 (95% CI: 1.77, 3.35), p<0.00001
			Placebo	366	87 (23.8)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.6.3 Fremanezumab

Episodic migraine

One RCT reported response rate (>75%) among patients with episodic migraine and was assessed to be at low RoB.[85] The response rate was significantly greater among patients receiving fremanezumab 225 mg and 675 mg compared to placebo at 1–4 weeks, 5–8 weeks and 9–12 weeks (***Table 65***).[85]

Table 65 Response rate (>75%), fremanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Bigal et al 2015b[85]	Low	Weeks 1–4	FRE 225 mg	95	28 (29)	OR 5.01 (95% CI: 2.15, 11.68), p=0.0001
			FRE 675 mg	96	22 (23)	OR 3.57 (95% CI: 1.50, 8.47), p=0.0026
			Placebo	104	8 (8)	NA
		Weeks 5–8	FRE 225 mg	95	30 (32)	OR 2.74 (95% CI: 1.36, 5.50), p=0.0039
			FRE 675 mg	96	34 (35)	OR 3.25 (95% CI: 1.63, 6.48), p=0.0006
			Placebo	104	15 (14)	NA
		Weeks 9–12	FRE 225 mg	95	34 (36)	OR 2.34 (95% CI: 1.23, 4.45), p=0.0087
			FRE 675 mg	96	39 (41)	OR 2.87 (95% CI: 1.52, 5.42), p=0.0009
			Placebo	104	20 (19)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients and was at low RoB.[91] The response rate was significantly greater among patients receiving fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 66***).

Table 66 Response rate (>75%), fremanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
FOCUS[91]*	Low	3 months	FRE quarterly	276	23 (8)	OR 4.2 (95% CI: 1.7, 10.6), p=0.0021
			FRE monthly	283	35 (12)	OR 6.6 (95% CI: 2.7, 16.1), p<0.0001
			Placebo	278 279	6 (2)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for chronic migraine, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.6.4 Galcanezumab

Episodic migraine

Data reporting response rate (>75%) were available in 4 RCTs, all at low RoB.[92-94,96] None were suitable for combining in a meta-analysis because they either reported different timepoints or reported mean percentage responses rather than raw numbers. The response rate (>75%) was significantly greater among patients randomised to galcanezumab 120 mg or 240 mg compared to placebo in all 4 trials at all timepoints (***Table 67***).

Table 67 Response rate (>75%), galcanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Dodick et al 2014[96]	Low	3 months	GAL150 mg	98	48 (49)	OR 2.54 (90% CI: 1.56, 4.13), p=0.001
			Placebo	104	28 (26.9)	
EVOLVE-1[92]	Low	6 months	GAL 120 mg	210	Mean 38.8% (SE 2.4)	OR 2.65 (95% CI: 2.04, 3.45), p<0.001
			GAL 240 mg	208	Mean 38.5% (SE 2.4)	OR 2.62 (95% CI: 2.01, 3.41), p<0.001
			Placebo	425	Mean 19.3% (SE 1.4)	NA
EVOLVE-2[93]	Low	1–6 months	GAL 120 mg	226	Mean 33.5% (SE 2.3)	p<0.001
			GAL 240 mg	220	Mean 34.3% (SE 2.3)	p<0.001
			Placebo	450	Mean 17.8% (SE 1.3)	NR
Sakai et al 2020a[94]	Low	1–6 months	GAL 120 mg	115	29 (25.5)	OR 3.19 (95% CI: 1.73, 5.86), p<0.001
			GAL 240 mg	114	28 (25)	OR 3.08 (95% CI: 1.67, 5.68), p<0.001
			Placebo	230	22 (9.6)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One trial reported response rate (>75%) among patients with chronic migraine and was at low RoB.[50,123] The response rate (>75%) was significantly greater among patients receiving galcanezumab 120 mg or 240 mg compared to placebo across an average of 1–3 months (***Table 68***).

Table 68 Response rate (>75%), galcanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
REGAIN[50,123]	Low	Averages across months 1–3	GAL 120 mg	273	7.0 (1.4)	OR 1.6 (95% CI: 1.0, 2.5), p=0.031
			GAL 240 mg	274	8.8 (1.7)	OR 2.0 (95% CI: 1.4, 3.1), p<0.001
			Placebo	538	4.5 (0.9)	NA

Abbreviations
CI = confidence interval, GAL = galcanezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RoB** = risk of bias.

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients and was at high RoB.[97] There was no difference in the response rate (>75%) for patients receiving galcanezumab 120 mg compared to galcanezumab 240 mg at 12 months (***Table 69***).

Table 69 Response rate (>75%), galcanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
CGAJ[97]*	High	12 months	GAL 120 mg	135	60 (44.5)	OR 0.72 (95% CI: 0.45, 1.16), p=0.18
			GAL 240 mg	135	71 (52.5)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group, 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

Chronic migraine patients with ≥2 prior treatment failures

One RCT reported data among a subgroup of patients with ≥2 prior treatment failures who had chronic migraine.[122] The response rate (>75%) was significantly greater among patients receiving galcanezumab 240 mg compared to placebo across an average of 1–3 months. There were no differences between galcanezumab 120 mg and placebo (***Table 70***).

Table 70 Response rate (>75%), galcanezumab chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
REGAIN[122]	Low	months 1–3	GAL 120 mg	NR	6.3 (2.2)	OR 2.27 (95% CI: 0.95, 5.42)*
			GAL 240 mg	NR	5 (1.6)	OR 2.87 (95% CI: 1.11, 7.41)
			Placebo	NR	2.3 (0.8)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RoB** = risk of bias.
Notes
*We were unable to calculate p values for the REGAIN trial because the number of participants in the subgroup was unclear.

No RCTs were identified that reported data for subgroups of episodic patients with ≥2 prior treatment failures or among episodic and chronic patients combined with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.7 Response rate (100%)

7.2.3.7.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting response rate (100%) for erenumab 70 mg compared to placebo were available in one RCT assessed to be at high RoB.[76] Response rate was defined as 100% reduction in MMDs. There were no differences between erenumab and placebo at 1 month or 2 months, but the response rate was significantly greater in patients randomised to erenumab 70 mg at 3 months (***Table 71***).

Table 71 Response rate (100%), erenumab episodic migraine patients 70 mg

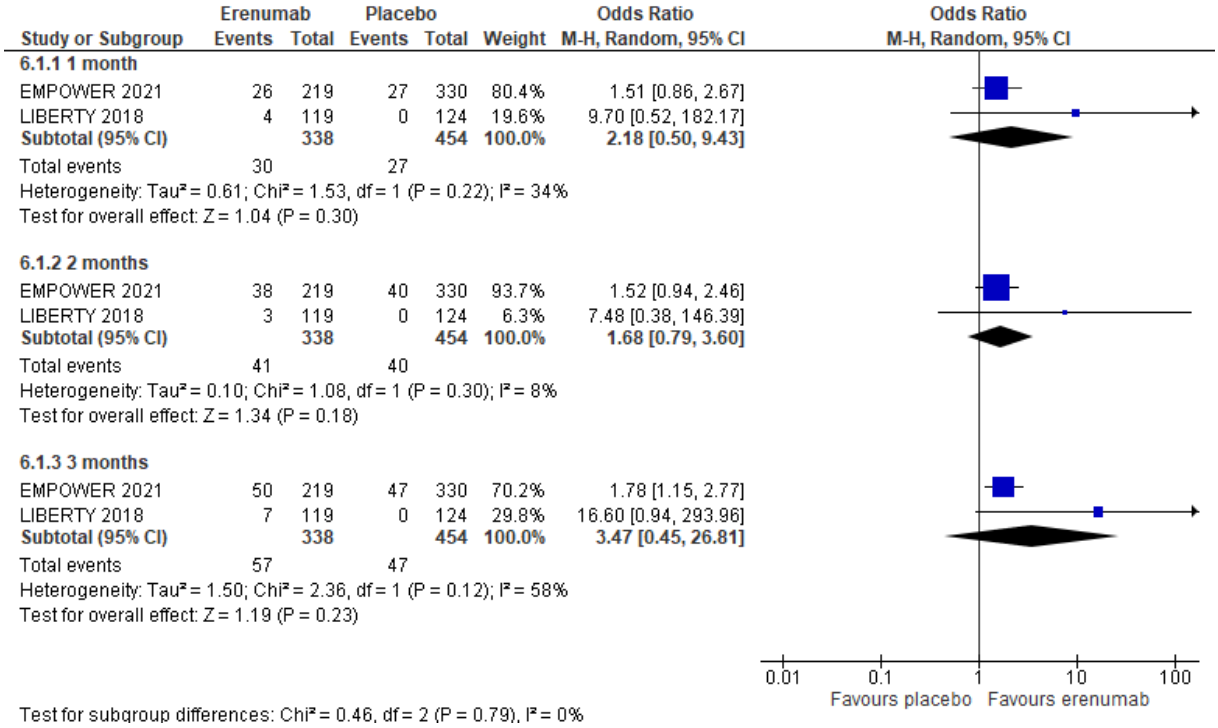
Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
EMPOwER[76]	High	1 month	ERU 70 mg	329	22 (6.7)	OR 0.8 (95% CI: 0.5, 1.4), p=0.467
			ERU 140 mg	219	26 (11.9)	OR 1.5 (95% CI: 0.9, 2.7), p=0.151
			Placebo	330	27 (8.2)	NA
		2 months	ERU 70 mg	329	47 (14.3)	OR 1.2 (95% CI: 0.8, 1.9), p=0.403
			ERU 140 mg	219	38 (17.4)	OR 1.5 (95% CI: 0.9, 2.5), p=0.084
			Placebo	330	40 (12.1)	NA
		3 months	ERU 70 mg	329	73 (22.2)	OR 1.7 (95% CI: 1.2, 2.6), p=0.008
			ERU 140 mg	219	50 (22.8)	OR 1.8 (95% CI: 1.2, 2.8), p=0.009
			Placebo	330	47 (14.2)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.

Erenumab 140 mg

Data reporting response rate (100%) for erenumab 140 mg compared to placebo were available in 2 RCTs; 1 at low RoB[49] and the other at high RoB.[76] Both RCTs were suitable for combining in a meta-analysis. There was no difference in response rate (100%) between patients randomised to erenumab 140 mg or placebo at 1 month, 2 months or 3 months (***Figure 20***). There was moderate heterogeneity reported at most timepoints. When sensitivity analyses were conducted excluding the trial at high RoB, there were no significant differences in response rate (100%) between erenumab 140 mg and placebo (***Appendix H, Figure A10***).

Figure 20 Response rate (100%), erenumab in episodic migraine patients receiving 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel **OR** = odds ratio.

No RCTs were identified that reported response rate (100%) data for chronic migraine; episodic and chronic migraine combined; episodic patients with ≥2 prior treatment failures; or episodic and chronic patients combined with ≥2 prior treatment failures in patients who received erenumab.

7.2.3.7.2 Eptinezumab

Episodic migraine

One RCT assessed to be at high RoB, reported response rate (100%) averaged across 1–12 weeks and 13–24 weeks among patients with episodic migraine randomised to eptinezumab.[107] The response rate was significantly greater among patients receiving eptinezumab 300 mg compared to placebo at 1–12 weeks and 13–24 weeks. There were no differences between eptinezumab 100 mg compared to placebo at either timepoint (***Table 72***).

Table 72 Response rate (100%), eptinezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-1[107]	High	1–12 weeks	EPT 100 mg	221	25 (11.43)	OR 1.29 (95% CI: 0.69, 2.39), p=0.42
			EPT 300 mg	222	37 (16.79)	OR 2.02 (95% CI: 1.13, 3.61), p=0.02
			Placebo	222	20 (9.14)	NA
		13–24 weeks	EPT 100 mg	221	44 (19.71)	OR 1.48 (95% CI: 0.90, 2.43), p=0.13
			EPT 300 mg	222	54 (24.45)	OR 1.91 (95% CI: 1.18, 3.10), p=0.009
			Placebo	222	32 (14.26)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One RCT assessed to be at low RoB[109,110] reported response rate (100%) averaged across 1–12 weeks and 13–24 weeks among patients with chronic migraine randomised to eptinezumab.[109] The response rate was significantly greater among patients receiving eptinezumab 100 mg and 300 mg compared to placebo at 1–12 weeks and 13–24 weeks (***Table 73***).

Table 73 Response rate (100%), eptinezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-2[109,110]	Low	1–12 weeks	EPT 100 mg	356	38 (10.8)	OR 2.1 (95% CI: 1.23, 3.86), p<0.0001
			EPT 300 mg	350	53 (15.1)	OR 2.4 (95% CI: NR), p<0.0001
			Placebo	366	19 (5.1)	NA
		13–24 weeks	EPT 100 mg	356	63 (17.8)	OR 2.10 (95% CI: 1.34, 3.28), p=0.001
			EPT 300 mg	350	73 (20.8)	OR 2.57 (95% CI: 1.66, 3.98), p<0.0001
			Placebo	366	34 (9.3)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.7.3 Fremanezumab

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients and was at low RoB.[91] There were no differences in response rate (100%) between patients receiving fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 74***).

Table 74 Response rate (100%), fremanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
FOCUS[91]*	Low	3 months	FRE quarterly	276	0	Not estimable
			FRE monthly	283	4 (1)	OR 8.97 (95% CI: 0.48, 167.35), p=0.14
			Placebo	278	0	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for episodic or chronic migraine, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.7.4 Galcanezumab

Episodic migraine

Data reporting response rate (100%) were available in 4 RCTs, all at low RoB.[92-94,96] None were suitable for combining in a meta-analysis because they reported either different timepoints or reported mean percentage responses rather than raw data. The response rate (100%) was significantly greater among patients randomised to galcanezumab 120 mg or 240 mg compared to placebo in all 4 trials at all timepoints (***Table 75***).

Table 75 Response rate (100%), galcanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Dodick et al 2014a[96]	Low	3 months	GAL 150 mg	98	31 (31.6)	OR 2.16 (90% CI: 1.24-3.75), p=0.02
			Placebo	104	18 (17.3)	
EVOLVE-1[92]	Low	6 months	GAL 120 mg	210	Mean 15.6% (SE 1.6)	OR 2.80 (95% CI: 1.96, 4.01), p<0.001
			GAL 240 mg	208	Mean 14.6% (SE 1.6)	OR 2.61 (95% CI: 1.81, 3.75), p<0.001
			Placebo	425	Mean 6.2% (SE 0.8)	NA
EVOLVE-2[93]	Low	1–6 months	GAL 120 mg	226	Mean 11.5% (SE 1.4)	p<0.001
			GAL 240 mg	220	Mean 13.8% (SE 1.5)	<0.001
			Placebo	450	Mean 5.7% (SE 0.7)	NA
Sakai et al 2020a[94]	Low	1–6 months	GAL 120 mg	115	10 (9)	OR 3.03 (95% CI: 1.12, 8.19), p<0.001
			GAL 240 mg	114	9 (8.1)	OR 2.73 (95% CI: 0.99, 7.53), p<0.001
			Placebo	230	7 (2.8)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One trial reported response rate (100%) among patients with chronic migraine and was at low RoB.[50,123] There were no differences in the response rate (100%) between patients receiving galcanezumab 120 mg or 240 mg compared to placebo across an average of 1–3 months (***Table 76***).

Table 76 Response rate (100%), galcanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
REGAIN[50,123]	Low	1–3 months	GAL 120 mg	273	0.7 (0.4)	OR 1.4 (95% CI: 0.4, 4.4), p=0.597
			GAL 240 mg	274	1.3 (0.6)	OR 2.6 (95% CI: 1.0, 7.0), p=0.058
			Placebo	538	0.5 (0.3)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias.

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients and was at high RoB.[97] There was no difference in the response rate (100%) for patients receiving galcanezumab 120 mg compared to 240 mg at 12 months (***Table 77***).

Table 77 Response rate (100%), galcanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
CGAJ[97]*	High	12 months	GAL 120 mg	135	29 (21.4)	Not estimable*
			GAL 240 mg	135	29 (21.4)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **RoB** = risk of bias.
Notes
*The difference between groups in the CGAJ trial was not estimable because the number of patients and number of responses were the same in both groups.

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.8 Migraine-Specific Quality of Life Questionnaire (MSQ)

The MSQ represents patient functioning. It is a 14-item questionnaire that measures QoL impacts in 3 domains (scored 0–100, with higher scores indicating improved functioning):

- Role Function–Restrictive (RFR): 7 items that measure the functional impact of migraine through limitations on daily social and work activities
- Role Function–Preventive (RFP): 4 items that measure the impact of migraine through prevention of daily work and social activities
- Emotional Function (EF): 3 items that assess the emotional impact of migraine.[129]

7.2.3.8.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting MSQ for erenumab 70 mg compared to placebo were available in 3 RCTs, all at low RoB (***Table 78***).[75,78,101] None were suitable for combining in a meta-analysis because they all reported MSQ at different timepoints. Two trials reported significant improvements among patients who received erenumab for all MSQ domains (RFR, RFP and EF) at 3 months[75] and across an average of 4–6 months[101] compared to patients who received placebo. One trial reported no significant differences between erenumab and placebo for any MSQ domain.[78] An MD greater than the between-group minimal important difference (MID) of 3.2 points was reported across all RCTs for MSQ RFR, except for the 3-month timepoint of Sun et al 2016.[78]

Erenumab 140 mg

Data reporting MSQ for erenumab 140 mg compared to placebo were available in one RCT assessed to be at low RoB.[101] The trial reported significant improvements among patients who received erenumab

for all MSQ domains (RFR, RFP and EF) across an average of 4–6 months compared to patients who received placebo (***Table 78***). This RCT[101] reported an MD greater than the between-group MID of 3.2 points for MSQ RFR, and an MD greater than the between-group MID of 4.6 points for MSQ RFP.

Table 78 MSQ, erenumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
ARISE[75]	Low	3 months	MSQ RFR	ERU 70 mg	282	15.2 (SE 1.0)	MD 5.5 (95% CI: 2.8, 8.2), p<0.001
				Placebo	288	9.7 (SE 1.0)	
			MSQ RFP	ERU 70 mg	282	12.0 (SE 0.9)	MD 3.6 (95% CI: 1.1, 6.0), p=0.005
				Placebo	288	8.4 (SE 0.9)	
			MSQ EF	ERU 70 mg	282	11.8 (SE 1.1)	MD 4.5 (95% CI: 1.6, 7.4), p=0.002
				Placebo	288	7.3 (SE 1.1)	
STRIVE[101]	Low	4–6 months	MSQ RFR	ERU 70 mg	312	16.8 (SE 0.85)	MD 5.1 (95% CI:2.8, 7.4), p<0.001
				ERU 140 mg	318	18.1 (SE 0.84)	MD 6.5 (95% CI:4.2, 8.8), p<0.001
				Placebo	316	11.7 (SE 0.85)	NA
			MSQ RFP	ERU 70 mg	312	12.7 (SE 0.76)	MD 4.2 (95% CI:2.2, 6.3), p<0.001
				ERU 140 mg	318	13.9 (SE 0.75)	MD 5.4 (95% CI:3.4, 7.5), p<0.001
				Placebo	316	8.5 (SE 0.76)	NA
			MSQ EF	ERU 70 mg	312	12.9 (SE 0.87)	MD 5.2 (95% CI:2.8, 7.6), p<0.001
				ERU 140 mg	318	14.4 (SE 0.87)	MD 6.7 (95% CI:4.4, 9.1), p<0.001
				Placebo	316	7.7 (SE 0.88)	NA
Sun et al 2016[78]	Low	4 weeks	MSQ RFR	ERU 70 mg	104	NR	MD 3.8 (95% CI: -0.4, 8.0), p=0.08
				Placebo	151	NR	
			MSQ RFP	ERU 70 mg	104	NR	MD 2.8 (95% CI: -1.0, 6.5), p=0.15
				Placebo	151	NR	
			MSQ EF	ERU 70 mg	104	NR	MD 3.4 (95% CI: -1.0, 7.7), p=0.13
				Placebo	151	NR	
		8 weeks	MSQ RFR	ERU 70 mg	104	NR	MD 3.9 (95% CI: -0.4, 8.1), p=0.076
				Placebo	151	NR	
			MSQ RFP	ERU 70 mg	104	NR	MD 1.9 (95% CI: -1.9, 5.6), p=0.33
				Placebo	151	NR	
			MSQ EF	ERU 70 mg	104	NR	MD 3.0 (95% CI: -1.3, 7.4), p=0.17
				Placebo	151	NR	
		12 weeks	MSQ RFR	ERU 70 mg	104	NR	MD 1.8 (95% CI: -2.5, 6.1), p=0.41
				Placebo	151	NR	
			MSQ RFP	ERU 70 mg	104	NR	MD 0.5 (95% CI: -3.3, 4.3), p=0.79
				Placebo	151	NR	
			MSQ EF	ERU 70 mg	104	NR	MD 1.9 (95% CI: -2.6, 6.3), p=0.41
				Placebo	151	NR	

Abbreviations

CI = confidence interval, **EF** = Emotional Function, **ERU** = erenumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine

Data reporting MSQ for erenumab 70 mg and 140 mg compared to placebo were available in one RCT assessed to be at low RoB.[104] The trial reported significant improvements among patients who received erenumab for all MSQ domains (RFR, RFP and EF) at 3 months compared to patients who received placebo (***Table 79***). In this RCT,[104] the between-group MDs for all MSQ domains (RFR, RFP and EF), except MSQ RFP comparing erenumab 70 mg to placebo, were greater than the reported MIDs in ***Appendix E***.

Table 79 MSQ, erenumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
Tepper et al 2017[104]	Low	3 months	MSQ RFR	ERU 70 mg	188	17.7 (95% CI: 14.9, 20.6)	MD 6.0 (95% CI: 2.3, 9.6), p=0.002
				ERU 140 mg	187	19.1 (95% CI: 16.3, 22.0)	MD 7.4 (95% CI: 3.7, 11), p<0.001
				Placebo	281	11.8 (95% CI: 9.4, 14.1)	NA
			MSQ RFP	ERU 70 mg	188	13.0 (95% CI: 10.5, 15.6)	MD 4.1 (95% CI: 0.9, 7.4), p=0.013
				ERU 140 mg	187	13.8 (95% CI: 11.3, 16.4)	MD 4.9 (95% CI: 1.7, 8.2), p=0.003
				Placebo	281	8.9 (95% CI: 6.8, 11.0)	NA
			MSQ EF	ERU 70 mg	188	18.2 (95% CI: 15.0, 21.3)	MD 8.3 (95% CI: 4.3, 12.4), p=0.013
				ERU 140 mg	187	18.8 (95% CI: 15.6, 21.9)	MD 8.9 (95% CI: 4.9, 13), p<0.001
				Placebo	281	9.9 (95% CI: 7.3, 12.5)	NA

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **ERU** = erenumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias.

No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.8.2 Eptinezumab

No studies were identified that reported MSQ in patients randomised to eptinezumab.

7.2.3.8.3 Fremanezumab

Episodic migraine

No studies were identified that reported MSQ in patients with episodic migraine randomised to fremanezumab.

Chronic migraine

Data reporting MSQ for fremanezumab 225 mg and 675 mg compared to placebo were available in one RCT assessed to be at low RoB.[114] The trial reported significant improvements in MSQ among patients who received fremanezumab 225 mg and 675 mg for all MSQ domains (RFR, RFP and EF) at 4 weeks and 12 weeks compared to patients who received placebo (***Table 80***). At 4 weeks and 12 weeks the between-group MD for MSQ RFR was greater than the MID of 3.2 points for both doses; at 4 weeks the between-group MD for MSQ RFP was greater than the MID of 4.6 points for both doses.[114]

Table 80 MSQ, fremanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
HALO CM[114]	Low	4 weeks	MSQ RFR	FRE 225 mg	375	19.4 (SE NR)	MD 7.4 (SE 1.43), p<0.0001
				FRE 675 mg	375	19.1 (SE NR)	MD 7.1 (SE 1.35), p<0.0001
				Placebo	371	12 (SE NR)	NA
			MSQ RFP	FRE 225 mg	375	15.8 (SE NR)	MD 6.3 (SE 1.15), p<0.0001
				FRE 675 mg	375	15.3 (SE NR)	MD 5.9 (SE 1.14), p<0.0001
				Placebo	371	9.4 (SE NR)	NA
			MSQ EF	FRE 225 mg	375	19.5 (SE NR)	MD 7.4 (SE 1.54), p<0.0001
				FRE 675 mg	375	19.1 (SE NR)	MD 7.1 (SE 1.54), p<0.0001
				Placebo	371	12.1 (SE NR)	NA
		12 weeks	MSQ RFR	FRE 225 mg	375	21 (SE NR)	MD 6.3 (SE 1.42), p<0.0001
				FRE 675 mg	375	20.3 (SE NR)	MD 5.6 (SE 1.42), p<0.0001
				Placebo	371	14.7 (SE NR)	NA
			MSQ RFP	FRE 225 mg	375	15.5 (SE NR)	MD 3.9 (SE 1.26), p=0.0017
				FRE 675 mg	375	15.9 (SE NR)	MD 4.3 (SE 1.25), p=0.0007
				Placebo	371	11.6 (SE NR)	NA
			MSQ EF	FRE 225 mg	375	20.3 (SE NR)	MD 3.3 (SE 1.55), p=0.0348
				FRE 675 mg	375	20.9 (SE NR)	MD 3.9 (SE 1.55), p=0.0126
				Placebo	371	17 (SE NR)	NA

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **FRE** = fremanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Chronic and episodic migraine

Data reporting MSQ for fremanezumab quarterly and monthly compared to placebo were available in one RCT assessed to be at low RoB.[91] The trial reported significant improvements among patients who received fremanezumab quarterly and monthly for the MSQ total score at 4 months compared to patients who received placebo (***Table 81***).

Table 81 MSQ, fremanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
FOCUS[91]*	Low	4 months	MSQ total	FRE quarterly	276	15.7 (SE 1.5)	MD 8.8 (95% CI: 5.7, 11.9), p<0.0001
				FRE monthly	283	17.5 (SE 1.5)	MD 10.6 (95% CI: 7.5, 13.7), p<0.0001
				Placebo	278	6.9 (SE 1.5)	NA

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **FRE** = fremanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

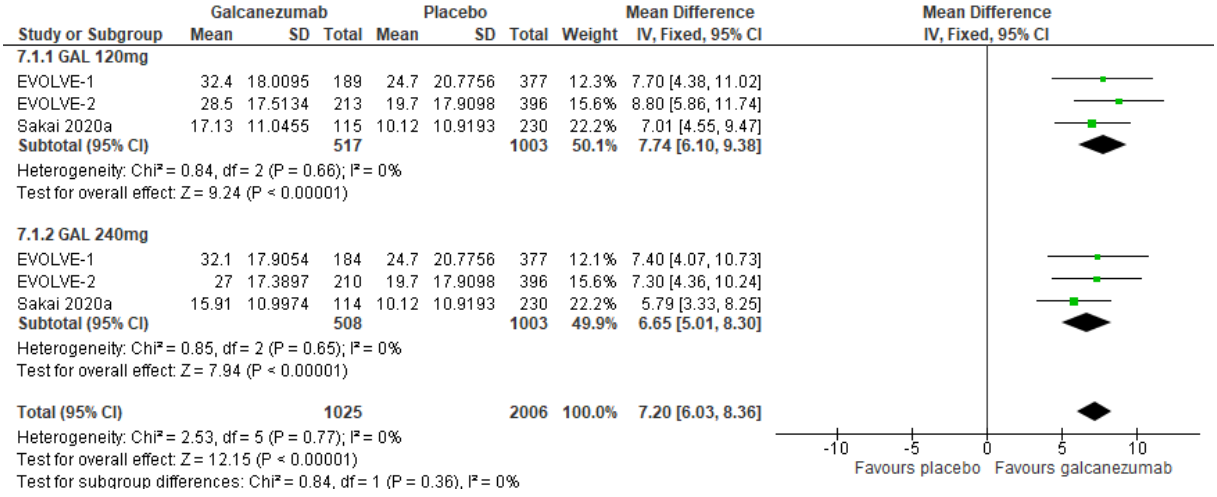
7.2.3.8.4 Galcanezumab

Episodic migraine

Data reporting MSQ for galcanezumab 120 mg compared to placebo were available in 3 RCTs, all at low RoB.[92-94,117,118,121] Three of the trials reported MSQ RFR at the same timepoint (average across 4–6 months) and were included in a meta-analysis. This showed significant improvements among patients who received galcanezumab 120 mg for the MSQ RFR domain across an average of 4–6 months compared to patients who received placebo (***Figure 21***).[92-94,117,118] After meta-analysis the combined MDs for galcanezumab 120 mg and galcanezumab 240 mg compared to placebo were greater than the between-group MID of 3.2 points for MSQ RFR.

Additional MSQ domains (RFP, EF and total score) were reported by 2 trials (***Table 82***). One trial reported the change from baseline for galcanezumab 120 mg, 240 mg and placebo for the MSQ RFP, EF and total score across an average of 4–6 months, but did not report any measures of variance or undertake statistical analyses for these outcomes. A second trial reported significant improvements among patients randomised to galcanezumab 120 mg for MSQ RFP, EF and total score at 3 months compared to placebo.[121] All individual MSQ domains (RFP, RFR and EF) reported in Skljarevski et al 2018[121] were greater than the reported MIDs in ***Appendix E***.

Figure 21 MSQ-RFR, galcanezumab in episodic migraine patients (4–6 months)



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 82 MSQ, galcanezumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
Sakai et al 2020a[94,11] [7,118]	Low	6 months	MSQ RFR	GAL 120 mg	112	16.6 (NR)	NR
				GAL 240 mg	112	16.3 (NR)	NR
				Placebo	228	9.7 (NR)	NR
		4–6 months	MSQ RFP	GAL 120 mg	112	9.64 (NR)	NR
				GAL 240 mg	112	8.35 (NR)	NR
				Placebo	228	4.8 (NR)	NR
			MSQ EF	GAL 120 mg	112	10.04 (NR)	NR
				GAL 240 mg	112	7.73 (NR)	NR
				Placebo	228	3.46 (NR)	NR
			MSQ total	GAL 120 mg	112	13.46 (NR)	NR
				GAL 240 mg	112	11.98 (NR)	NR
				Placebo	228	7.14 (NR)	NR
Skljarevski et al 2018[121]	Low	3 months	MSQ RFP	GAL 120 mg	60	19.8 (SE NR)	MD 6.3 (95% CI: 0.476,12.185), p=0.0342
				Placebo	127	13.4 (SE NR)	
			MSQ RFR	GAL 120 mg	60	31.9 (SE NR)	MD 9.6 (95% CI: 2.636, 16.518), p=0.0071
				Placebo	127	22.4 (SE NR)	
			MSQ EF	GAL 120 mg	60	26.6 (SE NR)	MD 9.7 (95% CI: 2.789, 16.674), p=0.0063
				Placebo	127	16.9 (SE NR)	
			MSQ total	GAL 120 mg	60	27.4 (SE NR)	MD 8.7 (95% CI: 2.450, 15.008), p=0.0067
				Placebo	127	18.6 (SE NR)	

Abbreviations

CI = confidence interval, **EF** = Emotional Function, **GAL**= galcanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine

Data reporting MSQ for galcanezumab 120 mg and 240 mg compared to placebo were available in one RCT assessed to be at low RoB.[50] The trial reported significant improvements among patients who received galcanezumab 120 mg and 240 mg for all MSQ domains (RFR, RFP and EF) at 3 months compared to patients who received placebo (***Table 83***). In this RCT, the reported MDs for MSQ RFR and MSQ RFP were greater than the MIDs reported for both galcanezumab 120 mg and 240 mg compared to placebo.

Table 83 MSQ, galcanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
REGAIN[50]	Low	3 months	MSQ RFR	GAL 120 mg	273	21.8 (SE 1.4)	MD 5.1 (95% CI: 2.1, 8.0), p<0.001
				GAL 240 mg	274	23.1 (SE 1.6)	MD 6.3 (95% CI: 3.0, 9.6), p<0.001
				Placebo	538	16.8 (SE 1.2)	NA
			MSQ RFP	GAL 120 mg	273	18.0 (SE 1.4)	MD 7.0 (95% CI: 4.2, 9.8), p<0.001
				GAL 240 mg	274	16.1 (SE 1.4)	MD 5.1 (95% CI: 2.3, 7.9), p<0.001
				Placebo	538	11.0 (SE 1.2)	NA
			MSQ EF	GAL 120 mg	273	21.0 (SE 1.9)	MD 7.0 (95% CI: 3.2, 10.8), p<0.001
				GAL 240 mg	274	20.7 (SE 1.9)	MD 6.6 (95% CI: 2.8, 10.4), p<0.001
				Placebo	538	14.1 (SE 1.6)	NA

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **GAL**= galcanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Chronic and episodic migraine

Data reporting MSQ for galcanezumab 120 mg compared to 240 mg for patients with both episodic and chronic migraine were available in one RCT assessed to be at high RoB.[97,130] The trial reported no significant differences between patients who received galcanezumab 120 mg compared to 240 mg at 12 months. Additional data reporting outcomes at 14 months and 16 months using 12-month data as a baseline also reported no significant differences between the 2 doses of galcanezumab (***Table 84***).

Table 84 MSQ, galcanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
CGAJ[97] 130*	High	12 months	MSQ RFR	GAL 120 mg	130	31.6 (SE 1.2)	MD 1.9 (95% CI: -1.3, 5.0)
				GAL 240 mg	135	33.4 (SE 1.2)	
			MSQ RFP	GAL 120 mg	NR	NR	MD 1.3 (95% CI: -1.7, 4.2)
				GAL 240 mg	NR	NR	
			MSQ EF	GAL 120 mg	NR	NR	MD 3.1 (95% CI: -0.5, 6.6)
				GAL 240 mg	NR	NR	
		14 months**	MSQ RFR	GAL 120 mg	100	-7.1 (SE 1.8)	MD -2.4 (95% CI: -7.1, 2.3)
				GAL 240 mg	113	-9.5 (SE 1.7)	
			MSQ RFP	GAL 120 mg	100	-5.6 (SE 1.6)	MD -1.1 (95% CI: -5.4, 3.2)
				GAL 240 mg	113	-6.7 (SE 1.5)	
			MSQ EF	GAL 120 mg	100	-9.1 (SE 2.0)	MD 1.4 (95% CI: -3.9, 6.6)
				GAL 240 mg	113	-7.8 (SE 1.9)	
		16 months[p]	MSQ RFR	GAL 120 mg	99	-8.7 (SE 1.9)	MD -1.6 (95% CI: -6.5, 3.3)
				GAL 240 mg	115	-10.3 (SE 1.7)	
			MSQ RFP	GAL 120 mg	99	-6.6 (SE 1.7)	MD -1.6 (95% CI: -6.1, 2.9)
				GAL 240 mg	115	-8.2 (SE 1.6)	
			MSQ EF	GAL 120 mg	99	-8.4 (SE 2.2)	MD -1.5 (95% CI: -7.2, 4.2)
				GAL 240 mg	115	-9.9 (SE 2.0)	

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **GAL**= galcanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.
* In the CGAJ trial there were two treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group, 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.
** In the CGAJ trial, 12-month data were used as the baseline for outcomes measured at 14 and 16 months.

Episodic migraine patients with ≥2 prior treatment failures

One RCT reported data among a subgroup of patients with ≥2 prior treatment failures who had episodic migraine.[98,124] The trial reported significant improvements in MSQ-RFR among patients who received galcanezumab 120 mg with 2 prior treatment failures at 3 months, and among all MSQ domains (RFR, RFP and EF) among patients with 3–4 prior treatment failures at 3 months compared to patients who received placebo (***Table 85***). In this RCT,[98,124] the MDs were greater than the between-group MIDs for all MSQ domains (RFR, RFP and EF) as reported in ***Appendix E***.

Table 85 MSQ, galcanezumab episodic patients with ≥2 prior treatment failures

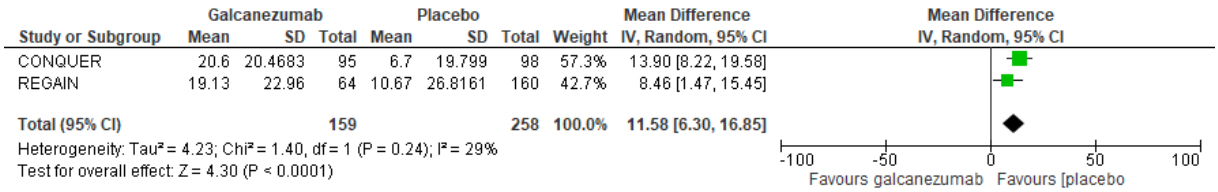
Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
CONQUER[98,124]	Low	3 months, patients with 2 prior treatment failures	MSQ RFR	GAL 120 mg	137	23.4 (SE 1.8)	MD 11.5 (95% CI: 7.1, 15.9), p<0.0001
				Placebo	132	11.9 (SE 1.8)	
	Low	3 months, patients with 3–4 prior treatment failures	MSQ RFR	GAL 120 mg	54	22.7 (SE 3.4)	MD 8.2 (SE 4.0), p=0.0426
				Placebo	43	14.5 (SE 3.6)	
			MSQ RFP	GAL 120 mg	54	19.2 (SE 3.0)	MD 8.3 (SE 3.6), p=0.0233
				Placebo	43	10.9 (SE 3.2)	
			MSQ EF	GAL 120 mg	54	24.2 (SE 4.0)	MD 9.5 (SE 4.7), p=0.0479
				Placebo	43	14.7 (SE 4.1)	

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **GAL**= galcanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine patients with ≥2 prior treatment failures

Two RCTs reported data among a subgroup of patients with ≥2 prior treatment failures who had chronic migraine (***Table 86***).[98,122,124] Both trials reported data for the MSQ-RFR at 3 months, showing significant improvements among patients who received galcanezumab 120 mg compared to placebo (***Figure 22***). Additional data from one trial reported significant improvements across all MSQ domains (RFR, RFP and EF) among patients with 3–4 prior treatment failures at 3 months who received galcanezumab 120 mg compared to patients who received placebo.[98,124] The second trial reported additional data showing significant improvements in MSQ-RFR among patients with ≥2 prior treatment failures receiving galcanezumab 240 mg at 3 months compared to patients who received placebo.[122] Across both RCTs,[98,122,124] the MDs were greater than the between-group MIDs for all MSQ domains (RFR, RFP and EF) as reported in ***Appendix E***.

Figure 22 MSQ RFR, galcanezumab 120 mg in chronic patients with ≥2 prior treatment failures



Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 86 MSQ, galcanezumab chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
CONQUER[98,124]	Low	3 months, patients with 2 prior treatment failures	MSQ RFR	GAL 120 mg	95	20.6 (SE 2.1)	MD 13.9 (95% CI: 8.9, 18.9), p<0.0001
				Placebo	98	6.7 (SE 2.0)	
	Low	3 months, patients with 3–4 prior treatment failures	MSQ RFR	GAL 120 mg	40	25.2 (SE 3.6)	MD 20.5 (SE 4.2), p<0.0001
				Placebo	41	4.7 (SE 3.4)	
			MSQ RFP	GAL 120 mg	40	18.7 (SE 3.3)	MD 15.2 (SE 3.8), p=0.0001
				Placebo	41	3.5 (SE 3.1)	
			MSQ EF	GAL 120 mg	40	28.3 (SE 4.4)	MD 19.0 (SE 5.0), p=0.0003
				Placebo	41	9.2 (SE 4.0)	
REGAIN[122]	Low	3 months	MSQ RFR	GAL 120 mg	64	19.13 (SE 2.87)	MD 8.45 (SE 2.99), p<0.01
				GAL 240 mg	94	19.24 (SE 2.61)	MD 8.57 (SE 2.64), p<0.01
				Placebo	160	10.67 (SE 2.12)	NA

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **GAL**= galcanezumab, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number of patients, **NA** = not applicable, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

No RCTs were identified that reported data subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.9 Headache Impact Test (HIT-6)

HIT-6 is a short, 6-item self-administered questionnaire using functionally relevant domains based on the internet HIT question pool, which evaluates how often headaches impact activities or cause distress. Six domains assess the frequency of pain severity, headache limiting daily activity (household, work, school, social), wanting to lie down when headache is experienced, feeling too tired to work or do daily activities because of headache, feeling 'fed up' or irritated because of headache, and headache limiting one's ability to concentrate or work on daily activities. Each of the 6 questions was answered using 1 of 5 response categories: never, rarely, sometimes, very often, always. For each HIT-6 item, 6, 8, 10, 11 or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 scores are categorised into 4 grades, representing little or no impact (≤49), some impact (50–55), substantial impact (56–59) and severe impact (60–78) due to headache, with higher scores suggesting a more negative impact.[131]

7.2.3.9.1 Erenumab

Episodic migraine

Erenumab 70 mg

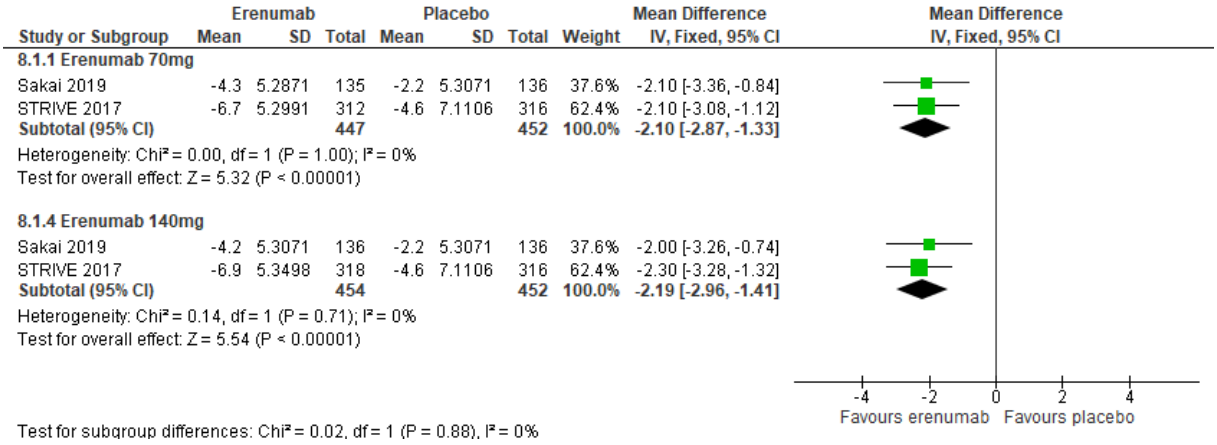
Data reporting HIT-6 scores for erenumab 70 mg compared to placebo were available in 5 RCTs; 4 at low RoB[48,75,77,78,101] and one at high RoB.[76] Of the 5 RCTs, 2 were suitable for combining in a meta-analysis at 4–6 months, which found mean HIT-6 score was significantly reduced in patients who received erenumab 70 mg across a mean of 4–6 months. No heterogeneity was reported (***Figure 23***).[48,77] The remaining 3 trials reported data at different timepoints and/or did not report data in a suitable format for meta-analysis. These are reported in ***Table 87***.[75,76,78]

- At one month, mean HIT-6 score was significantly reduced among patients who received erenumab 70 mg in one trial;[76] a second trial reported no differences between erenumab 70 mg and placebo.[78]
- At 2 months, mean HIT-6 score was significantly reduced among patients who received erenumab 70 mg in 2 trials[76,78]
- At 3 months, mean HIT-6 score was significantly reduced among patients who received erenumab 70 mg in 2 trials;[75,76] a third trial reported no differences between erenumab 70 mg and placebo.[78]

Erenumab 140 mg

Data reporting HIT-6 scores for erenumab 140 mg compared to placebo were available in 4 RCTs, 3 at low RoB[48,77,100] and one at high RoB.[76] Of the 4 RCTs, 2 were suitable for combining in a meta-analysis at 4–6 months, which found the mean HIT-6 score was significantly reduced in patients who received erenumab 140 mg across a mean of 4–6 months (***Figure 23***).[48,77] No heterogeneity was reported or identified at any timepoint. The remaining 2 trials reported data at different timepoints and/or did not report data in a suitable format for meta-analysis. These are reported in ***Table 87***.[76,100] The mean HIT-6 score was significantly reduced in patients who received erenumab 140 mg at 1 month, 2 months and 3 months in both trials (***Figure 23***).[76,100]

Figure 23 HIT-6, erenumab in episodic migraine patients receiving 70 mg and 140 mg, 4–6 months



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 87 HIT-6, erenumab in episodic migraine patients receiving 70 mg and 140 mg

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
ARISE[75]	Low	3 months	ERU 70 mg	282	-4.9 (SE 0.4)	MD -2.3 (95% CI: -3.3 to -1.3), p<0.001
			Placebo	288	-2.6 (SE 0.4)	
EMPOwER[76]	High	1 month	ERU 70 mg	329	-5.33 (SE 0.39)	MD -1.90 (95% CI: -2.96 to -0.85), p<0.001
			ERU 140 mg	219	-6.10 (SE 0.47)	MD -2.67 (95% CI: -3.85 to -1.49), p<0.001
			Placebo	330	-3.43 (SE 0.39)	NA
		2 months	ERU 70 mg	329	-7.63 (SE 0.44)	MD -2.01 (95% CI: -3.20 to -0.83), p<0.001
			ERU 140 mg	219	-8.11 (SE 0.53)	MD -2.49 (95% CI: -3.81 to -1.17), p<0.001
			Placebo	330	-5.61 (SE 0.43)	NA
		3 months	ERU 70 mg	329	-8.39 (SE 0.45)	MD -1.77 (95% CI: -2.99 to -0.56), p=0.004
			ERU 140 mg	219	-9.34 (SE 0.54)	MD -2.71 (95% CI: -4.07 to -1.36), p<0.001
			Placebo	330	-6.62 (SE 0.44)	NA
LIBERTY[100]	Low	4 weeks	ERU 140 mg	119	-4.1 (SE NR)	MD -1.9 (95% CI: -3.1, -0.6), p=0.003
			Placebo	124	-2.2 (SE NR)	
		8 weeks	ERU 140 mg	119	-5.5 (SE NR)	MD -3.4 (95% CI: -4.8, -2.0), p<0.001
			Placebo	124	-2.1 (SE NR)	
		12 weeks	ERU 140 mg	119	-5.3 (SE NR)	MD -3.0 (95% CI: -4.5, -1.4), p<0.001
			Placebo	124	-2.4 (SE NR)	
Sakai et al 2019[77]	Low	4–6 months	ERU 70 mg	135	-4.3 (95% CI: -5.2, -3.4)	MD -2.1 (95% CI: -3.3, -0.9), p<0.001
			ERU 140 mg	136	-4.2 (95% CI: -5.1, -3.3)	MD -2.0 (95% CI: -3.2, -0.8), p=0.001
			Placebo	136	-2.2 (95% CI: -3.1, -1.3)	NA
STRIVE[101]	Low	4–6 months	ERU 70 mg	312	-6.7 (SE 0.3)	MD -2.1 (95% CI: -3.0, -1.1), p<0.001
			ERU 140 mg	318	-6.9 (SE 0.3)	MD -2.3 (95% CI: -3.2, -1.3), p<0.001
			Placebo	316	-4.6 (SE 0.4)	NA
Sun et al 2016[78]	Low	4 weeks	ERU 70 mg	104	NR	MD -1.2 (95% CI: -2.7, 0.4), p=0.13
			Placebo	151	NR	
		8 weeks	ERU 70 mg	104	NR	MD -2.1 (95% CI: -3.6, -0.6), p=0.007
			Placebo	151	NR	
		12 weeks	ERU 70 mg	104	NR	MD -1.0 (95% CI: -2.5, 0.6), p=0.22
			Placebo	151	NR	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine

Data reporting HIT-6 for erenumab 70 mg and 140 mg compared to placebo were available in one RCT assessed to be at low RoB.[104] The trial reported significant improvements in HIT-6 score among patients who received erenumab at 3 months compared to patients who received placebo (***Table 88***).

Table 88 HIT-6, erenumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Tepper et al 2017[104]	Low	3 months	ERU 70 mg	188	-5.6 (95% CI: -6.5, -4.6)	MD -2.5 (95% CI: -3.7, -1.2), p<0.001
			ERU 140 mg	187	-5.6 (95% CI: -6.5, -4.6)	MD -2.5 (95% CI: -3.7, -1.2), p<0.001
			Placebo	281	-3.1 (95% CI: -3.9, -2.3)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias.

Episodic and chronic migraine

Data reporting HIT-6 for erenumab 70 mg or 140 mg compared to topiramate 25–100 mg were available in one RCT assessed to be at low RoB.[80] The trial reported significant improvements in HIT-6 score among patients who received erenumab at an average of 4–6 months compared to patients who received topiramate (***Table 89***).

Table 89 HIT-6, erenumab in episodic and chronic patients (combined)

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
HER-MES[80]*	Low	4–6 months	ERU 70 or 140 mg	379	-10.9 (SE 0.4)	MD -3.2 (95% CI: -4.3, -2.1), p<0.001
			Topiramate 25-100 mg	377	-7.7 (SE 0.4)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.
* In HER-MES, the following number of patients were included: For Erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%) Chronic (≥15 MMDs) = 42 (10.8%).

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.9.2 Eptinezumab

Chronic migraine

Data reporting HIT-6 scores for eptinezumab 100 mg and 300 mg compared to placebo were available in 2 RCTs (***Table 90***). One trial was assessed to have some methodological concerns[83] while the second was at low RoB.[84] One trial reported significant improvements in HIT-6 score among patients who received eptinezumab 300 mg compared to placebo at 3 months; there were no differences between eptinezumab 100 mg and placebo. The second trial reported significant improvements in HIT-6 score among patients who received eptinezumab 100 mg and 300 mg compared to placebo at 3 months

(***Table 90***).[84] Data appear to be significant at 1 month, but measures of variance were not reported so this could not be confirmed.

Table 90 HIT-6, eptinezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Dodick et al 2019[83]	Some concerns	3 months	EPT 300 mg	106	-10.0 (SD 8.4)	MD -4.20 (95% CI: -6.31, -2.09), p<0.0001
			EPT 100 mg	107	-6.9 (SD 7.4)	MD -1.10 (95% CI: -3.07, 0.87), p=0.27
			Placebo	110	-5.8 (SD 7.4)	NA
PROMISE-2[84]	Low	week 4	EPT 100 mg	356	-6.9 (NR)	MD -2.3 (95% CI: -3.4, -1.2), p=NR
			EPT 300 mg	350	-8.6 (NR)	MD -4.0 (95% CI: -5.1, -2.8), p=NR
			Placebo	366	-4.6 (NR)	NA
		week 12	EPT 100 mg	356	-6.2 (Range: -34, 10)	MD -1.7 (95% CI: -2.8, -0.7), p=0.001
			EPT 300 mg	350	-7.3 (Range: -40, 10)	MD -2.9 (95% CI: -3.9, -1.8), p<0.0001
			Placebo	366	-4.5 (Range: -32, 15)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS-calculated comparisons.

There were no RCTs identified that reported data for episodic migraine, episodic and chronic migraine patients combined, or for subgroups of patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.3.9.3 Fremanezumab

Chronic migraine

Two trials reported HIT-6 scores among patients with chronic migraine; both were at low RoB.[89,90] The trials were not suitable for combining in a meta-analysis because data were reported at different time periods (***Table 91***). One trial reported significant improvements in HIT-6 score in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 12 weeks.[89]The other reported significant improvements in HIT-6 score in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 16 weeks.[90]

Table 91 HIT-6, fremanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
HALO CM[89]	Low	12 weeks	FRE 225 mg	375	-6.8 (SE 0.4)	MD -2.4 (95% CI: -3.55, -1.05), p=0.0003
			FRE 675 mg	375	-6.4 (SE 0.5)	MD -1.9 (95% CI: -3.29, -0.51), p=0.007
			Placebo	371	-4.5 (SE 0.5)	NA
Sakai et al 2021a[90]	Low	16 weeks	FRE 225 mg	182	-8.1 (SE 0.7)	MD -1.6 (95% CI: -2.94, -0.19), p=0.026
			FRE 675 mg	180	-8.0 (SE 0.7)	MD -1.5 (95% CI: -2.91, -0.15), p=0.030
			Placebo	179	-6.5 (SE 0.7)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic and episodic migraine

Data reporting HIT-6 scores for fremanezumab quarterly and monthly compared to placebo were available in one RCT assessed to be at low RoB.[91] The trial reported significant improvements in HIT-6 scores among patients who received fremanezumab quarterly and monthly at 4 months compared to patients who received placebo (***Table 92***).

Table 92 HIT-6, fremanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
FOCUS[91]*	Low	4 months	FRE quarterly	276	-5.2 (SE 0.6)	MD -3.0 (95% CI: -4.1 to -1.8), p<0.0001
			FRE monthly	283	-6.1 (SE 0.5)	MD -3.8 (95% CI: -5.0 to -2.7), p<0.0001
			Placebo	279	-2.2 (SE 0.5)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Episodic and chronic migraine patients with ≥2 prior treatment failures

One RCT reported HIT-6 scores for a subgroup of patients who had both episodic and chronic migraine with 2, 3 or 4 prior treatment failures.[116] The trial reported significant improvements in HIT-6 scores among patients randomised to fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 93***).

Table 93 HIT-6, fremanezumab episodic and chronic patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
FOCUS[116]*	Low	3 months 2 Tx failures	FRE quarterly	140	-5.3 (0.78)	MD -2.5 (95% CI: -4.21, -0.88), p=0.003
			FRE monthly	133	-6.4 (0.78)	MD -3.6 (95% CI: -5.32, -1.93), p<0.0001
			Placebo	141	-2.7 (0.77)	NA
		3 months 3 Tx failures	FRE quarterly	85	-5.4 (0.96)	MD -2.8 (95% CI: -4.95, -0.57), p=0.014
			FRE monthly	98	-5.8 (0.94)	MD -3.2 (95% CI: -5.28, -1.11), p=0.003
			Placebo	82	-2.6 (0.90)	NA
		3 months 4 Tx failures	FRE quarterly	49	-5.0 (1.18)	MD -5.6 (95% CI: -8.16, -3.03), p<0.001
			FRE monthly	50	-6.2 (1.04)	MD -6.8 (95% CI: -9.25, -4.43), p<0.001
			Placebo	54	0.6 (1.19)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error, **Tx** = treatment.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for episodic migraine, or for subgroups of episodic or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.3.9.4 Galcanezumab

Episodic migraine

Data reporting HIT-6 for galcanezumab 120 mg compared to placebo were available in one RCT assessed to be at low RoB.[121] The trial reported no differences between galcanezumab and placebo at 3 months (***Table 94***).

Table 94 HIT-6, galcanezumab in episodic patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Skljarevski et al 2018[121]	Low	3 months	GAL 120 mg	60	-10.2 (SE NR)	MD -2.5 (95% CI: -5.107, 0.144), p=0.0638
			Placebo	127	-7.7 (SE NR)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **HIT-6** = Headache Impact Test, **MD** = mean difference, **n** = number of patients, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

No RCTs were identified that reported data for chronic migraine, episodic and chronic migraine patients combined, or for subgroups of patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.10 Migraine Disability Assessment (MIDAS)

MIDAS is a numerical score representing the number of days patients missed or lost productivity at work or school, or missed days from family/social/leisure activities. MIDAS ranges from little or no disability (0–5) to severe disability (>20). The standard version asks patients to recall impacts over the past 3 months, whereas the modified MIDAS asks patients to recall over the past month.[132]

7.2.3.10.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting MIDAS scores for erenumab 70 mg compared to placebo were available in 4 RCTs: 3 at low RoB[75,78,101] and 1 at high RoB.[76] None of the RCTs were suitable for combining in a meta-analysis because they reported different timepoints and different versions of the MIDAS score (***Table 95***).

- At 1 month, mean MIDAS score was significantly reduced in patients who received erenumab 70 mg in one trial.[76]
- At 2 months, mean MIDAS score was significantly reduced in patients who received erenumab 70 mg in one trial.[76]
- At 3 months, mean MIDAS score was significantly reduced in patients who received erenumab 70 mg in two trials,[75,76] whereas a third trial reported no differences between erenumab 70 mg and placebo.[78]
- At 4–6 months, mean MIDAS score was significantly reduced in patients who received erenumab 70 mg in one trial.[76]
- One RCT[78] reported an MD greater than the minimal important change (MIC) of 4.5 points.

Erenumab 140 mg

Data reporting MIDAS scores for erenumab 140 mg compared to placebo were available in 2 RCTs; one was at low RoB[101] while one was at high RoB (***Table 95***).[76] The two trials reported data at different timepoints and were not suitable for meta-analysis. The mean MIDAS score was significantly reduced in patients who received erenumab 140 mg at 1 month, 2 months and 3 months in one trial[76] and was significantly reduced in patients who received erenumab 140 mg at 4–6 months.[101]

Table 95 MIDAS, erenumab in episodic migraine patients receiving 70 mg and 140 mg

Trial name	RoB	MIDAS type	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
ARISE[75]	Low	mMIDAS	3 months	ERU 70 mg	282	-5.5 (SE 0.5)	MD -1.7 (95% CI: -3.1 to -0.3), p=0.021
				Placebo	288	-3.8 (SE 0.5)	
EMPOwER[76]	High	mMIDAS	1 month	ERU 70 mg	329	-5.89 (SE 0.49)	-2.41 (95% CI: -3.75 to -1.08), p=0.0005
				ERU 140 mg	219	-6.44 (SE 0.60)	-2.96 (95% CI: -4.46 to -1.47), p=0.0001
				Placebo	330	-3.48 (SE 0.49)	NA
			2 months	ERU 70 mg	329	-7.51 (SE 0.48)	-2.48 (95% CI: -3.78 to -1.18), p=0.0002
				ERU 140 mg	219	-7.83 (SE 0.58)	-2.80 (95% CI: -4.24 to -1.35), p=0.0002
				Placebo	330	-5.04 (SE 0.47)	NA
			3 months	ERU 70 mg	329	-8.11 (SE 0.43)	-1.52 (95% CI: -2.69 to -0.35), p=0.011
				ERU 140 mg	219	-8.99 (SE 0.52)	-2.40 (95% CI: -3.70 to -1.10), p=0.0004
				Placebo	330	-6.59 (SE 0.43)	NA
STRIVE[101]	Low	mMIDAS	4–6 months	ERU 70 mg	312	-6.7 (SE 0.4)	-2.1 (95% CI: -3.3, -0.9), p<0.001
				ERU 140 mg	318	-7.5 (SE 0.4)	-2.8 (95% CI: -4.0, -1.7), p<0.001
				Placebo	316	-4.6 (SE 0.4)	NA
Sun et al 2016[78]	Low	MIDAS	12 weeks	ERU 70 mg	93	NR	MD -5.3 (95% CI: -10.9, 0.3), p=0.064
				Placebo	134	NR	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = Mean difference, **MIDAS** = Migraine Disability Assessment, **mMIDAS** = modified Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SD** = standard deviation, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Data reporting the MIDAS for erenumab 70 mg and 140 mg compared to placebo were available in one RCT assessed to be at low RoB.[104] The trial reported significant improvements in MIDAS score among patients who received erenumab at 3 months compared to patients who received placebo (***Table 96***). This trial[104] reported an MD greater than the MIC of 4.5 points.

Table 96 MIDAS, erenumab in chronic migraine patients receiving 70 mg and 140 mg

Trial name	RoB	MIDAS type	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
Tepper et al 2017[104]	Low	MIDAS	3 months	ERU 70 mg	188	-19.4 (95% CI: -25.2, -13.6)	MD -11.9 (95% CI: -19.3, -4.4), p=0.002
				ERU 140 mg	187	-19.8 (95% CI: -25.6, -14.0)	MD -12.2 (95% CI: -19.7, -4.8), p=0.001
				Placebo	281	-7.5 (95% CI: -12.4, -2.7)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = Mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable.

No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.10.2 Eptinezumab

No studies were identified that reported MIDAS in patients randomised to eptinezumab.

7.2.3.10.3 Fremanezumab

Episodic migraine

Three RCTs reported MIDAS scores among patients with episodic migraine: 2 at low RoB[85,87] and 1 at high RoB.[86] None of the RCTs were suitable for combining in a meta-analysis because data were reported at different time periods. There were significant improvements in MIDAS score among patients randomised to fremanezumab 225 mg and 675 mg compared to placebo at 9–12 weeks in one trial;[85] at 12 weeks in the second trial[86] and at 16 weeks in the third trial (***Table 97***).[87] All three RCTs reported an MD greater than the MIC of 4.5 points.

Table 97 MIDAS, fremanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
Bigal et al 2015b[85]	Low	9–12 weeks	FRE 225 mg	NR	NR	MD -14.50 (-26.79 to -2.20), p=0.021
			FRE 675 mg	NR	NR	MD -15.20 (-27.62 to -2.78), p=0.017
			Placebo	NR	NR	NA
HALO EM[86]	High	12 weeks	FRE 225 mg	287	-24.6 (95% CI: -27.68, -21.45)	MD -7.0 (95% CI: -10.51, -3.53), p<0.001
			FRE 675 mg	288	-23.0 (95% CI: -26.10, -19.82)	MD -5.4 (95% CI: -8.90, -1.93), p=0.002
			Placebo	290	-17.5 (95% CI: -20.62, -14.47)	NA
Sakai et al 2021b[87]	Low	16 weeks	FRE 225 mg	118	-12.6 (SE 1.4)	MD -5.2 (95% CI: -8.14, -2.33), p<0.0001
			FRE 675 mg	113	-12.6 (SE 1.5)	MD -5.1 (95% CI: -8.09, -2.20), p<0.0001
			Placebo	112	-7.4 (SE 1.5)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SD** = standard deviation, **SE** = standard error.

Chronic and episodic migraine

Data reporting MIDAS for fremanezumab quarterly and monthly compared to placebo were available in one RCT assessed to be at low RoB.[91] The trial reported significant improvements in MIDAS among patients who received fremanezumab quarterly and monthly at 4 months compared to patients who received placebo (***Table 98***). This trial[91] reported an MD greater than the MIC of 4.5 points.

Table 98 MIDAS, fremanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
FOCUS[91]*	Low	4 months	FRE quarterly	276	-19.7 (SE 3.3)	MD -12.7 (95% CI: -19.5 to -6.0), p=0.0002
			FRE monthly	283	-24.7 (SE 3.2)	MD -17.7 (95% CI: -24.5 to -11.0), p<0.0001
			Placebo	279	-7.0 (SE 3.2)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Episodic and chronic migraine patients with ≥2 prior treatment failures

One RCT reported MIDAS scores among a subgroup of patients who had both episodic and chronic migraine with 2, 3 or 4 prior treatment failures.[116] This RCT reported an MD greater than the MIC of 4.5 points.[116] The trial reported:

- significant improvements in MIDAS scores among patients with 2 or 3 prior treatment failures randomised to fremanezumab monthly compared to placebo at 4 months, but no reported differences for patients randomised to fremanezumab quarterly (***Table 99***)
- significant improvements in MIDAS scores among patients with 4 prior treatment failures randomised to fremanezumab quarterly or monthly compared to placebo at 4 months (***Table 99***).

Table 99 MIDAS, fremanezumab episodic and chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
FOCUS[116]*	Low	4 months 2 Tx failures	FRE quarterly	140	-14.7 (SD 4.15)	MD -8.7 (95% CI: -17.47, 0.15), p=0.054
			FRE monthly	133	-21.5 (SD 4.11)	MD -15.5 (95% CI: -24.47, -6.46), p<0.001
			Placebo	141	-6.1 (SD 4.10)	NA
		4 months 3 Tx failures	FRE quarterly	85	-18.9 (SD 5.69)	MD -9.8 (95% CI: -22.68, 3.08), p=0.14
			FRE monthly	98	-25.3 (SD 5.56)	MD -16.2 (95% CI: -28.51, -3.90), p=0.010
			Placebo	82	-9.1 (SD 5.34)	NA
		4 months 4 Tx failures	FRE quarterly	49	-25.0 (SD 10.43)	-31.7 (95% CI: -54.07, -9.37), p=0.006
			FRE monthly	50	-23.2 (SD 9.12)	-29.9 (95% CI: -51.12, -8.70), p=0.006
			Placebo	54	6.7 (SD 10.59)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error, **Tx**= treatment.
Notes
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for chronic migraine, or for subgroups of episodic or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

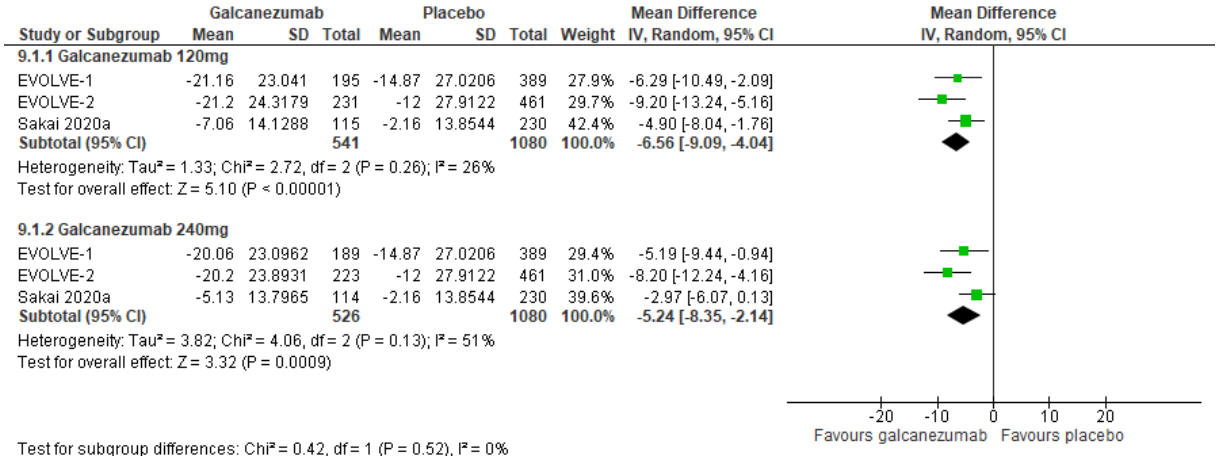
7.2.3.10.4 Galcanezumab

Episodic migraine

Four RCTs reported MIDAS scores among patients with episodic migraine, all at low RoB.[92-94,98] Three of the RCTs were suitable for combining in a meta-analysis, where there were significant improvements in MIDAS score among patients randomised to galcanezumab 120 mg and 240 mg compared to placebo

(***Figure 24***).[92-94] When combined in a meta-analysis, the 4 RCTs[92-94,98] reported an MD greater than the MIC of 4.5 points. One additional trial reported significant improvements in MIDAS score among patients randomised to galcanezumab 120 mg at 3 months (***Table 100***).[98] This RCT reported an MD greater than the MIC of 4.5 points.[98]

Figure 24 MIDAS, galcanezumab in episodic migraine patients receiving 120 mg and 240 mg



Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 100 MIDAS, galcanezumab in episodic migraine patients

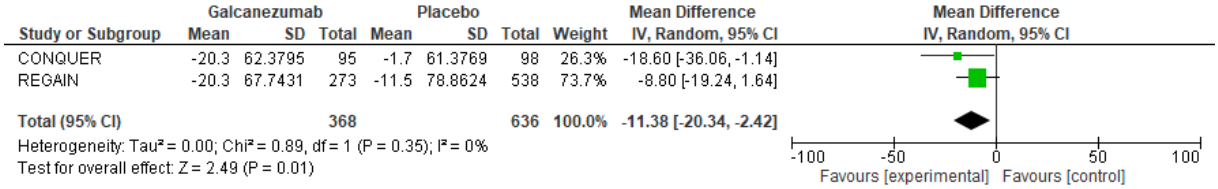
Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
CONQUER[98]	Low	3 months	GAL 120 mg	137	-19.0 (SE 3.6)	MD -16.4 (95% CI: -24.9 to -7.9), p=0.0002
			Placebo	132	-2.6 (SE 3.7)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine

Two trials reported MIDAS scores among patients with chronic migraine; both were at low RoB.[50,98] The RCTs were suitable for combining in a meta-analysis, where there were significant improvements in MIDAS score among patients randomised to galcanezumab 120 mg compared to placebo (***Figure 25***). When combined in a meta-analysis, the two RCTs reported an MD greater than the MIC of 4.5 points. [50,98] One study also reported data for galcanezumab 240 mg, where there were no significant improvements in the MIDAS score compared to placebo (***Table 101***).[50] This RCT reported an MD greater than the MIC of 4.5 points.[50]

Figure 25 MIDAS, galcanezumab in chronic migraine patients receiving 120 mg



Abbreviations
CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

Table 101 MIDAS, galcanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
CONQUER[98]	Low	3 months	GAL 120 mg	95	-20.3 (SE 6.4)	MD -18.6 (95% CI: -33.4 to -3.8), p=0.0142
			Placebo	98	-1.7 (SE 6.2)	
REGAIN[50]	Low	3 months	GAL 120 mg	273	-20.3 (SE 4.1)	MD -8.7 (95% CI: -16.4, -1.1), p=0.025
			GAL 240 mg	274	-17.0 (SE 4.1)	MD -5.5 (95% CI: -13.1, 2.1), p= 0.157
			Placebo	538	-11.5 (SE 3.4)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Episodic and chronic migraine

One RCT reported data for a population with both episodic and chronic migraine patients; it was at high RoB.[97] Patients were randomised to galcanezumab 120 mg or 240 mg and no significant differences were reported between groups (***Table 102***).

Table 102 MIDAS, galcanezumab in episodic and chronic patients (combined)

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
CGAJ[97]*	High	12 months	GAL 120 mg	124	-33.6 (SE 2.1)	MD 0.9 (95% CI: -4.7 to 6.5), p=0.76
			GAL 240 mg	130	-32.7 (SE 2.0)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups GAL 120 mg and GAL 240 mg. In the GAL 120 mg group, 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

Episodic migraine patients with ≥2 prior treatment failures

One RCT reported MIDAS scores for a subgroup of patients with ≥2 prior treatment failures who had episodic migraine.[124] There were significant improvements in MIDAS score among patients randomised to galcanezumab 120 mg compared to placebo at 3 months (***Table 103***). This RCT reported an MD greater than the MIC of 4.5 points.[124]

Table 103 MIDAS, galcanezumab episodic and chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between treatments
CONQUER[124]	Low	3 months	GAL 120 mg	55	-18.2 (SE 5.2)	MD -10.2 (95% CI: -12.32, -8.08), p<0.0001
			Placebo	43	-8.0 (SE 5.4)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine patients with ≥2 prior treatment failures

One RCT reported MIDAS scores for a subgroup of patients with ≥2 prior treatment failures who had chronic migraine.[124] There were significant improvements in MIDAS score among patients randomised to galcanezumab 120 mg compared to placebo at 3 months (***Table 104***). This RCT reported an MD greater than the MIC of 4.5 points.[124]

Table 104 MIDAS, galcanezumab episodic and chronic patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between treatments
CONQUER[124]	Low	3 months	GAL 120 mg	40	-31.0 (SE 11.8)	MD -39.93 (95% CI: -44.74, -35.06), p<0.0001
			Placebo	42	8.9 (SE 10.5)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.3.11 EuroQol 5 Dimension – 5 Levels (EQ-5D-5L)

The EQ-5D-5L is a patient-reported outcome designed to measure a patient's wellbeing. It comprises 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems), from which a single summary index (from 0 to 1)

can be calculated. The VAS is scored separately and ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

7.2.3.11.1 Erenumab

Episodic migraine

One RCT reported EQ-5D-5L data among patients with episodic migraine; it was assessed to be at high RoB.[76] The trial reported significant improvements in EQ-5D-5L in patients who received erenumab 70 mg and erenumab 140 mg compared to placebo at 1 month and 2 months. At 3 months, significant improvements were only reported for those randomised to erenumab 140 mg when compared to placebo (***Table 105***).

Table 105 EQ-5D, erenumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	EQ-5D type	Intervention and dose	n	Mean change in EQ-5D	Difference between interventions
Episodic migraine							
EMPOwER [76]	High	1 month	EQ-5D-5L	ERU 70 mg	329	4.98 (SE 0.75)	MD 3.01 (95% CI: 0.97, 5.04), p=0.004
				ERU 140 mg	219	6.31 (SE 0.91)	MD 4.34 (95% CI: 2.06, 6.61), p<0.001
				Placebo	330	1.97 (SE 0.74)	NA
		2 months		ERU 70 mg	329	6.32 (SE 0.74)	MD 2.43 (95% CI: 0.43, 4.44), p=0.018
				ERU 140 mg	219	7.55 (SE 0.89)	MD 3.66 (95% CI: 1.43, 5.89), p=0.001
				Placebo	330	3.89 (SE 0.73)	NA
		3 months		ERU 70 mg	329	7.08 (SE 0.79)	MD 1.86 (95% CI: −0.28, 4.00), p=0.088
				ERU 140 mg	219	8.13 (SE 0.96)	MD 2.91 (95% CI: 0.52, 5.29), p=0.017
				Placebo	330	5.22 (SE 0.78)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **EQ-5D** = EuroQol 5-dimension questionnaire, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

7.2.3.11.2 Fremanezumab

Episodic and chronic migraine

One RCT reported EQ-5D data among patients with episodic and chronic migraine; it was assessed to be at low RoB.[91] The trial reported significant improvements in EQ-5D-5L in patients who received fremanezumab monthly and fremanezumab quarterly at 4 months compared to placebo (***Table 106***).

Table 106 EQ-5D, fremanezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	EQ-5D type	Intervention and dose	n	Mean change in EQ-5D	Difference between interventions
Episodic and chronic migraine							
FOCUS [91]	Low	4 months	EQ-5D	FRE quarterly	276	4.7 (SE 1.4)	3.0 (95% CI: 0.1, 5.9), p=0.0426
				FRE monthly	283	7.2 (SE 1.4)	5.6 (95% CI: 2.7, 8.5), p=0.0002
				Placebo	278	1.6 (SE 1.4)	NA

Abbreviations
CI = confidence interval, **EQ-5D** = EuroQol 5-dimension questionnaire, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error.

Chronic migraine

One RCT reported EQ-5D-5L data among patients with chronic migraine; it was assessed to be at low RoB.[114] The trial reported significant improvements in EQ-5D-5L in patients who received fremanezumab 225 mg and fremanezumab 675 mg at 16 weeks compared to placebo (***Table 107***).

Table 107 EQ-5D, fremanezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	EQ-5D type	Intervention and dose	n	Mean change in EQ-5D	Difference between interventions
Chronic migraine							
HALO CM[114]	Low	16 weeks	EQ-5D-5L	FRE 225 mg	375	4.8 (SE NR)	2.6 (SE 1.18), p=0.0291
				FRE 675 mg	375	4.6 (SE NR)	2.4 (SE 1.18), p=0.0402
				Placebo	371	2.2 (SE NR)	NA

Abbreviations
CI = confidence interval, **EQ-5D** = EuroQol 5-dimension questionnaire, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

7.2.3.12 SF-36 Health Survey (SF-36)

The SF-36 is a health survey containing 36 questions, comprising 8 scaled scores to measure QoL over the previous 4 weeks. The 8 sections measured are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

7.2.3.12.1 Erenumab

Episodic and chronic migraine

One RCT assessed to be at low RoB reported SF-36 data among patients with episodic and chronic migraine randomised to erenumab or topiramate.[80] Significant improvements in both physical and mental components of SF-36 were reported in patients randomised to erenumab 70 mg or 140 mg compared to topiramate at 4–6 months (***Table 108***).

Table 108 SF-36, erenumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	SF-36 domain	Intervention and dose	n	Mean change in SF-36	Difference between interventions
Episodic and chronic migraine							
HER-MES[80]*	Low	4–6 months	Physical component	ERU 70 or 140 mg	378	5.5 (SE 0.4)	1.9 (95% CI: 1.0, 2.8), p<0.001
				Placebo	374	3.6 (SE 0.4)	NA
			Mental component	ERU 70 or 140 mg	378	1.0 (SE 0.5)	2.2 (95% CI: 1.0, 3.3), p<0.001
				Placebo	374	-1.2 (SE 0.5)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RoB** = risk of bias, **SE** = standard error, **SF-36** = 36-Item Short Form Health Survey.
Notes
* In HER-MES, the following number of patients were included: For Erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%) Chronic (≥15 MMDs) = 42 (10.8%).

7.2.3.12.2 Eptinezumab

Episodic and chronic migraine

One RCT assessed to be at high RoB reported SF-36 data among patients with episodic and chronic migraine.[107,108] The trial reported mean change in both physical and mental components of SF-36 at 6 months, but no statistical analyses were undertaken comparing eptinezumab 100 mg or eptinezumab 300 mg with placebo. (***Table 109***).

Table 109 SF-36, eptinezumab in episodic and chronic migraine patients

Trial name	RoB	Timepoint of assessment	SF-36 domain	Intervention and dose	n	Mean change in SF-36	Difference between interventions
Episodic and chronic migraine							
PROMISE-1[107 108]	High	6 months	Physical component	EPT 100 mg	221	2.7 (SD 6.84)	NR
				EPT 300 mg	222	3.2 (SD 6.02)	NR
				Placebo	222	1.3 (SD 6.42)	NA
			Mental component	EPT 100 mg	221	0.5 (SD 8.89)	NR
				EPT 300 mg	222	1.4 (SD 7.86)	NR
				Placebo	222	0.6 (SD 7.63)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error, **SF-36** = 36-Item Short Form Health Survey.

7.2.3.13 Migraine/headache pain intensity

7.2.3.13.1 Erenumab

Episodic migraine

One RCT reporting migraine pain intensity among episodic migraine patients was at low RoB.[78] Patients were randomised to erenumab 70 mg or placebo and no significant differences were reported between groups (***Table 110***).

Table 110 Migraine pain intensity, erenumab in episodic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Mean change in migraine pain intensity	Difference between interventions
Sun et al 2016[78]	Low	12 weeks	ERU 70 mg	101	-0.1 (SE 0.04)	MD 0.1 (95% CI: -0.04, 0.2), p=0.2
			Placebo	153	-0.2 (SE 0.04)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **RoB** = risk of bias, **SE** = standard error.

No RCTs were identified that reported data for chronic migraine, episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.3.13.2 Eptinezumab

No studies were identified that reported migraine pain intensity in patients randomised to eptinezumab.

7.2.3.13.3 Fremanezumab

No studies were identified that reported migraine pain intensity in patients randomised to fremanezumab.

7.2.3.13.4 Galcanezumab

No studies were identified that reported migraine pain intensity in patients randomised to galcanezumab.

7.2.3.14 Treatment adherence

No trials were identified that reported treatment adherence for any CGRP antagonist.

7.2.4 Findings: safety

In this section, results are presented by drug type, then by population type. The RoB was assessed using the Cochrane RoB 2.0 tool. Scores shown are the overall score assigned to each study. Further details about RoB are reported in ***Section 7.2.2.3***. The following points apply to data reported in the safety section:

- Where a single timepoint is reported (e.g. 3 months) this indicates that the outcome was recorded at this timepoint only. Where timepoints for outcomes are reported in ranges (e.g. 1–12 weeks) this indicates that the outcome was derived from averaging the scores or counts for the outcomes over each week or month.
- Blue text reported in data tables indicates comparisons calculated by the Royal Australasian College of Surgeons (RACS). These analyses were added to provide a complete data set.
- One trial reporting galcanezumab 150 mg was included and assumed to be equivalent to galcanezumab 120 mg (reported in the text as such).[96]
- The GRADE summary of findings table for SAEs appears in ***Section 7.2.5*** (***Table 149***).
- Data extraction tables for all effectiveness and safety outcomes appear in ***Appendix G*** (***Table A22*** to ***Table A76***).

7.2.4.1 Summary of findings – safety

Adverse events were not well reported in the included studies for all drug types. Where reported, most trials showed no differences in the number of AEs, TRAEs, SAEs or AEs leading to discontinuation compared to placebo. No studies reported AEs upon discontinuation (rebound effect) or mortality. There was more evidence for patients with episodic migraine than for chronic migraine and a greater number of trials conducted for erenumab, fremanezumab and galcanezumab compared to eptinezumab. Subgroup analyses of patients with more than 2 prior treatment failures were reported for studies of

erenumab and fremanezumab. While almost all trials of CGRP antagonists reported no differences in any type of AE, the evidence was strongest for erenumab, followed by fremanezumab and galcanezumab. A detailed summary of serious adverse events is reported in ***Section 7.2.5***.

7.2.4.2 Mortality

No trials were identified that reported mortality for any CGRP antagonist.

7.2.4.3 Adverse events (AEs)

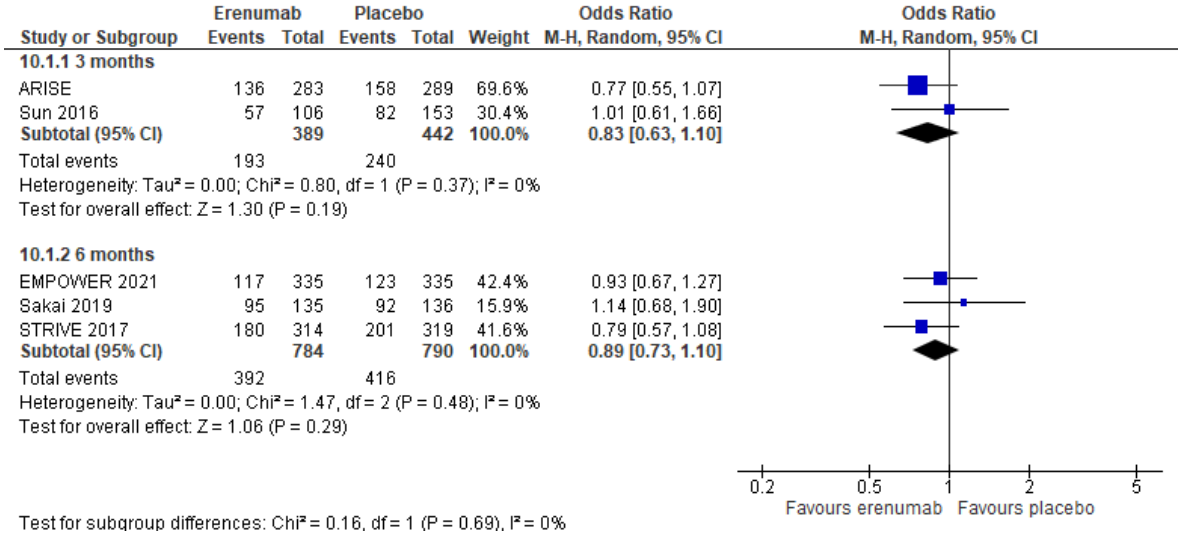
7.2.4.3.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting AEs for erenumab 70 mg compared to placebo were available in 5 RCTs: 4 at low RoB[48,77,78,99] and one at high RoB.[76] All RCTs were suitable for combining in a meta-analysis. There were no significant differences in the number of AEs reported between erenumab 70 mg and placebo at 3 months or 6 months (***Figure 26***).[48,75,76,78] There was no heterogeneity identified at either timepoint. Sensitivity analyses excluding the single RCT at high RoB did not alter results (***Appendix H, Figure A11***).

Figure 26 AEs, erenumab in episodic migraine patients receiving 70 mg



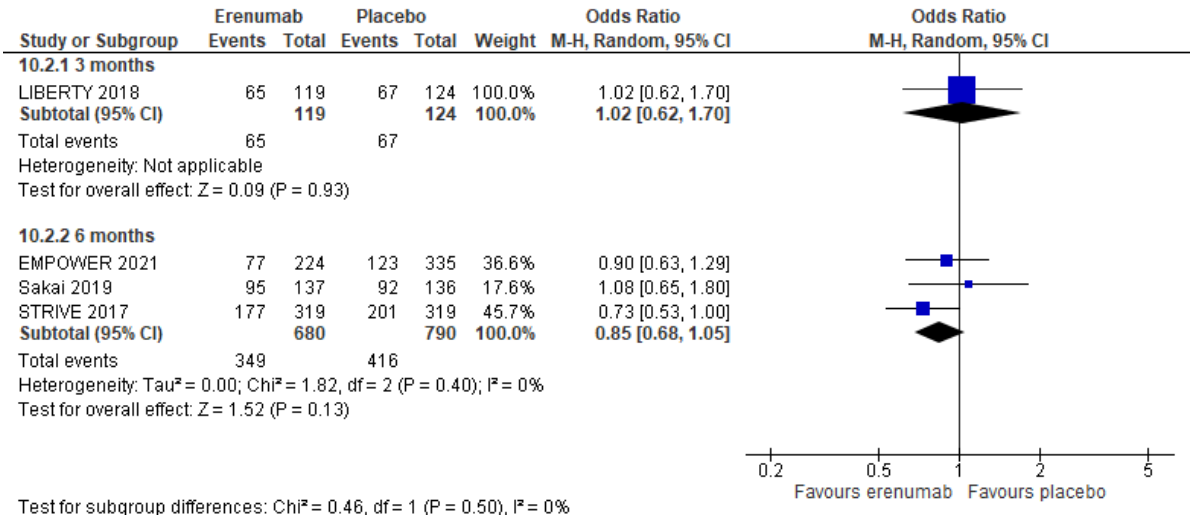
Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Erenumab 140 mg

Data reporting AEs for erenumab 140 mg compared to placebo were available in 4 RCTs: 3 at low RoB[48,49,77] and 1 at high RoB.[48,49,76,77] All RCTs were suitable for combining in a meta-analysis. There

were no significant differences in the number of AEs reported between erenumab 140 mg and placebo at 3 months or 6 months (***Figure 27***). There was no heterogeneity identified at any timepoint. Sensitivity analysis did not alter the results (***Appendix H, Figure A12***).

Figure 27 AEs, erenumab in episodic migraine patients receiving 140 mg



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine who were randomised to erenumab or placebo.[79] There were no significant differences in AEs between erenumab 70 mg or 140 mg and placebo at 3 months (***Table 111***).

Table 111 AEs, erenumab chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Tepper et al 2017[79]	Low	3 months	ERU 70 mg	190	83 (44)	OR 1.21 (95% CI: 0.83, 1.76), p=0.31
			ERU 140 mg	188	88 (47)	OR 1.38 (95% CI: 0.95, 2.00), p=0.09
			Placebo	282	110 (39)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Subgroup of patients with ≥2 prior treatment failures: episodic migraine

One RCT assessed to be at low RoB reported data among episodic migraine patients who had failed ≥2 prior preventative treatments.[103] There were no significant differences in AEs between erenumab 70 mg and placebo at 3 months, while patients randomised to erenumab 140 mg reported significantly fewer AEs than placebo patients (***Table 112***).

Table 112 AEs, erenumab episodic migraine patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	92	39 (42.4)	OR 0.94 (95% CI: 0.55, 1.59), p=0.81
			ERU 140 mg	92	53 (57.6)	OR 1.73 (95% CI: 1.02, 2.94), p=0.04
			Placebo	141	62 (44.0)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Subgroup of patients with ≥2 prior treatment failures: chronic migraine

One RCT assessed to be at low RoB reported data among chronic migraine patients who had failed 2 or more prior preventative treatments.[48] There were no significant differences in AEs between erenumab 70 mg or 140 mg and placebo at 6 months (***Table 113***).

Table 113 AEs, erenumab chronic migraine patients with ≥2 prior treatment failures

Trial name	RoB	Timepoint of assessment	Intervention	n	Number (%) of adverse events	Difference between groups
STRIVE[48]	Low	6 months	ERU 70 mg	49	33 (67.3)	OR 0.87 (95% CI: 0.38, 2.00), p=0.74
			ERU 140 mg	58	35 (60.3)	OR 0.64 (95% CI: 0.29, 1.41), p=0.27
			Placebo	54	38 (70.4)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.4.3.2 Eptinezumab

No studies were identified that reported AEs in patients randomised to eptinezumab.

7.2.4.3.3 Fremanezumab

Episodic migraine

One RCT assessed to be at high RoB reported data among patients with episodic migraine who were randomised to fremanezumab.[86] There were significantly fewer AEs among patients randomised to fremanezumab 225 mg and 675 mg at 3 months compared to placebo (***Table 114***).

Table 114 AEs, fremanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
HALO EM[86]	High	3 months	FRE 225 mg	290	192 (66.2)	OR 1.40 (95% CI: 1.0, 1.96), p=0.05
			FRE 675 mg	291	193 (66.3)	OR 1.41 (95% CI: 1.0, 1.97), p=0.05
			Placebo	293	171 (58.4)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine randomised to fremanezumab.[89] There were significantly fewer AEs among patients randomised to fremanezumab 225 mg at 3 months, but no differences between fremanezumab 675 mg and placebo (***Table 115***).

Table 115 AEs, fremanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
HALO CM[89]	Low	3 months	FRE 225 mg	379	270 (71)	OR 1.39 (95% CI: 1.03, 1.89), p=0.03
			FRE 675 mg	376	265 (70)	OR 1.34 (95% CI: 0.99, 1.82), p=0.06
			Placebo	375	240 (64)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Episodic and chronic migraine

One RCT assessed to be at low RoB reported data in both episodic and chronic migraine patients.[91] There were no significant differences in the number of AEs reported between fremanezumab quarterly or monthly at 3 months (***Table 116***).

Table 116 AEs, fremanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
FOCUS[91]	Low	3 months	FRE quarterly	276	151 (55)	OR 1.29 (95% CI: 0.92, 1.80), p=0.14
			FRE monthly	285	129 (45)	OR 0.88 (95% CI: 0.63, 1.23), p=0.46
			Placebo	277	134 (48)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Subgroup of patients with ≥2 prior treatment failures: episodic and chronic migraine

One RCT reported data (in both episodic and chronic migraine patients) for subgroups of patients with 2, 3 and 4 prior treatment failures.[116] There were no significant differences in the number of AEs reported between fremanezumab quarterly or monthly and placebo at 3 months in any subgroup (***Table 117***).

Table 117 AEs, fremanezumab in patients with ≥2 prior treatment failures: episodic and chronic migraine

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
FOCUS[116]*	Low	3 months, patients with 2 prior Tx failures	FRE quarterly	140	67 (48)	OR 1.20 (95% CI: 0.75, 1.93), p=0.44
			FRE monthly	134	58 (43)	OR 1.0 (95% CI: 0.62, 1.61), p=1.0
			Placebo	141	61 (43)	NA
		3 months, patients with 3 prior Tx failures	FRE quarterly	85	51 (60)	OR 1.62 (95% CI: 0.87, 2.99), p=0.13
			FRE monthly	99	47 (47)	OR 0.97 (95% CI: 0.54, 1.75), p=0.93
			Placebo	81	39 (48)	NA
		3 months, patients with 4 prior Tx failures	FRE quarterly	49	31 (63)	OR 1.01 (95% CI: 0.45, 2.26), p=0.97
			FRE monthly	50	23 (46)	OR 0.50 (95% CI: 0.23, 1.10), p=0.08
			Placebo	54	34 (63)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **Tx** = treatment.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for chronic migraine, or for subgroups of episodic or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.4.3.4 Galcanezumab

Episodic migraine

One RCT assessed to be at low RoB reported data among patients with episodic migraine randomised to galcanezumab.[96] There were no significant differences in the number of AEs reported between galcanezumab 150 mg and placebo at 6 months (***Table 118***).

Table 118 AEs, galcanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Dodick et al 2014a[96]	Low	6 months	GAL 150 mg	107	77 (72)	OR 1.25 (95% CI: 0.70, 2.23), p=0.45
			Placebo	110	74 (67)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for chronic migraine, episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.4.4 Treatment-related adverse events (TRAEs)

7.2.4.4.1 Erenumab

Episodic migraine

One RCT assessed to be at high RoB reported data in episodic migraine patients.[76] There were no significant differences in the number of TRAEs reported between erenumab 70 mg or 140 mg and placebo at 6 months (***Table 119***).

Table 119 TRAEs, erenumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
EMPOwER[76]	High	6 months	ERU 70 mg	335	38 (11.3)	OR 1.21 (95% CI: 0.74. 1.99), p=0.45
			ERU 140 mg	224	24 (10.7)	OR 1.14 (95% CI: 0.65, 1.99), p=0.65
			Placebo	335	32 (9.6)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue indicates RACS calculated comparisons.

Episodic and chronic migraine

One RCT assessed to be at low RoB reported data in both episodic and chronic migraine patients.[80] Patients randomised to erenumab 70 mg or 140 mg had significantly fewer TRAEs compared to patients randomised to topiramate 25–100 mg at 24 weeks (***Table 120***).

Table 120 TRAEs, erenumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
HER-MES[80]*	Low	24 weeks	ERU 70 or 140 mg	388	215 (55.4)	OR 0.29 (95% CI: 0.21, 0.40), p<0.00001
			Topiramate 25-100 mg	388	315 (81.2)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.
* In HER-MES, the following number of patients were included: for erenumab, 4–7 MMDs = 94 (24.2%), episodic = 248 (63.9%), chronic = 43 (11.1%); for topiramate, 4–7 MMDs = 92 (23.7%); episodic (8–14 MMDs) = 254 (65.5%); chronic (≥15 MMDs) = 42 (10.8%).

No RCTs were identified that reported data for chronic migraine or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.4.4.2 Eptinezumab

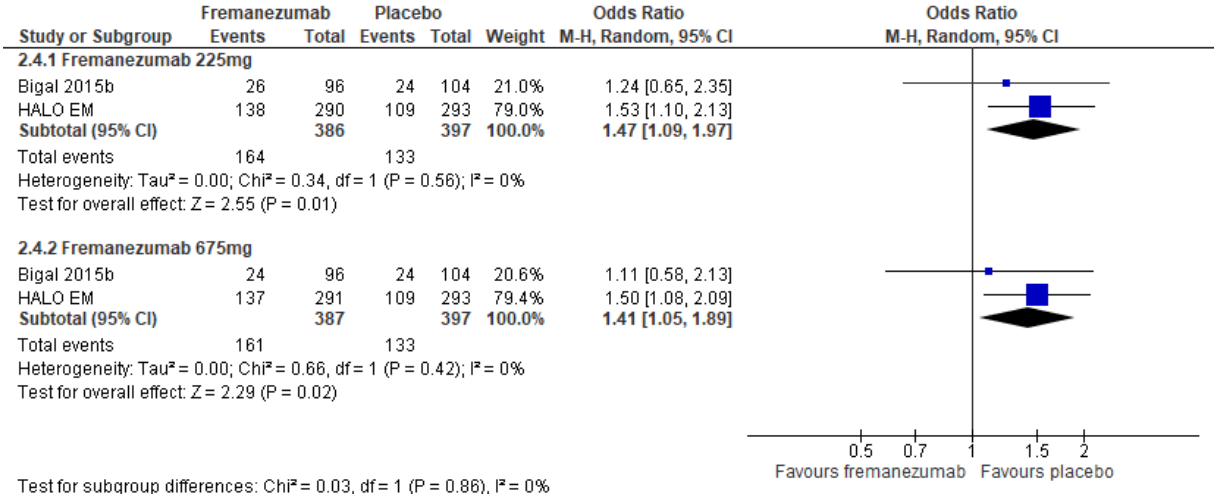
There were no studies reporting TRAEs among patients receiving eptinezumab.

7.2.4.4.3 Fremanezumab

Episodic migraine

Data reporting TRAEs for fremanezumab 140 mg compared to placebo were available in 2 RCTs.[85,86] Both were suitable for combining in a meta-analysis, where TRAEs were significantly more frequent in patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 3 months (***Figure 28***). The larger trial contributing most of the weight to the analysis was at high RoB, so results for this outcome should be interpreted with caution. Sensitivity analyses excluding this trial (***Appendix H, Figure A13***) showed no differences between fremanezumab and placebo. There was no heterogeneity identified.

Figure 28 TRAEs, fremanezumab in episodic migraine patients



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Chronic migraine

One RCT assessed to be at low RoB reported data in chronic migraine patients.[88] There were no significant differences in the number of TRAEs reported between fremanezumab 225/675 mg and placebo at 3 months (***Table 121***).

Table 121 TRAEs, fremanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Bigal et al 2015a[88]	Low	3 months	FRE 675/225 mg*	88	25 (29)	OR 1.96 (95% CI: 0.95, 4.03), p=0.07
		3 months	Placebo	89	15 (17)	

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.

Episodic and chronic migraine

One RCT assessed to be at low RoB reported data in episodic and chronic migraine patients.[91] There were no significant differences in the number of TRAEs reported between fremanezumab 225/675 mg and placebo at 3 months (***Table 122***).

Table 122 TRAEs, fremanezumab in episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
FOCUS[91]*	Low	3 months	FRE quarterly	276	57 (21)	OR 1.05 (95% CI: 0.69, 1.59), p=0.82
		3 months	FRE monthly	285	55 (19)	OR 0.97 (95% CI: 0.64, 1.46), p=0.87
		3 months	Placebo	277	55 (20)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.4.4.4 Galcanezumab

Episodic migraine

One RCT assessed to be at low RoB reported data in episodic migraine patients.[92] There were no significant differences in the number of TRAEs reported between galcanezumab 120 mg or 240 mg and placebo at 6 months (***Table 123***).

Table 123 TRAEs, galcanezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
EVOLVE-1[92]	Low	6 months	GAL 120 mg	206	135 (65.5)	OR 1.25 (95% CI: 0.88, 1.76), p=0.21
			GAL 240 mg	220	149 (67.7)	OR 1.37 (955CI: 0.98, 1.94), p=0.07
			Placebo	432	261 (60.4)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for chronic migraine, episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.4.5 Serious adverse events (SAEs)

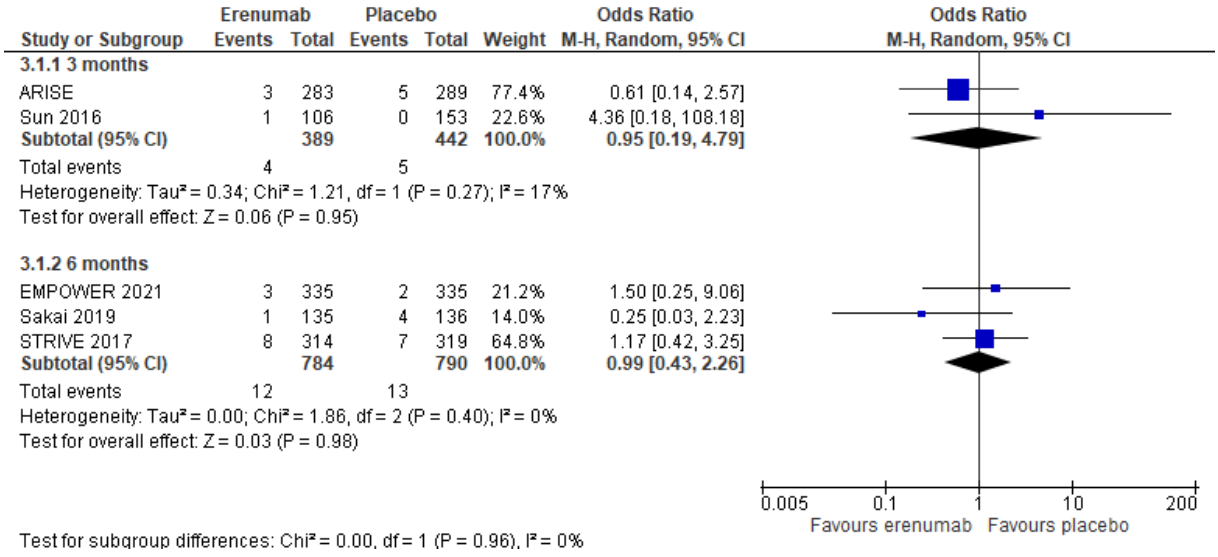
7.2.4.5.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting SAEs for erenumab 70 mg compared to placebo were available in 5 RCTs; 4 at low RoB[48,77,78,99] and one at high RoB.[76] All RCTs were suitable for combining in a meta-analysis, where there were no significant differences in the number of SAEs reported between erenumab 70 mg and placebo at 3 months or 6 months (***Figure 29***).[48,75,76,78] There was no heterogeneity identified at either timepoint. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A14***).

Figure 29 SAEs, erenumab in episodic migraine patients receiving 70 mg

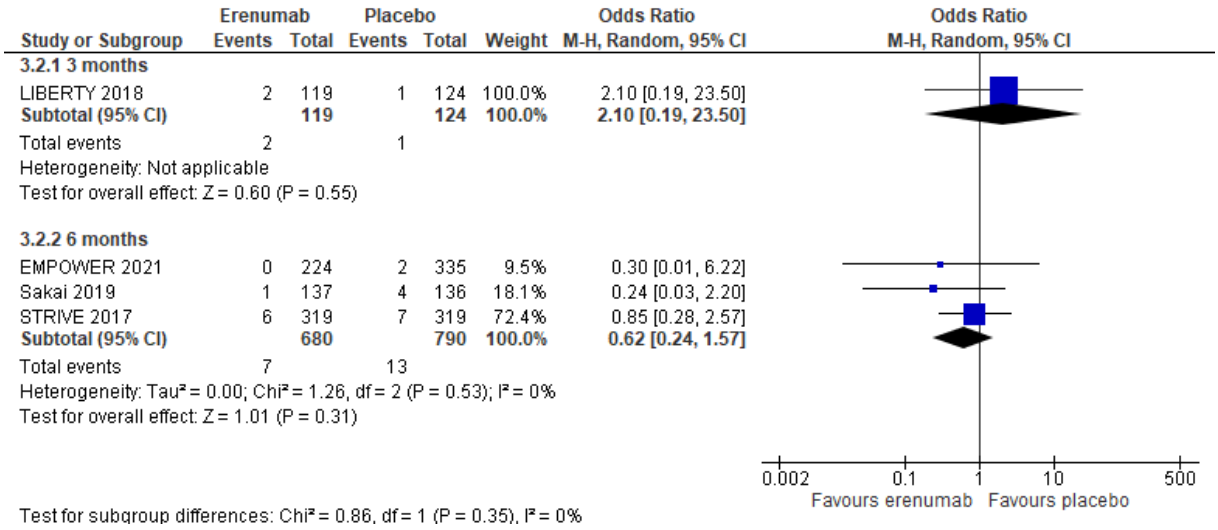


Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Erenumab 140 mg

Data reporting SAEs for erenumab 140 mg compared to placebo were available in 4 RCTs; 3 at low RoB[48,49,77] and one at high RoB.[48,49,76,77] All RCTs were suitable for combining in a meta-analysis, where there were no significant differences in the number of SAEs reported between erenumab 140 mg and placebo at 3 months or 6 months (***Figure 30***). Sensitivity analyses (***Appendix H, Figure A15***) did not alter the results. There was no heterogeneity identified at any timepoint.

Figure 30 SAEs, erenumab in episodic migraine patients receiving 140 mg



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine randomised to erenumab or placebo.[79] There were no differences in SAEs between erenumab 70 mg or 140 mg and placebo at 3 months (***Table 124***).

Table 124 SAEs, erenumab chronic patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Tepper et al 2017[79]	Low	3 months	ERU 70 mg	190	6 (3)	OR 1.28 (95% CI: 0.42, 3.87), p=0.66
			ERU 140 mg	188	2 (1)	OR 0.42 (95% CI: 0.09, 2.06), p=0.29
			Placebo	282	7 (2)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

Episodic and chronic migraine

Two RCTs reported SAEs for populations with both episodic and chronic migraine patients; both studies were at low RoB (***Table 125***). The trials were not suitable for combining in a meta-analysis because the comparators were different. There were no differences in SAEs between patients randomised to erenumab 70 mg or placebo at 6 months in one trial,[81] and no differences in the number of SAEs between patients randomised to erenumab 70 mg or 140 mg compared to topiramate at 24 weeks.[105]

Table 125 SAEs, erenumab in episodic and chronic patients (combined)

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Takeshima et al 2021[81]	Low	6 months	ERU 70 mg	130	2 (1.5)	OR 1.01 (95% CI: 0.14, 7.26), p=0.99
			Placebo	131	2 (1.5)	
HER-MES[105]*	Low	24 weeks	ERU 70 or 140 mg	388	10 (2.58)	OR 0.51 (95% CI: 0.24, 1.12), p=0.09
			Topiramate 25-100 mg	388	19 (4.90)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.
* In HER-MES, the following numbers of patients were included: for erenumab, 4–7 MMDs = 94 (24.2%), episodic = 248 (63.9%), chronic = 43 (11.1%); for topiramate, 4–7 MMDs = 92 (23.7%), episodic (8–14 MMDs) = 254 (65.5%), chronic (≥15 MMDs) = 42 (10.8%).

Subgroup of patients with ≥2 prior treatment failures: episodic migraine

One RCT assessed to be at low RoB reported data among a subgroup of patients with episodic migraine who had 2 or more prior treatment failures.[103] There were no differences in the number of SAEs between erenumab 70 mg or 140 mg and placebo at 3 months (***Table 126***).

Table 126 SAEs, erenumab episodic patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	92	3 (3.3)	OR 1.15 (95% CI: 0.25, 5.28), p=0.85
			ERU 140 mg	92	1 (1.1)	OR 0.38 (95% CI: 0.04, 3.42), p=0.39
			Placebo	141	4 (2.8)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

Subgroup of patients with ≥2 prior treatment failures: chronic migraine

One RCT assessed to be at low RoB reported data among a subgroup of patients with chronic migraine who had 2 or more prior treatment failures.[102] There were no differences in the number of SAEs between erenumab 70 mg or 140 mg and placebo at 6 months (***Table 127***).

Table 127 SAEs, erenumab chronic patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
STRIVE[102]	Low	6 months	ERU 70 mg	49	2 (4.1)	OR 5.74 (95% CI: 0.27, 122.50), p=0.26
			ERU 140 mg	58	3 (5.2)	OR 6.87 (95% CI: 0.35, 136.24), p=0.21
			Placebo	54	0 (0.0)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.4.5.2 Eptinezumab

Episodic migraine

One RCT assessed to be at high RoB reported SAEs at 56 weeks among patients with episodic migraine randomised to eptinezumab.[108] There were no differences in the number of SAEs among patients receiving eptinezumab 100 mg or 300 mg compared to placebo (***Table 128***).

Table 128 SAEs, eptinezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
PROMISE-1[108]	High	56 weeks	EPT 100 mg	223	4 (1.79)	OR 0.66 (95% CI: 0.18, 2.36), p=0.52
			EPT 300 mg	224	3 (1.34)	OR 0.49 (95% CI: 0.12, 1.98), p=0.32
			Placebo	222	6 (2.7)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

Two RCTs reported SAEs among patients with chronic migraine. One trial was assessed to have some methodological concerns[83] while the other was at low RoB.[84,109,110] There were no differences between patients randomised to eptinezumab 100 mg or 300 mg compared to placebo at 3 months[83] and across 1–32 weeks (***Table 129***).[84,109,110]

Table 129 SAEs, eptinezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Dodick et al 2019[83]	Some concerns	3 months	EPT 300 mg	121	7 (5.8)	OR 7.37 (95% CI: 0.89, 60.83), p=0.06
			EPT 100 mg	122	4 (3.3)	OR 4.07 (95% CI: 0.45, 36.93), p=0.21
			Placebo	121	1 (0.8)	NA
PROMISE-2[84,109,110]	Low	1–32 weeks	EPT 100 mg	356	3 (0.84)	OR 1.03 (95% CI: 0.21, 5.13), p=0.97
			EPT 300 mg	350	4 (1.14)	OR 1.40 (95% CI: 0.31, 6.30), p=0.66
			Placebo	366	3 (0.82)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

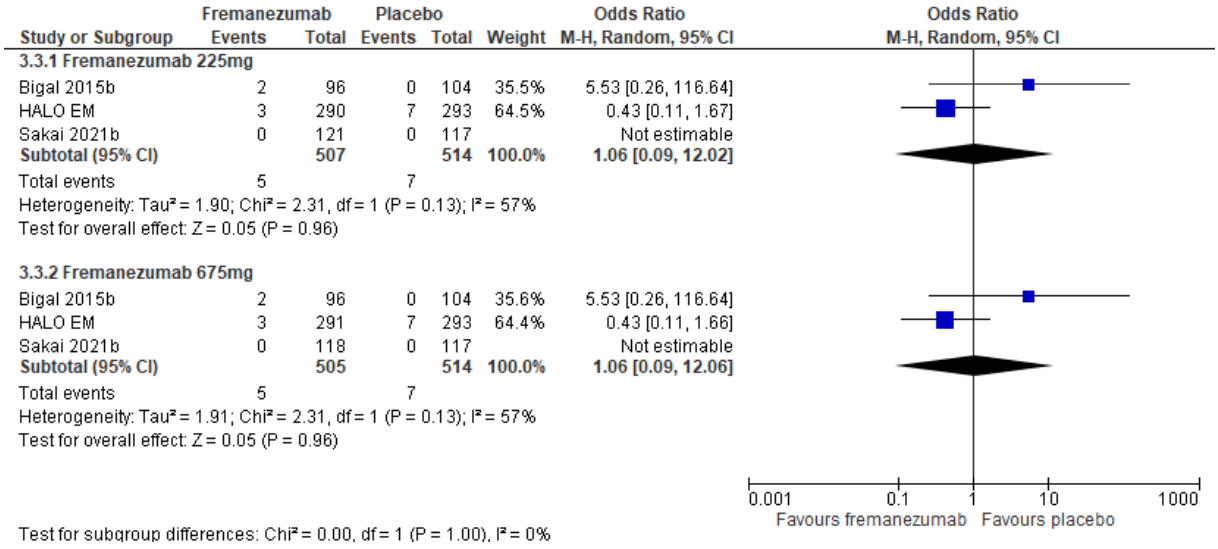
No RCTs were identified that reported data for episodic and chronic migraine combined, or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.4.5.3 Fremanezumab

Episodic migraine

Three RCTs reported SAEs among patients with episodic migraine: 2 were at low RoB[85,87] and 1 was at high RoB.[86] All of the RCTs were suitable for combining in a meta-analysis. There was no difference in the number of SAEs among patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 3 months (***Figure 31***). There was no heterogeneity identified. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A16***). One trial did not contribute to the outcomes subgrouped by fremanezumab dose (reported in ***Figure 31***) because there were no events in either the fremanezumab or placebo groups, therefore the odds ratio of the trial was not estimable.

Figure 31 SAEs fremanezumab in episodic migraine patients (3 months)

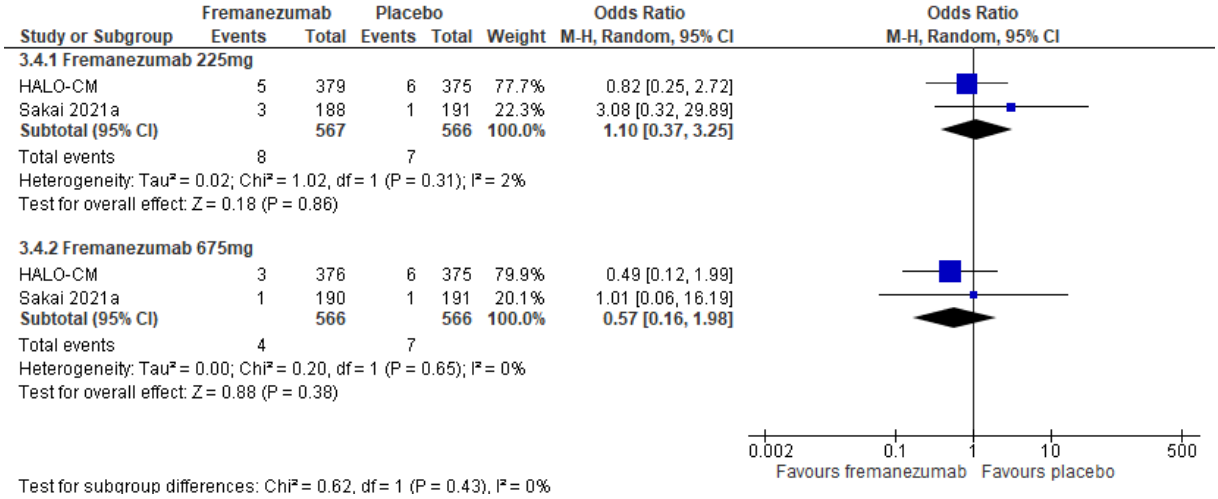


Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Chronic migraine

Three RCTs reported SAEs among patients with chronic migraine; all were at low RoB.[88-90] Two RCTs were suitable for combining in a meta-analysis, where there was no difference in the number of SAEs among patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 3 months (***Figure 32***). There was no heterogeneity identified. One additional RCT (reporting data for fremanezumab 225 mg and 675 mg patients combined) reported similar results with no differences in SAEs between fremanezumab and placebo (***Table 130***).

Figure 32 SAEs fremanezumab in chronic migraine patients (3 months)



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Table 130 SAEs, fremanezumab in chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Bigal et al 2015a[88]	Low	3 months	FRE 675/225 mg*	88	1 (1)	OR 1.01 (95% CI: 0.06, 16.43), p=0.99
			Placebo	89	1 (1)	

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.
* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.

Episodic and chronic migraine

One RCT assessed to be at low RoB reported data among patients with episodic and chronic migraine randomised to fremanezumab or placebo.[91] There were no differences in SAEs between fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 131***).

Table 131 SAEs, fremanezumab episodic and chronic

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
FOCUS[91]*	Low	3 months	FRE quarterly	276	2 (<1)	OR 0.50 (95% CI: 0.09, 2.74), p=0.42
			FRE monthly	285	4 (1)	OR 0.97 (95% CI: 0.24, 3.92), p=0.97
			Placebo	277	4 (1)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

Subgroup of patients with ≥2 prior treatment failures: episodic and chronic migraine

One RCT reported data (in both episodic and chronic migraine patients) for subgroups of patients with 2, 3 and 4 prior treatment failures.[116] There were no significant differences in the number of SAEs reported between fremanezumab quarterly or monthly and placebo at 3 months in any subgroup (***Table 132***).

Table 132 SAEs, fremanezumab episodic and chronic, plus subgroup

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
FOCUS[116]*	Low	3 months 2 Tx failures	FRE quarterly	140	1 (<1)	OR 0.25 (95% CI: 0.03, 2.23), p=0.21
			FRE monthly	134	2 (1)	OR 0.52 (95% CI: 0.09, 2.88), p=0.45
			Placebo	141	4 (3)	NA
		3 months 3 Tx failures	FRE quarterly	85	0	Not estimable
			FRE monthly	99	2 (2)	OR 4.18 (95% CI: 0.20, 88.30), p=0.36
			Placebo	81	0	NA
		3 months 4 Tx failures	FRE quarterly	49	1 (2)	OR 3.37 (95% CI: 0.13, 84.70), p=0.46
			FRE monthly	50	0	Not estimable
			Placebo	54	0	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events, **Tx** = treatment.
Notes
Blue text indicates RAC- calculated comparisons.
*In the FOCUS trial there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine, 169 (61%) had chronic migraine. In the FRE monthly group, 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) patients had episodic migraine while 167 (60%) had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic or chronic patients with ≥2 prior treatment failures among patients who received fremanezumab.

7.2.4.5.4 Galcanezumab

Episodic migraine

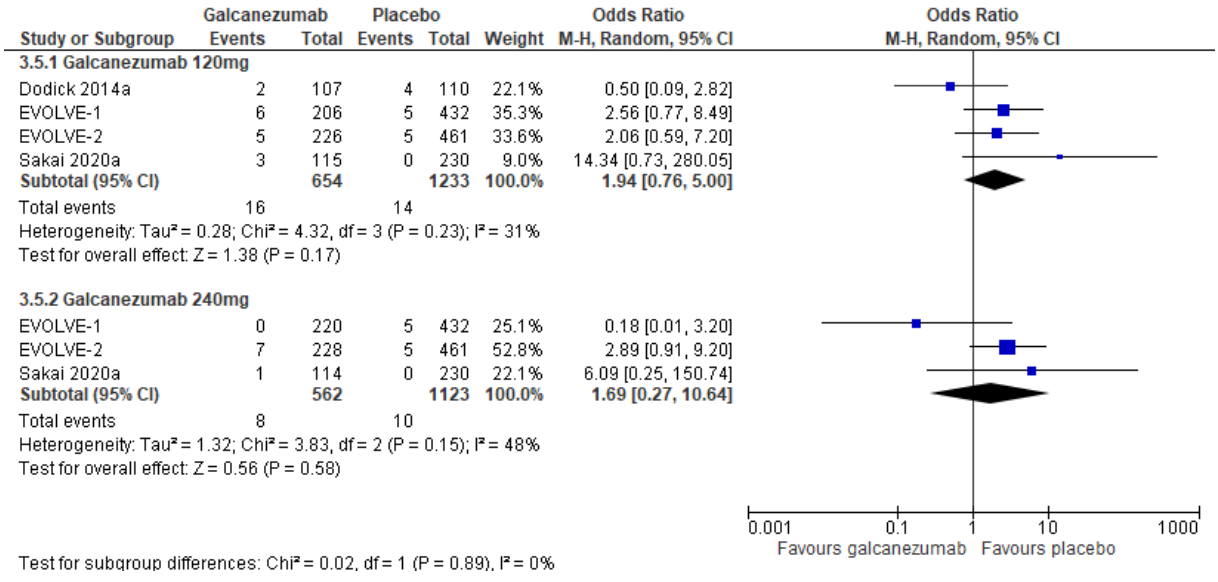
Galcanezumab 120 mg

Data reporting SAEs for galcanezumab 120 mg compared to placebo were available in 5 RCTs; all at low RoB.[92-96,120] Four RCTs were suitable for combining in a meta-analysis, where there were no differences in the number of SAEs between patients randomised to galcanezumab 120 mg or placebo at 6 months (***Figure 33***).[92-94,96] There was low heterogeneity identified. One additional RCT (reporting average SAEs across 1–12 weeks and 13–24 weeks) reported similar results with no significant differences between groups (***Table 133***).[95,120]

Galcanezumab 240 mg

Data reporting SAEs for galcanezumab 240 mg compared to placebo were reported in 3 RCTs; all at low RoB.[92-94] All RCTs were suitable for combining in a meta-analysis, where there were no differences in the number of SAEs between patients randomised to galcanezumab 240 mg or placebo at 6 months (***Figure 33***).[92-94,96] Moderate heterogeneity was identified.

Figure 33 SAEs galcanezumab in episodic migraine patients (6 months)



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

Table 133 SAEs, galcanezumab episodic patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Skljarevski et al 2018[95,120]	Low	1–12 weeks	GAL 120 mg	70	1 (1.43)	OR 5.94 (95% CI: 0.24, 147.6), p=0.28
			Placebo	137	0 (0)	
		12–24 weeks	GAL 120 mg	63	0 (0)	Not estimable
			Placebo	125	0 (0)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine randomised to galcanezumab or placebo.[50] There were no differences in the number of SAEs between galcanezumab 120 mg or 240 mg compared to placebo at 3 months (***Table 134***).

Table 134 SAEs, galcanezumab chronic patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
REGAIN[50]	Low	3 months	GAL 120 mg	273	1 (<1)	OR 0.51 (95% CI: 0.06, 4.58), p=0.55
			GAL 240 mg	282	5 (1.77)	OR 2.50 (95% CI: 0.67, 9.38), p=0.17
			Placebo	558	4 (<1)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic and episodic migraine

Two RCTs reported data among patients with episodic and chronic migraine randomised to galcanezumab or placebo; one was assessed to be at high RoB[97] and the other assessed to be at low RoB.[98] There were no differences in the number of SAEs between galcanezumab 120 mg compared to 240 mg at 12 months[97] or between galcanezumab 120 mg compared to placebo at 3 months (***Table 135***).[98]

Table 135 SAEs, galcanezumab episodic and chronic patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
CGAJ[97]*	High	12 months	GAL 120 mg	129	3 (2.3)	OR 0.46 (95% CI: 0.12, 1.80), p=0.26
			GAL 240 mg	141	7 (5.0)	
CONQUER[98]**	Low	3 months	GAL 120 mg	232	2 (1)	OR 0.99 (95% CI: 0.14, 7.10), p=0.99
			Placebo	230	2 (1)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **SAE** = serious adverse events.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.
** In the CONQUER trial there were 2 treatment groups: GAL 120 mg and placebo. In the GAL 120 mg group, 59% of patients had episodic migraine and 41% had chronic migraine. In the placebo group, 58% of patients had episodic migraine and 43% had chronic migraine.

No RCTs were identified that reported data for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.4.6 AEs leading to discontinuation

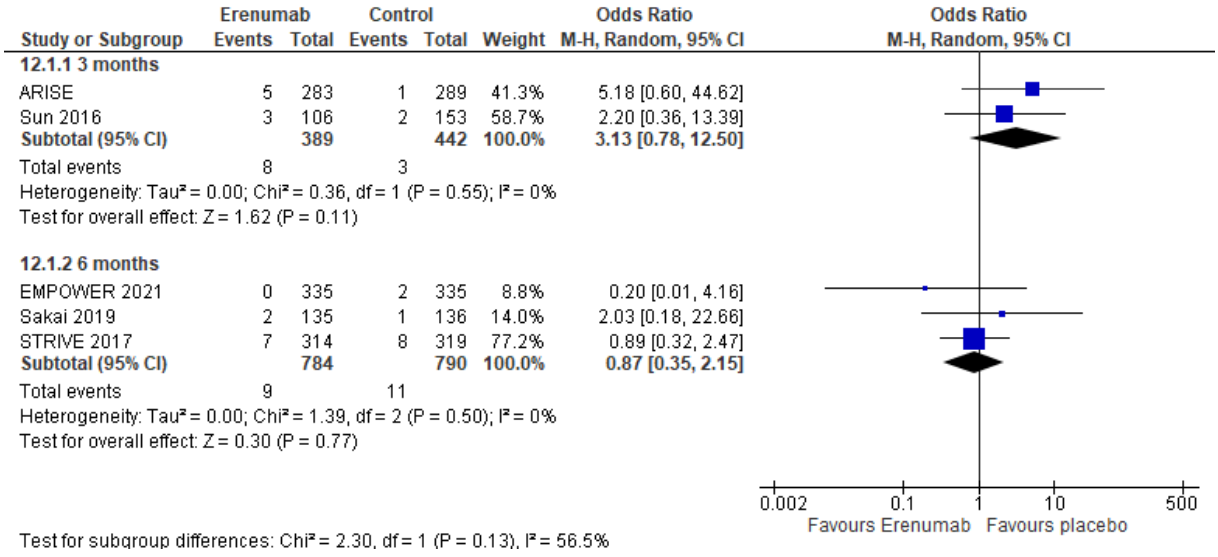
7.2.4.6.1 Erenumab

Episodic migraine

Erenumab 70 mg

Data reporting AEs leading to discontinuation for erenumab 70 mg compared to placebo were available in 5 RCTs; 4 at low RoB[48,77,78,99] and 1 at high RoB.[76] All RCTs were suitable for combining in a meta-analysis, where there were no significant differences in the number of AEs leading to discontinuation reported between erenumab 70 mg and placebo at 3 or 6 months (***Figure 34***).[48,75,76,78] There was no heterogeneity identified at either timepoint. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A17***).

Figure 34 AEs leading to discontinuation, erenumab in episodic migraine patients receiving 70 mg

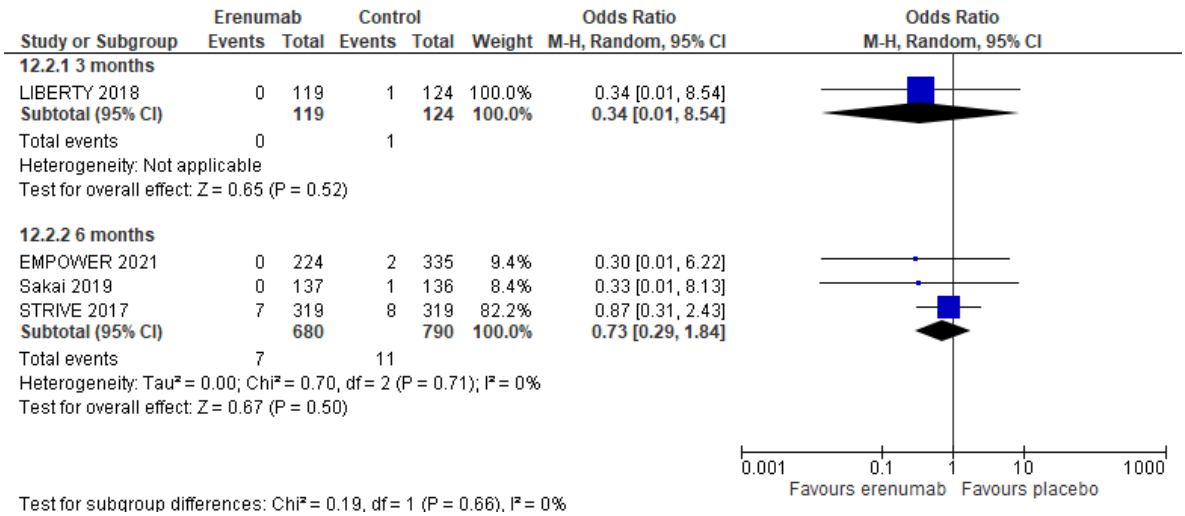


Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Erenumab 140 mg

Data reporting AEs leading to discontinuation for erenumab 140 mg compared to placebo were available in 4 RCTs; 3 at low RoB[48,49,77] and 1 at high RoB.[76] All RCTs were suitable for combining in a meta-analysis, where there were no significant differences in the number of AEs leading to discontinuation reported between erenumab 140 mg and placebo at 3 or 6 months (***Figure 35***). There was no heterogeneity identified. Sensitivity analyses excluding the single RCT at high RoB did not alter the results (***Appendix H, Figure A18***).

Figure 35 AEs leading to discontinuation, erenumab in episodic migraine patients receiving 140 mg



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Chronic migraine

One RCT assessed to be at low RoB reported data among patients with chronic migraine who were randomised to erenumab or placebo.[79] There were no significant differences in the number of AEs leading to discontinuation between erenumab 70 mg or 140 mg and placebo at 3 months (***Table 136***).

Table 136 AEs leading to discontinuation, erenumab chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
Tepper et al 2017[79]	Low	3 months	ERU 70 mg	190	0 (0)	OR 0.29 (95% CI: 0.01, 6.17), p=0.43
			ERU 140 mg	188	2 (1)	OR 1.51 (95% CI: 0.21, 10.78), p=0.68
			Placebo	282	2 (<1)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Episodic and chronic migraine

Two RCTs reported data for populations with both episodic and chronic migraine patients; both studies were at low RoB (***Table 137***).[80,81,106] The trials were not suitable for combining in a meta-analysis because the comparators were different. AEs leading to discontinuation were significantly less frequent among patients randomised to erenumab 70 mg or 140 mg compared to topiramate across a 4–6 month time period in one trial.[80] The second trial reported no differences in AEs leading to discontinuation between patients randomised to erenumab 70 mg compared to placebo across a 4– 6 month time period.[81,106]

Table 137 AEs leading to discontinuation, erenumab episodic and chronic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between treatments
HER-MES[80]*	Low	4–6 months	ERU 70 or 140 mg	388	41 (10.6)	OR 0.19 (95% CI: 0.13, 0.27) RR 0.27 (95% CI: 0.20, 0.37), p<0.001
			Topiramate 25–100 mg	388	151 (38.9)	
Takeshima et al 2021[81,106]**	Low	4–6 months	ERU 70 mg	130	0 (0)	Not estimable
			Placebo	131	0 (0)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **RR** = relative risk.
Notes
Blue text indicates RACS-calculated comparisons.
* In HER-MES, the following number of patients were included: for erenumab, 4–7 MMDs = 94 (24.2%), episodic = 248 (63.9%), chronic = 43 (11.1%); for topiramate, 4–7 MMDs = 92 (23.7%), episodic (8–14 MMDs) = 254 (65.5%), chronic (≥15 MMDs) = 42 (10.8%).
** Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.

Subgroup of patients with ≥2 prior treatment failures: episodic migraine

One RCT assessed to be at low RoB reported data among episodic migraine patients who had failed 2 or more prior preventative treatments.[102] There were no significant differences in the number of AEs leading to discontinuation between erenumab 70 mg or 140 mg at 6 months (***Table 138***).

Table 138 AEs leading to discontinuation, erenumab episodic migraine patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
STRIVE[102]	Low	6 months	ERU 70 mg	49	1 (2.0)	OR 3.37 (95% CI: 0.13, 84.70), p=0.46
			ERU 140 mg	58	4 (6.9)	OR 9.00 (95% CI: 0.47, 171.23), p=0.14
			Placebo	54	0 (0)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Subgroup of patients with ≥2 prior treatment failures: chronic migraine

One RCT assessed to be at low RoB reported data among chronic migraine patients who had failed 2 or more prior preventative treatments.[103] There were no significant differences in the number of AEs leading to discontinuation between erenumab 70 mg or 140 mg at 3 months (***Table 139***).

Table 139 AEs leading to discontinuation, erenumab chronic migraine patients with ≥2 prior treatment failures

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
Tepper et al 2017[103]	Low	3 months	ERU 70 mg	92	0 (0.0)	OR 0.51 (95% CI: 0.02, 12.56), p=0.68
			ERU 140 mg	92	0 (0.0)	OR 0.51 (95% CI: 0.02, 12.56), p=0.68
			Placebo	141	1 (0.7)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

No RCTs were identified that reported data for subgroups of episodic and chronic patients with ≥2 prior treatment failures among patients who received erenumab.

7.2.4.6.2 Eptinezumab

Episodic migraine

One RCT assessed to be at high RoB reported AEs leading to discontinuation across 1–12 weeks among patients with episodic migraine randomised to eptinezumab.[82] There were no significant differences in the number of AEs leading to discontinuation between eptinezumab 100 mg or 300 mg compared to placebo 1–12 weeks (***Table 140***).

Table 140 AEs leading to discontinuation, eptinezumab in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between treatments
PROMISE-1[82]	High	1–12 weeks	EPT 100 mg	223	6 (2.7)	OR 1.00 (95% CI: 0.32, 3.13), p=0.99
			EPT 300 mg	224	5 (2.2)	OR 0.82 (95% CI: 0.25, 2.73), p=0.75
			Placebo	222	6 (2.7)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

Chronic migraine

One RCT reported AEs leading to discontinuation among patients with chronic migraine; it was at low RoB.[84] There were no significant differences in the number of AEs leading to discontinuation between eptinezumab 100 mg or 300 mg compared to placebo at 1–12 weeks (***Table 141***).

Table 141 AEs leading to discontinuation, eptinezumab in chronic migraine patients

Trial name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between treatments
PROMISE-2[84]	Low	1–12 weeks	EPT 100 mg	356	3 (<1)	OR 1.55 (95% CI: 0.26, 9.31), p=0.63
			EPT 300 mg	350	8 (2.3)	OR 4.26 (95% CI: 0.90, 20.19), p=0.07
			Placebo	366	2 (<1)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.

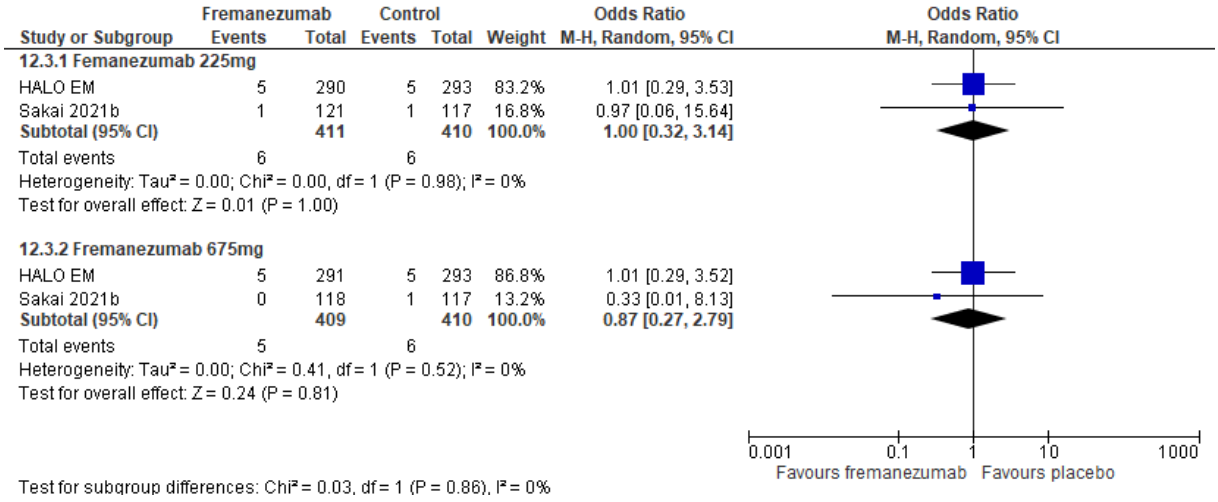
There were no RCTs identified that reported data for episodic and chronic migraine patients combined, or for subgroups of patients with ≥2 prior treatment failures among patients who received eptinezumab.

7.2.4.6.3 Fremanezumab

Episodic migraine

Two RCTs reported AEs leading to discontinuation among patients with episodic migraine; one was at low RoB[87] and the other was at high RoB.[86] Both of the RCTs were suitable for combining in a meta-analysis, where there were no differences in the number of AEs leading to discontinuation among patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 3 months. Sensitivity analyses did not alter the results (***Appendix H, Figure A19***). There was no heterogeneity identified (***Figure 36***).

Figure 36 AEs leading to discontinuation, fremanezumab in episodic migraine patients

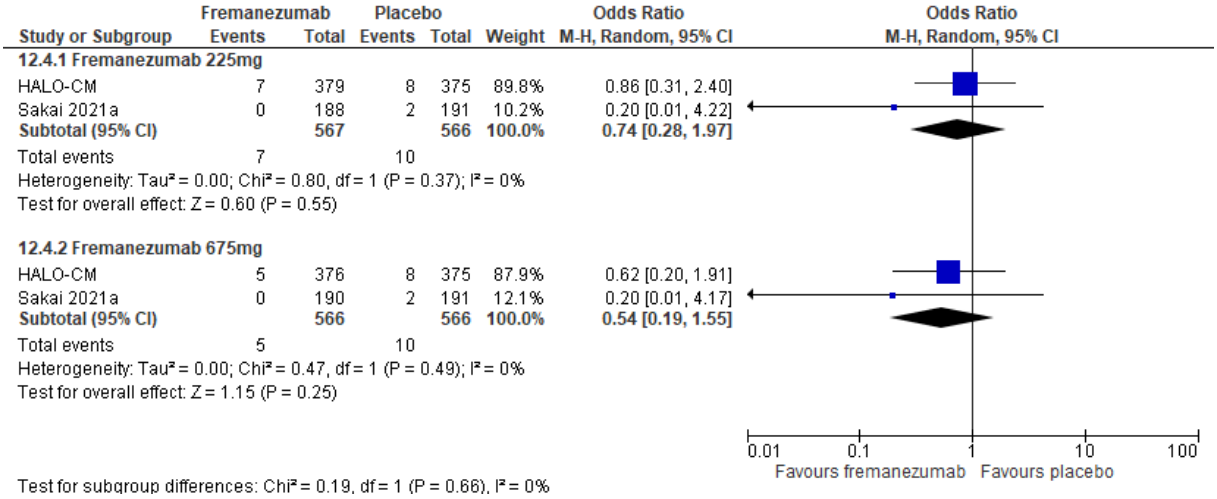


Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Chronic migraine

Two RCTs reported AEs leading to discontinuation among patients with chronic migraine; both at low RoB.[89,90] Both RCTs were suitable for combining in a meta-analysis, where there were no differences in the number of AEs leading to discontinuation among patients randomised to fremanezumab 225 mg or 675 mg compared to placebo at 3 months. There was no heterogeneity identified (***Figure 37***).

Figure 37 AEs leading to discontinuation, fremanezumab in chronic migraine patients



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Episodic and chronic migraine

One RCT assessed to be at low RoB reported AEs leading to discontinuation among patients with episodic and chronic migraine randomised to fremanezumab or placebo.[91]There were no differences in AEs leading to discontinuation between fremanezumab quarterly or monthly compared to placebo at 3 months (***Table 142***).

Table 142 AEs leading to discontinuation, fremanezumab episodic and chronic

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
FOCUS[91]*	Low	3 months	FRE quarterly	276	2 (<1)	OR 0.50 (95% CI: 0.09, 2.74), p=0.42
			FRE monthly	285	4 (1)	OR 0.97 (95% CI: 0.24, 3.92), p=0.97
			Placebo	277	4 (1)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial, there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group, 110 patients (39%) had episodic migraine and received 225 mg FRE monthly, while 173 patients (61%) had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 patients (40%) had episodic migraine, while 167 (60%) had chronic migraine.

Subgroup of patients with ≥2 prior treatment failures: episodic and chronic migraine

One RCT reported data (in both episodic and chronic migraine patients) for subgroups of patients with 2, 3 and 4 prior treatment failures.[116] There were no significant differences in the number of AEs leading to discontinuation between fremanezumab quarterly or monthly and placebo at 3 months in any subgroup (***Table 143***)

Table 143 AEs leading to discontinuation, fremanezumab subgroup of patients with ≥2 prior treatment failures: episodic and chronic migraine

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number (%) discontinued	Difference between groups
FOCUS[116]*	Low	3 months 2 Tx failures	FRE quarterly	140	1 (<1)	OR 0.33 (95% CI: 0.03, 3.22), p=0.34
			FRE monthly	134	1 (<1)	OR 0.35 (95% CI: 0.04, 3.37), p=0.36
			Placebo	141	3 (2)	NA
		3 months 3 Tx failures	FRE quarterly	85	0	Not estimable**
			FRE monthly	99	3 (3)	Not estimable**
			Placebo	81	0	NA
		3 months 4 Tx failures	FRE quarterly	49	0	Not estimable**
			FRE monthly	50	0	Not estimable**
			Placebo	54	0	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias, **Tx** = treatment.
Notes
Blue text indicates RACS-calculated comparisons.
*In the FOCUS trial, there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group, 110 patients (39%) had episodic migraine and received 225 mg FRE monthly, while 173 patients (61%) had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 patients (40%) had episodic migraine, while 167 (60%) had chronic migraine.
** The odds ratio was not estimable because there were no events in either the fremanezumab group or the placebo group.

7.2.4.6.4 Galcanezumab

Episodic migraine

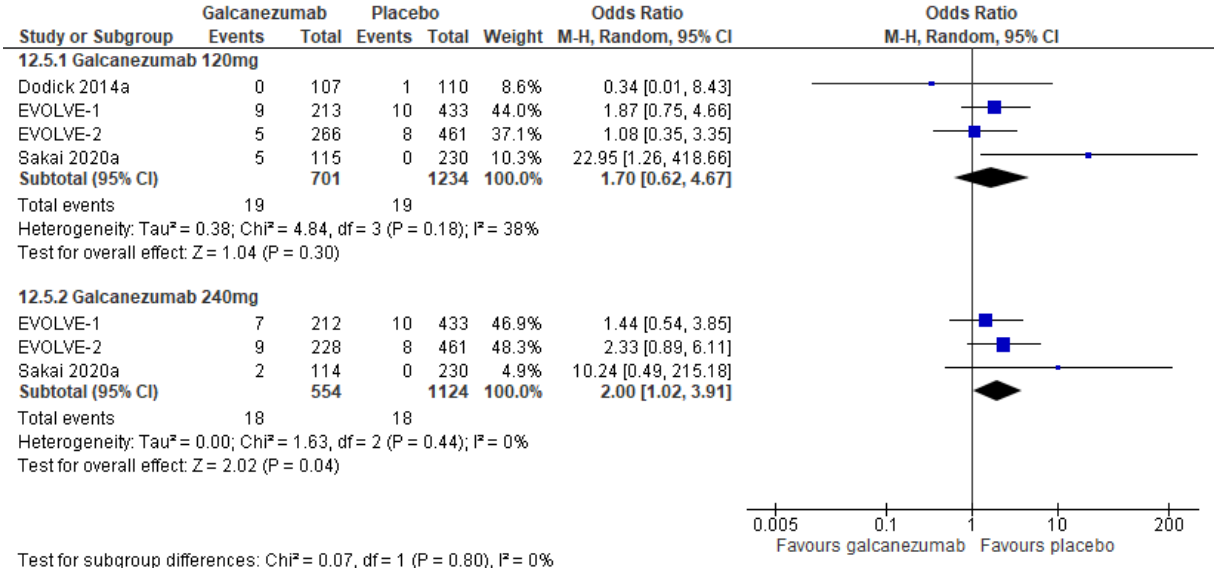
Galcanezumab 120 mg

Data reporting AEs leading to discontinuation for galcanezumab 120 mg compared to placebo were available in 5 RCTs; all at low RoB.[92-96,120] Four RCTs were suitable for combining in a meta-analysis, where there were no differences in the number of AEs leading to discontinuation between patients randomised to galcanezumab 120 mg or placebo at 6 months (***Figure 38***).[92-94,96] There was low heterogeneity identified. One additional RCT (reporting average AEs leading to discontinuation across 1–12 weeks and 13–24 weeks) reported similar results with no significant differences (and no events) between groups (***Table 144***).[120]

Galcanezumab 240 mg

Data reporting AEs leading to discontinuation for galcanezumab 240 mg compared to placebo were reported in 3 RCTs; all at low RoB.[92-94] All RCTs were suitable for combining in a meta-analysis, where there were significantly more AEs leading to discontinuation in the galcanezumab group compared to the placebo group at 6 months. No heterogeneity was identified (***Figure 38***).

Figure 38 AEs leading to discontinuation, galcanezumab in episodic migraine patients, 6 months



Abbreviations
CI = confidence interval, **M-H** = Mantel-Haenszel.

Table 144 AEs leading to discontinuation, galcanezumab 120 mg in episodic migraine patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
Skljarevski et al 2018[120]	Low	1–12 weeks	GAL 120 mg	70	0 (0)	Not estimable*
			Placebo	137	0 (0)	
		12–24 weeks	GAL 120 mg	63	0 (0)	Not estimable*
			Placebo	125	0 (0)	

Abbreviations
GAL = galcanezumab, **n** = number of patients, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
* The odds ratio between groups was not estimable because there were no events in either group.

Chronic and episodic migraine

Two RCTs reported data among patients with episodic and chronic migraine randomised to galcanezumab or placebo; one was assessed to be at high RoB[97] and the other was assessed to be at low RoB.[98] There were no differences in the number of AEs leading to discontinuation between galcanezumab 120 mg compared to 240 mg at 12 months[97], or between galcanezumab 120 mg or 240 mg compared to placebo at 3 months (***Table 145***).[98]

Table 145 AEs leading to discontinuation, galcanezumab episodic and chronic patients

Study name	RoB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
CGAJ[97]*	High	12 months	GAL 120 mg	129	6 (4.7)	OR 0.89 (95% CI: 0.28, 2.62), p=0.79
			GAL 240 mg	130	7 (5.0)	
CONQUER[98]**	Low	3 months	GAL 120 mg	232	1 (<1)	OR 2.99 (95% CI: 0.12, 73.71), p=0.50
			Placebo	230	0	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RACS** = Royal Australasian College of Surgeons, **RoB** = risk of bias.
Notes
Blue text indicates RACS-calculated comparisons.
* In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.
** In the CONQUER trial there were 2 treatment groups: GAL 120 mg and placebo. In the GAL 120 mg group, 59% of patients had episodic migraine and 41% had chronic migraine. In the placebo group, 58% of patients had episodic migraine and 43% had chronic migraine.

No RCTs were identified that reported data for chronic migraine or for subgroups of episodic and/or chronic patients with ≥2 prior treatment failures among patients who received galcanezumab.

7.2.4.7 Adverse events upon discontinuation of calcitonin gene-related peptide (CGRP) antagonists (i.e. rebound effect)

No trials were identified that reported AEs upon discontinuation of any CGRP antagonist.

7.2.5 GRADE summary of findings tables

The following tables (***Table 146*** to ***Table 149***) summarise the overall strength of evidence supporting the key findings related to the effectiveness and safety of the drugs under investigation. As per the GRADE approach, only key outcomes are reported in the summary of findings tables for each comparison.[64] These outcomes include MMDs, response rate (>50%), MSQ and SAEs. Data are shown at the latest timepoint reported by each study. For example, if a study reported monthly outcomes to 6 months, only the 6-month data are shown in the table. The summary of findings tables have been modified from the standard GRADE templates, to accommodate the complexity of the analysis presented in this HTA.

Green highlighting of table cells indicates a favourable outcome for the study drug vs placebo; orange highlighting indicates no difference between the study drug and placebo. Two trials were not compared to placebo; one comparing erenumab 70/140 mg to topiramate and one comparing different doses of galcanezumab. These trials are included in the table for information only and are not highlighted. For MMD, response rate (>50%) and MSQ, green highlighting indicates a significant difference in favour of the study drug, while orange highlighting indicates no difference. For SAEs, green highlighting indicates no difference between the study drug and placebo, while orange highlighting indicates a difference in favour of placebo.

The certainty of evidence supporting an outcome, as scored according to the GRADE approach, is defined in the following categories:[64]

- **High certainty** ⊕⊕⊕⊕: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty** ⊕⊕⊕◯: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty** ⊕⊕◯◯: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty** ⊕◯◯◯: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 146 Summary of evidence for monthly migraine days (MMDs)

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
Episodic	3	70 mg, 4 RCTs (n=2,071) MD -1.15 (95% CI: -1.48, -0.83) Certainty ⊕⊕⊕◯ 140 mg, 3 RCTs (n=1,288) MD -1.72 (95% CI: -2.16, -1.27) Certainty ⊕⊕⊕◯	3-6	100 mg, 1 RCT (n=443) MD -0.76 (95% CI: -1.40, -0.11) Certainty ⊕⊕◯◯ 300 mg, 1 RCT (n=444) MD -1.02 (95% CI: -1.66, -0.37) Certainty ⊕⊕◯◯	1-3	225 mg, 1 RCT (n=237) MD -3.0 (95% CI: -3.74, -2.23) Certainty ⊕⊕⊕◯ 675 mg, 1 RCT (n=233) MD -3.0 (95% CI: -3.76, -2.24) Certainty ⊕⊕⊕◯	1-6	120 mg, 3 RCTs (n=1656) MD -2.29 (95% CI: -2.96, -1.61) Certainty ⊕⊕⊕◯ 240 mg, 3 RCTs (n=1647) MD -2.14 (95% CI: -2.72, -1.55) Certainty ⊕⊕⊕◯
	4-6	70 mg, 1 RCT (n=271) MD -1.4 (95% CI: -1.9, -0.9) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=272) MD -1.9 (95% CI: -2.3, -1.4) Certainty ⊕⊕⊕⊕			2-3	225 mg, 1 RCT (n=200) MD -2.81 (95% CI: -4.07, -1.55) Certainty ⊕⊕⊕⊕ 675 mg, 1 RCT (n=201) MD -2.64 (95% CI: -3.90, -1.38) Certainty ⊕⊕⊕◯	3	120 mg, 1 RCT (n=269) MD -2.6 (95% CI: -3.4, -1.7) Certainty ⊕⊕⊕⊕
					3	225 mg, 1 RCT (n=577) MD -1.5 (95% CI: -2.01, -0.93) Certainty ⊕⊕◯◯ 225 mg, 1 RCT (n=578) MD -1.3 (95% CI: -1.79, -0.72) Certainty ⊕⊕◯◯	1-3	120 mg, 1 RCT (n=203) MD -1.14 (95% CI: -2.02, -0.29) Certainty ⊕⊕⊕⊕
Chronic	3	70 mg, 1 RCT (n=469) MD -2.5 (95% CI: -3.5, -1.4) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=468) MD -2.5 (95% CI: -3.5, -1.4) Certainty ⊕⊕⊕⊕	3	100 mg, 1 RCT (n=234) MD -2.1 (95% CI: -3.8, -0.4) Certainty ⊕⊕⊕◯ 300 mg, 1 RCT (n=230) MD -2.7 (95% CI: -4.4, -0.9) Certainty ⊕⊕⊕◯	1-3	225 mg, 1 RCT (n=377) MD -2.1 (95% CI: -3.10, -1.12) Certainty ⊕⊕⊕◯ 675 mg, 1 RCT (n=379) MD -1.3 (95% CI: -2.27, -0.29) Certainty ⊕⊕⊕◯	3	120 mg, 1 RCT (n=193) MD -3.7 (95% CI: -5.2, -2.2) Certainty ⊕⊕⊕◯
			3-6	100 mg, 1 RCT (n=722) MD -1.98 (95% CI: -2.94, -1.01) Certainty ⊕⊕⊕⊕	2-3	225/675 mg, 1 RCT (n=177) MD -1.72 (95% CI: -3.7, 0.2) Certainty ⊕⊕⊕◯	1-3	120 mg, 1 RCT (n=811) MD -2.1 (95% CI: -2.9, -1.3) Certainty ⊕⊕⊕◯

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
				300 mg, 1 RCT (n=716) MD -2.65 (95% CI: -3.62, -1.68) Certainty ⊕⊕⊕⊕	3	225 mg, 1 RCT (n=746) MD -1.8 (SE 0.4) Certainty ⊕⊕⊕⊕ 675 mg, 1 RCT (n=746) MD -1.7 (SE 0.4) Certainty ⊕⊕⊕⊕		240 mg, 1 RCT (n=812) MD -1.9 (95% CI: -2.7, -1.1) Certainty ⊕⊕⊕◯
Episodic and chronic	4-6	70 mg, 1 RCT (n=257) MD -1.62 (95% CI: -2.52, -0.73) Certainty ⊕⊕⊕◯ 70/140 mg vs topiramate 1 trial (n=768) MD -1.84 (95% CI: -2.43, -1.25) Certainty ⊕⊕⊕⊕	-	-	3	FRE quarterly, 1 RCT (n=554) MD -3.1 (95% CI: -3.8, -2.4) Certainty ⊕⊕⊕⊕ FRE monthly, 1 RCT (n=561) MD -3.5 (95% CI: -4.2, -2.8) Certainty ⊕⊕⊕⊕	12	120 mg (n=135) vs 140 mg (n=135), 1 RCT MD 0.90 (95% CI: -0.03, 1.83) Certainty ⊕◯◯◯
Episodic with ≥2 Tx failure	3	140 mg, 1 RCT (n=145) MD -1.3 (95% CI: -2.7, 0.1) Certainty ⊕⊕⊕⊕		-		-		-
	4-6	70 mg, 1 RCT (n=159) MD -1.67 (95% CI: -2.56, -0.78) Certainty ⊕⊕⊕⊕ 70 mg, 1 RCT (n=103) MD -1.3 (95% CI: -2.6, 0.0) Certainty ⊕⊕◯◯ 140 mg, 1 RCT (n=112) MD -2.7 (95% CI: -4.0, -1.4) Certainty ⊕⊕⊕◯		-		-		-
Chronic with ≥2 Tx failures	3	70 mg, 1 RCT (n=235) MD -2.7 (95% CI: -4.2, -1.2) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=234) MD -4.3 (95% CI: -5.8, -2.8) Certainty ⊕⊕⊕⊕		-		-	1-3	120 mg, 1 RCT (n=246) MD -4.35 (SE 0.07) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=278) MD 1.77 (SE 0.63) Certainty ⊕⊕⊕◯
	4-6	70 mg, 1 RCT (n=102) MD -1.57 (95% CI: -3.39, 0.24) Certainty ⊕⊕⊕◯						

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
Episodic and chronic with ≥2 Tx failures		-		-	3	FRE quarterly*, 1 RCT (n=104) MD -3.4 (95% CI: -5.0, -1.8) Certainty ⊕⊕⊕◯ FRE monthly*, 1 RCT (n=114) MD -4.4 (95% CI: -6.0, -2.8) Certainty ⊕⊕⊕◯		-

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MMD** = monthly migraine days, **M** = months, **n** = numbers, **RCT** = randomised controlled trial, **SE** = standard error, **Tx** = treatment

Notes

GRADE levels of certainty: ⊕◯◯◯ Very low; ⊕⊕◯◯ Low; ⊕⊕⊕◯ Moderate; ⊕⊕⊕⊕ High

*In the FOCUS trial, there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine and 169 (61%) had chronic migraine. In the FRE monthly group 110 patients (39%) had episodic migraine and received 225 mg FRE monthly, while 173 (61%) had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 patients (40%) had episodic migraine and 167 (60%) had chronic migraine.

Table 147 Summary of evidence for response rate (>50%)

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
Episodic	3	70 mg, 4 RCTs (n=2100) OR 1.71 (95% CI: 1.43, 2.04) Certainty ⊕⊕⊕◯ 140 mg, 3 RCTs (n=1426) OR 2.43 (95% CI: 1.94, 3.05), Certainty ⊕⊕⊕◯	3-6	100 mg, 1 RCT (n=443) OR 1.55 (95% CI: 1.06, 2.26) Certainty ⊕⊕◯◯ 300 mg, 1 RCT (n=444) OR 1.78 (95% CI: 1.22, 2.61) Certainty ⊕⊕◯◯	3	225 mg, 3 RCTs (n=967) OR 2.66 (95% CI: 1.35, 5.23) Certainty ⊕⊕◯◯ 675 mg, 3 RCTs (n=970) OR 2.87 (95% CI: 1.32, 6.22) Certainty ⊕⊕◯◯	1-3	120 mg, 1 RCT (n=203) OR 2.10 (95% CI: 1.09, 4.06) Certainty ⊕⊕⊕⊕
							3	150 mg, 1 RCT (n=202) OR 2.88 (90% CI: 1.78, 4.69) Certainty ⊕⊕⊕◯
	4-6	70 mg, 2 RCTs (n=899) OR 3.08 (95% CI: 1.30, 7.29) Certainty ⊕⊕⊕◯ 140 mg, 2 RCTs, (n=906) OR 3.24 (95% CI: 2.01, 5.22) Certainty ⊕⊕⊕◯					1-6	120 mg, 1 RCT†, (n=345) OR 3.83 (95% CI: 2.35, 6.22) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=344) OR 3.63 (95% CI: 2.23, 5.91) Certainty ⊕⊕⊕◯
							6	120 mg, 1 RCT (n=635) OR 2.63 (95% CI: 2.05, 3.37) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=633) OR 2.48 (95% CI: 1.94, 3.18) Certainty ⊕⊕⊕◯
Chronic	3	70 mg, 1 RCT (n=469) OR 2.2 (95% CI: 1.5, 3.3) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=468) OR 2.3 (95% CI: 1.6, 3.5) Certainty ⊕⊕⊕⊕	1-3	100 mg, 2 RCTs, (n=956) OR 2.02 (95% CI: 1.56, 2.61) Certainty ⊕⊕⊕⊕ 300 mg, 2 trials (n=946) OR 2.32 (95% CI: 1.79, 3.01) Certainty ⊕⊕⊕⊕	1-3	225 mg, 2 RCTs (n=1122) OR 3.00 (95% CI: 2.26, 3.98) Certainty ⊕⊕⊕◯ 675 mg, 2 RCTs (n=1125) OR 2.73 (95% CI: 2.05, 3.62) Certainty ⊕⊕⊕◯	1-3	120 mg, 1 RCT (n=811) OR 2.1 (95% CI: 1.6, 2.8) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=812) OR 2.1 (95% CI: 1.6, 2.8) Certainty ⊕⊕⊕◯
					2-3	225 mg/675 mg‡, 1 RCT (n=176) OR 2.44 (95% CI: 1.3, 4.5) Certainty ⊕⊕⊕⊕		
Episodic and chronic	6	70/140 mg vs topiramate 1 RCT* (n=776) OR 2.76 (95% CI: 2.06, 3.71) ⊕⊕⊕⊕		-	3	FRE quarterly**, 1 RCT, (n=554) OR 5.8 (95% CI: 3.6, 9.6) Certainty ⊕⊕⊕⊕	12	120 mg (n=135) vs 140 mg (n=135), 1 RCT OR 0.70 (95% CI: 0.42, 1.19)

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
						FRE monthly**, 1 RCT, (n=561) OR 5.8 (95% CI: 3.6, 9.5) Certainty ⊕⊕⊕⊕		Certainty ⊕◯◯◯ ¥
Episodic with ≥2 Tx failure	3	70 mg, 1 RCT (n=103) OR 2.08 (95% CI: 0.78, 5.55) Certainty ⊕⊕⊕◯ 140 mg, 2 RCTs (n=260) OR 3.76 (95% CI: 1.99, 7.13) Certainty ⊕⊕⊕◯		-		-		-
Chronic with ≥2 Tx failures	3	70 mg, 1 RCT (n=235) OR 3.5 (95% CI: 1.8, 6.6) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=234) OR 4.2 (95% CI: 2.2, 7.9) Certainty ⊕⊕⊕⊕		-		-	1-3	120 mg, 1 RCT (n=NR) OR 2.22 (95% CI: 1.26, 3.92) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=NR) OR 4.05 (95% CI: 2.25, 7.31) Certainty ⊕⊕⊕◯
Episodic and chronic with ≥2 Tx failures	4-6	70 mg, 1 RCT (n=261) OR 2.33 (95% CI: 1.29, 4.23) Certainty ⊕⊕⊕◯		-		-		-

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **M** = months, **n** = number, **NR** = not reported, **OR** = odds ratio, **RCT** = randomised controlled trial, **Tx** = treatment

Notes

GRADE levels of certainty: ⊕◯◯◯ Very low; ⊕⊕◯◯ Low; ⊕⊕⊕◯ Moderate; ⊕⊕⊕⊕ High

* This study compared erenumab to topiramate

**In the FOCUS trial, there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine and 169 (61%) had chronic migraine. In the FRE monthly group 110 patients (39%) had episodic migraine and received 225 mg FRE monthly, while 173 (61%) had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 patients (40%) had episodic migraine and 167 (60%) had chronic migraine

¥ In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

† There was an additional trial reporting galcanezumab 120 mg from 1-6 months, however the trial did not report sufficient details to be included in a meta-analysis or to calculate an OR.

‡ In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.

Table 148 Summary of evidence for Migraine Specific Quality of Life (MSQ)

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
Episodic	3	<u>MSQ-RFR</u> 70 mg, 2 trials (n=825) Trial 1: MD 5.5 (95% CI: 2.8, 8.2) Certainty ⊕⊕⊕⊕ Trial 2: MD 1.8 (95% CI: -2.5, 6.1) Certainty ⊕⊕⊕⊕ <u>MSQ-RFP</u> 70 mg, 2 trials (n=825) Trial 1: MD 3.6 (95% CI: 1.1, 6.0) Certainty ⊕⊕⊕⊕ Trial 2: MD 0.5 (95% CI: -3.3, 4.3) Certainty ⊕⊕⊕⊕ <u>MSQ-EF</u> 70 mg, 2 trials (n=825) Trial 1: MD 4.5 (95% CI: 1.6, 7.4) Certainty ⊕⊕⊕⊕ Trial 2: MD 1.9 (95% CI: -2.6, 6.3) Certainty ⊕⊕⊕⊕		-		-	3	<u>MSQ total</u> 120 mg, 1 RCT (n=187) MD 8.7 (95% CI: 2.450, 15.008) Certainty ⊕⊕⊕⊕
							4-6	<u>MSQ-RFR</u> 120 mg, 3 RCTs (n=1520) MD 7.74 (95% CI: 6.10, 9.38) Certainty ⊕⊕⊕◯ 240 mg, 3 RCTs (n=1511) MD 6.65 (95% CI: 5.01, 8.30) Certainty ⊕⊕⊕◯
	4-6	<u>MSQ-RFR</u> 70 mg, 1 RCT (n=628) MD 5.1 (95% CI: 2.8, 7.4) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=634) MD 6.5 (95% CI: 4.2, 8.8) Certainty ⊕⊕⊕⊕ <u>MSQ RFP</u> 70 mg, 1 RCT (n=628) MD 4.2 (95% CI: 2.2, 6.3) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=634) MD 5.4 (95% CI: 3.4, 7.5) Certainty ⊕⊕⊕⊕		-		-		-

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
		MSQ EF 70 mg, 1 RCT (n=628) MD 5.2 (95% CI: 2.8, 7.6) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=634) MD 6.7 (95% CI: 4.4, 9.1) Certainty ⊕⊕⊕⊕						
Chronic	3	MSQ-RFR 70 mg, 1 RCT (n=469) MD 6.0 (95% CI: 2.3, 9.6) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=468) MD 7.4 (95% CI: 3.7, 11) Certainty ⊕⊕⊕⊕ MSQ RFP 70 mg, 1 RCT (n=469) MD 4.1 (95% CI: 0.9, 7.4) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=468) MD 4.9 (95% CI: 1.7, 8.2) Certainty ⊕⊕⊕⊕ MSQ EF 70 mg, 1 RCT (n=469) MD 8.3 (95% CI: 4.3, 12.4) Certainty ⊕⊕⊕⊕ 140 mg, 1 RCT (n=468) MD 8.9 (95% CI: 4.9, 13) Certainty ⊕⊕⊕⊕		-	3	MSQ-RFR 225 mg, 1 RCT (n=746) MD 6.3 (SE 1.42) Certainty ⊕⊕⊕⊕ 675 mg, 1 RCT (n=746) MD 5.6 (SE 1.42) Certainty ⊕⊕⊕⊕ MSQ RFP 225 mg, 1 RCT (n=746) MD 3.9 (SE 1.26) Certainty ⊕⊕⊕⊕ 675 mg, 1 RCT (n=746) MD 4.3 (SE 1.25) Certainty ⊕⊕⊕⊕ MSQ EF 225 mg, 1 RCT (n=746) MD 3.3 (SE 1.55) Certainty ⊕⊕⊕⊕ 675 mg, 1 RCT (n=746) MD 3.9 (SE 1.55) Certainty ⊕⊕⊕⊕	3	MSQ-RFR 120 mg, 1 RCT (n=811) MD 5.1 (95% CI: 2.1, 8.0) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=812) MD 6.3 (95% CI: 3.0, 9.6) Certainty ⊕⊕⊕◯ MSQ RFP 120 mg, 1 RCT (n=811) MD 7.0 (95% CI: 4.2, 9.8) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=812) MD 5.1 (95% CI: 2.3, 7.9) Certainty ⊕⊕⊕◯ MSQ EF 120 mg, 1 RCT (n=811) MD 7.0 (95% CI: 3.2, 10.8) Certainty ⊕⊕⊕⊕ 240 mg, 1 RCT (n=812) MD 6.6 (95% CI: 2.8, 10.4) Certainty ⊕⊕⊕◯
Episodic and chronic		-		-	4	MSQ total FRE quarterly*, 1 RCT (n=554) MD 8.8 (95% CI: 5.7, 11.9) Certainty ⊕⊕⊕⊕	12	MSQ-RFR 120 mg (n=135) vs 140 mg (n=135)**, 1 RCT MD 1.9 (95% CI: -1.3, 5.0) Certainty ⊕◯◯◯

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments	M	Difference between treatments
						FRE monthly*, 1 RCT (n=561) MD 10.6 (95% CI: 7.5, 13.7) Certainty ⊕⊕⊕⊕		<u>MSQ-RFP</u> 120 mg (n=135) vs 140 mg (n=135)**, 1 RCT MD 1.3 (95% CI: -1.7, 4.2) Certainty ⊕◯◯◯ <u>MSQ-EF</u> 120 mg (n=135) vs 140 mg (n=135)**, 1 RCT MD 3.1 (95% CI: -0.5, 6.6) Certainty ⊕◯◯◯
Episodic with ≥2 Tx failure		-		-		-	3	<u>MSQ-RFR</u> 120 mg, 1 RCT (n=269) MD 11.5 (95% CI: 7.1, 15.9) Certainty ⊕⊕⊕⊕
Chronic with ≥2 Tx failures		-		-		-	3	<u>MSQ-RFR</u> 120 mg, 2 RCTs (n=417) MD 11.58 (95% CI: 6.30, 16.85) Certainty ⊕⊕⊕◯ 240 mg, 1 RCT (n=254) MD 8.57 (SE 2.64) Certainty ⊕⊕⊕◯
Episodic and chronic with ≥2 Tx failures		-		-		-		-

Abbreviations

CI = confidence interval, **EF** = Emotional Function, **FRE** = fremanezumab, **M** = months, **MD** = mean difference, **MSQ** = migraine specific quality of life, **N** = number, **RCT** = randomised controlled trial, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **SE** = standard error, **Tx** = treatment

Notes

GRADE levels of certainty: ⊕◯◯◯ Very low; ⊕⊕◯◯ Low; ⊕⊕⊕◯ Moderate; ⊕⊕⊕⊕ High

*In the FOCUS trial, there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine and 169 (61%) had chronic migraine. In the FRE monthly group 110 patients (39%) had episodic migraine and received 225 mg FRE monthly, while 173 (61%) had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 patients (40%) had episodic migraine and 167 (60%) had chronic migraine.

** In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

Table 149 Summary of evidence for serious adverse events (SAEs)

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	N	Difference between treatments	N	Difference between treatments	N	Difference between treatments	N	Difference between treatments
Episodic	3	70 mg, 2 RCTs (n=831) OR 0.95 (95% CI: 0.19, 4.79) Certainty⊕⊕⊕◯ 140 mg, 1 RCT (n=243) OR 2.10 (95% CI: 0.19, 23.50) Certainty ⊕⊕⊕◯	13.5	100 mg, 1 RCT (n=445) OR 0.66 (95% CI: 0.18, 2.36) Certainty ⊕◯◯◯ 300 mg, 1 RCT (n=446) OR 0.49 (95% CI: 0.12, 1.98) Certainty ⊕◯◯◯	3	225 mg, 3 RCTs (n=1,021) OR 1.06 (95% CI: 0.09, 12.02) Certainty ⊕◯◯◯ 675 mg, 3 RCTs (n=1,019) OR 1.06 (95% CI: 0.09, 12.06) Certainty ⊕◯◯◯	0-3	120 mg, 1 RCT (n=207) OR 5.94 (95% CI: 0.24, 147.6) Certainty ⊕⊕◯◯
	6	70 mg, 3 RCTs (n=1,574) OR 0.99 (95% CI: 0.43, 2.26) Certainty ⊕⊕◯◯ 140 mg, 3 RCTs, (n=1,470) OR 0.62 (95% CI: 0.24, 1.57) Certainty ⊕⊕◯◯					6	120 mg, 4 RCTs (n=1,887) OR 1.94 (95% CI: 0.76, 5.00) Certainty ⊕⊕◯◯ 240 mg, 3 RCTs (n=1,685) OR 1.69 (95% CI: 0.27, 10.64) Certainty ⊕⊕◯◯
Chronic	3	70 mg, 1 RCT (n=472) OR 1.28 (95% CI: 0.42, 3.87) ⊕⊕⊕◯ 140 mg, 1 RCT (n=470) OR 0.42 (95% CI: 0.09, 2.06) ⊕⊕⊕◯	3	100 mg, 1 RCT (n=243) OR 4.07 (95% CI: 0.45, 36.93) Certainty ⊕⊕◯◯ 300 mg, 1 RCT (n=242) OR 7.37 (95% CI: 0.89, 60.83) Certainty ⊕⊕◯◯	3	225 mg, 2 RCTs (n=1,133) OR 1.10 (95% CI: 0.37, 3.25) Certainty ⊕⊕◯◯ 675 mg, 2 RCTs (n=1,132) OR 0.57 (95% CI: 0.16, 1.98), Certainty ⊕⊕◯◯ 225 mg/675 mg*, 1 RCT (n=177) OR 1.01 (95% CI: 0.06, 16.43) ⊕⊕⊕◯	3	120 mg, 1 RCT (n=831) OR 0.51 (95% CI: 0.06, 4.58) Certainty ⊕⊕◯◯ 240 mg, 1 RCT (n=840) OR 2.50 (95% CI: 0.67, 9.38) Certainty ⊕⊕◯◯
			1-7	100 mg, 1 RCT (n=722) OR 1.03 (95% CI: 0.21, 5.13) Certainty ⊕⊕⊕◯ 300 mg, 1 RCT (n=716) OR 1.40 (95% CI: 0.31, 6.30) Certainty ⊕⊕⊕◯				
Episodic and chronic	6	70 mg, 1 RCT (n=261) OR 1.01 (95% CI: 0.14, 7.26) Certainty ⊕⊕◯◯ 70/140 mg vs topiramate 1 RCT (n=776)		-	3	FRE quarterly, 1 RCT (n=553) OR 0.50 (95% CI: 0.09, 2.74) Certainty ⊕⊕⊕◯ FRE monthly, 1 RCT (n=562)	3	120 mg, 1 RCT (n=462) OR 0.99 (95% CI: 0.14, 7.10) Certainty ⊕⊕⊕◯

Population	Erenumab		Eptinezumab		Fremanezumab		Galcanezumab	
	N	Difference between treatments	N	Difference between treatments	N	Difference between treatments	N	Difference between treatments
		OR 0.51 (95% CI: 0.24, 1.12) Certainty ⊕⊕⊕◯				OR 0.97 (95% CI: 0.24, 3.92) Certainty ⊕⊕⊕◯	12	120 mg vs 240 mg¥, 1 RCT (n=270) OR 0.46 (95% CI: 0.12, 1.80) Certainty ⊕◯◯◯
Episodic with ≥2 Tx failure	3	70 mg, 1 RCT (n=233) OR 1.15 (95% CI: 0.25, 5.28) Certainty ⊕⊕⊕◯ 140 mg, 1 RCT (n=233) OR 0.38 (95% CI: 0.04, 3.42) Certainty ⊕⊕⊕◯		-		-		-
Chronic with ≥2 Tx failures	6	70 mg, 1 RCT (n=103) OR 5.74 (95% CI: 0.27, 122.50) Certainty ⊕◯◯◯ 140 mg, 1 RCT (n=112) OR 6.87 (95% CI: 0.35, 136.24) Certainty ⊕◯◯◯		-		-		-
Episodic and chronic with ≥2 Tx failures		-		-	3	FRE quarterly**, 1 RCT (n=281) OR 0.25 (95% CI: 0.03, 2.23) Certainty ⊕⊕⊕◯ FRE monthly**, 1 RCT (n=275) OR 0.52 (95% CI: 0.09, 2.88) Certainty ⊕⊕⊕◯		-

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **M** = months, **n** = number, **OR** = odds ratio, **RCT** = randomised controlled trial, **Tx** = treatment.

Notes

GRADE levels of certainty: ⊕◯◯◯ Very low; ⊕⊕◯◯ Low; ⊕⊕⊕◯ Moderate; ⊕⊕⊕⊕ High

* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles

**In the FOCUS trial, there were 3 treatment groups: FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE; 107 (39%) had episodic migraine and 169 (61%) had chronic migraine. In the FRE monthly group 110 patients (39%) had episodic migraine and received 225 mg FRE monthly, while 173 (61%) had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 patients (40%) had episodic migraine and 167 (60%) had chronic migraine.

¥ In the CGAJ trial there were 2 treatment groups: GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% had chronic migraine.

7.3 Postface: Update to original clinical evaluation

The available evidence on CGRP antagonists is continuously evolving; therefore, the original searches conducted in this HTA (reported in ***Section 7.2.1***) have been updated and reported in this postface. The objective of this update is to summarise the additional RCT evidence published after the original search date, and to describe the results in relation to the overall findings and conclusions of the original results of this HTA report. Due to the narrative nature of this additional body of work, results were not combined via meta-analysis. Instead, a strong emphasis was placed on the direction of effect of the RCT results compared with other trials with similar PICO characteristics and reported timepoints.

As this postface is a standalone body of work that updates the original HTA results, the tables, figures and citations are reported separately from those presented in the original HTA to prevent overlap.

7.3.1 Methodology

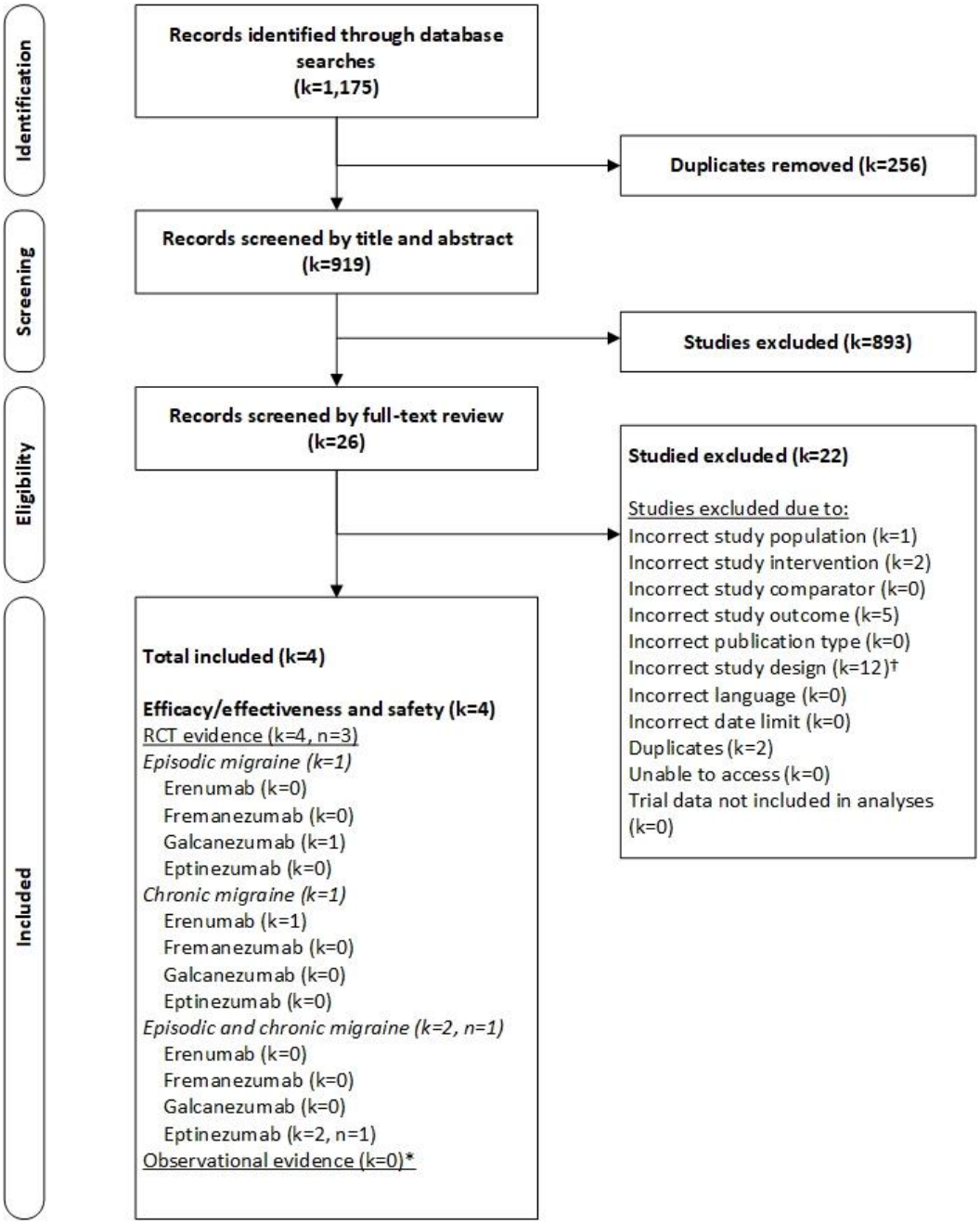
7.3.1.1 Study selection

Updated database searches were conducted to capture literature published between the original search date of 9 March 2022 and 27 January 2023 (Ovid) and 9 February 2023 (Cochrane Library, EconLit, INAHTA HTA Database and CEA Registry) (***Appendix B***, ***Table A13*** to ***Table A17***). Study selection followed the same methods described in ***Section 7.1.2***.

7.3.1.2 PRISMA flow diagram

The results of the systematic literature search are summarised in ***Figure PS7 1***.

Figure PS7 1 PRISMA flow diagram (updated literature search)



Abbreviations

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **RCT** = randomised controlled trial.

Notes

k: number of individual publications.

n: number of RCTs – an RCT can be included in multiple publications.

* A targeted screening of observational evidence was conducted to answer the additional question(s) (see ***Section 6.1*** of HTA Protocol) regarding 'switching of CGRP antagonists'; however, no evidence was identified.

† Publications excluded as incorrect study design are related to RCTs that have already been included in the HTA report, but deemed to add no further value to the current data/results reported.

7.3.2 Study characteristics

Overall, 3 additional RCTs (k = 4 publications) were identified and included in the assessment of clinical effectiveness and safety (***Appendix B***, ***Table A6***).[1-4] The characteristics of these additional trials are briefly described below and in ***Table PS7 1***.

7.3.2.1 Erenumab

One RCT[1]—DRAGON 2022 (NCT03867201)—investigated the use of erenumab in chronic migraine patients. The phase 3 trial was conducted across 64 sites in Asia (including China, India, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand and Vietnam) using ICHD-3 criteria to define headache. This RCT compared erenumab 70 mg to placebo, with both erenumab and matched placebo administered once per month for 3 months.

Total sample size was 557 participants, with 279 in the erenumab arm and 278 in the placebo arm. The majority of the included participants were female, with a reported mean age of 41.4 years in the erenumab arm and 41.9 years in the placebo arm.

For clinical effectiveness, the study outcomes included MMDs, acute medication use, response rate (50%) and modified Migraine Disability Assessment (mMIDAS). For safety, the study outcomes included AEs, TRAEs, SAEs and AEs leading to discontinuation.

7.3.2.2 Eptinezumab

One RCT (k = 2 publications)[3,4]—DELIVER 2022 (NCT04418765)—investigated the use of eptinezumab in a mixed population of chronic and episodic migraine patients. The phase 3b trial was conducted across 96 sites in 16 European countries (Belgium, Bulgaria, Czechia, Denmark, Finland, France, Georgia, Germany, Hungary, Italy, Poland, Russia, Slovakia, Spain, Sweden and UK), using the ICHD-3 criteria to define headache. This RCT compared both eptinezumab 100 mg and eptinezumab 300 mg to placebo, with all doses of the interventional product and the matched placebo administered by a single IV infusion at study baseline and 12 weeks. Duration of treatment was 6 months.

Total sample size was 890 participants, with 299 in the eptinezumab 100 mg treatment arm, 294 in the eptinezumab 300 mg treatment arm and 298 in the placebo arm. The majority of the participants were female, with a reported mean age of 44.6 years in the eptinezumab 100 mg arm, 43.1 years in the eptinezumab 300 mg arm and 43.8 years in the placebo arm.

For clinical effectiveness, the study outcomes included MMDs, response rate (50%, 75%), MSQ and HIT-6. For safety, the study outcomes included TRAEs, SAEs and AEs leading to discontinuation.

7.3.2.3 Galcanezumab

One RCT[2]—PERSIST 2022 (NCT03963232)—investigated the use of galcanezumab in episodic migraine patients. The phase 3 trial was conducted across 40 sites in China, India and Russia, using the ICHD-3 criteria to define headache. This RCT compared galcanezumab 120 mg (galcanezumab 240 mg loading dose) to placebo, with both galcanezumab and matched placebo administered once per month for 3 months.

Total sample size was 520 participants, with 261 in the galcanezumab arm and 259 in the placebo arm. The majority of participants were female, with a reported mean age of 37.2 years in the galcanezumab arm and 36.8 years in the placebo arm.

For clinical effectiveness, the study outcomes included MMDs, acute medication use, response rate (50%, 75%, 100%), MSQ and MIDAS. For safety, the study outcomes included TRAEs, SAEs and AEs leading to discontinuation.

See ***Appendix F, Table A21*** for additional study characteristics on the use of concomitant preventive migraine medication and the inclusion/exclusion of participants based on previous migraine preventive treatment failures across each included trial.

Table PS7 1 Characteristics of included RCTs assessing clinical effectiveness and safety (updated search)

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
Erenumab											
DRAGON 2022[1] NCT03867201	RCT; phase 3; 64 sites; Asia (China, India, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand, Vietnam)	Chronic	Erenumab 70 mg	Once a month	3 months	3 months	279	41.4 (10.9)	217 (77.8)	Novartis Pharma	MMDs APR RR (50%) mMIDAS AEs TRAEs SAEs discAEs
			Placebo	Once a month	3 months	3 months	278	41.9 (10.9)	237 (85.3)		
Eptinezumab											
DELIVER 2022[3] NCT04418765[4]	RCT; phase 3b; 96 sites; USA & 16 European countries ¶¶	Episodic: 162 (54) Chronic: 137 (46)	Eptinezumab 100 mg	Twice: BL & 12 weeks	6 months	6 months (DBP: 24 weeks)	299	44.6 (10.8)	277 (93)	H. Lundbeck A/S, Copenhagen, Denmark.	MMDs MHDs APRs RR (50%, 75%) MSQ HIT-6 EQ-5D TRAEs SAEs discAEs
		Episodic: 158 (54) Chronic: 134 (46)	Eptinezumab 300 mg	Twice: BL & 12 weeks	6 months	6 months (DBP: 24 weeks)	294	43.1 (10.2)	260 (89)		
		Episodic: 164 (55) Chronic: 134 (45)	Placebo	Twice: BL & 12 weeks	6 months	6 months (DBP: 24 weeks)	298	43.8 (10.8)	263 (88)		

Trial ID; year; core publication reference; NCT record number; associated references	Trial design details	Episodic/chronic migraine; n (%) [conforming to ICHD-3 unless otherwise noted]	Intervention; comparator	Scheduling	Duration of treatment	Duration of follow up	n	Age mean (SD) [years]	Gender n (%) [female]	Funding	Outcomes
Galcanezumab											
PERSIST 2022[2] NCT03963232	RCT; phase 3; 40 sites; China, India, Russia	Episodic	Galcanezumab 120 mg (240 mg loading dose)	Once a month	3 months	3 months	261	37.2 (9.3)	188 (72.0)	Eli Lilly and Co.	MMDs APR RR (50%, 75%, 100%) MSQ MIDAS TRAEs SAEs discAEs
			Placebo	Once a month	3 months	3 months	259	36.8 (9.8)	196 (75.7)		

Abbreviations

AEs = adverse events, **APR** = acute pain relievers, **BL** = baseline, **DBP:** double-blind phase, **discAEs** = adverse events leading to discontinuation, **EQ-5D** = EuroQol 5-dimension questionnaire, **HIT-6** = Headache Impact Test, **ICHD** = International Classification of Headache Disorders, **ID** = identification, **MHDs** = monthly headache days, **(m)MIDAS** = (modified) Migraine Disability Assessment, **MMD** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life questionnaire, **n** = number, **NCT** = National Clinical Trial, **RCT** = randomised controlled trial, **RR** = response rate, **SAEs** = serious adverse events, **SD** = standard deviation, **TRAEs** = treatment-related adverse events, **UK** = United Kingdom, **USA** = United States of America

Notes

¶¶ Countries: Belgium, Bulgaria, Czechia, Denmark, Finland, France, Georgia, Germany, Hungary, Italy, Poland, Russia, Slovakia, Spain, Sweden, UK

7.3.3 Risk of bias

The quality of the RCTs included from the updated literature search was evaluated using the Cochrane RoB 2.0 tool. RoB was assessed for all clinical effectiveness and safety outcomes combined. The RoB graph and RoB summary for the newly identified RCTs are reported in ***Figure PS7 2*** and

Figure PS7 3***,*** respectively.

7.3.3.1 Randomisation process

All RCTs provided adequate details and posed a low RoB for randomisation, allocation and baseline differences. Randomisation was typically assigned and concealed using a computer-generated randomisation sequence utilising an interactive web or voice response system. Drug allocation was concealed using identical packages, labelling, schedules of administration, appearance, taste and odour. Baseline differences between treatment groups appeared to be mostly balanced.

7.3.3.2 Deviation from intended intervention

All RCTs adequately reported and posed a low RoB for blinding of participants/personnel.

7.3.3.3 Missing outcome data

All studies utilised intent-to-treat or modified intent-to-treat analyses for primary outcomes. The studies utilising a modified intent-to-treat analysis required participants to have received at least one dose of the study drug and provide at least one post-baseline measurement for the outcome of interest. One RCT posed some concerns for bias due to missing outcomes data, with no details provided to account for differences in the total number of participants analysed across outcomes and timepoints.[1] This may have impacted the results; however, this omission was judged to likely not depend on its true value.

7.3.3.4 Measurement of the outcome

All RCTs posed a low RoB in measurement of the outcome. Most of the outcomes in this review were reported using patient headache diaries, which can be subjective and may be biased. However, details of how data were collected, measured and analysed were well-reported across the included RCTs, therefore it was determined that ascertainment of the outcome was unlikely to differ between intervention and comparator groups.

7.3.3.5 Selective reporting

All but one RCT had a published protocol, with adequate evidence that all outcomes and assessment timepoints were defined *a priori*.[1] Where a published protocol was unavailable, registration with a clinical trials database was checked. Although the DRAGON trial[1] was registered with a clinical trials database, no published results are currently available to check the adequate reporting of outcomes and timepoints. Therefore, this trial was judged to pose some concerns for selective reporting.

Figure PS7 2 Risk of bias graph for RCTs assessing clinical effectiveness and safety outcomes combined (updated literature search)

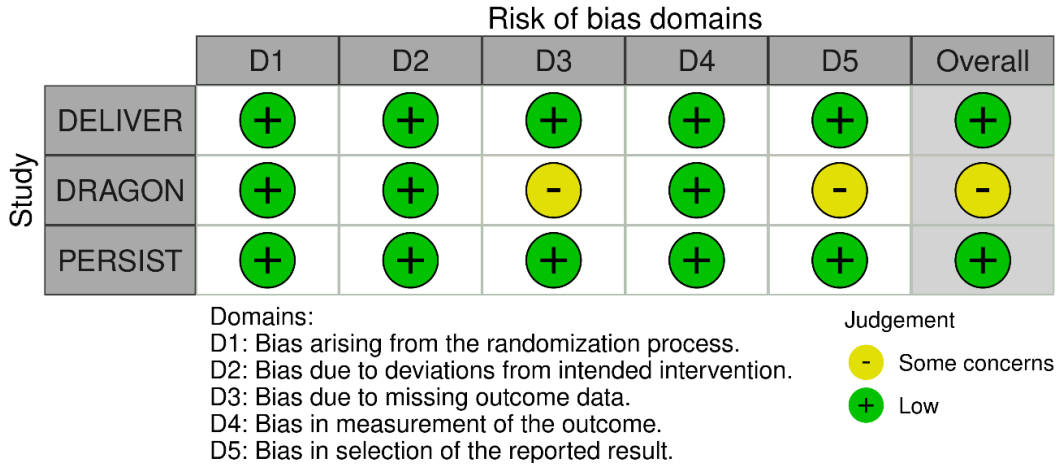
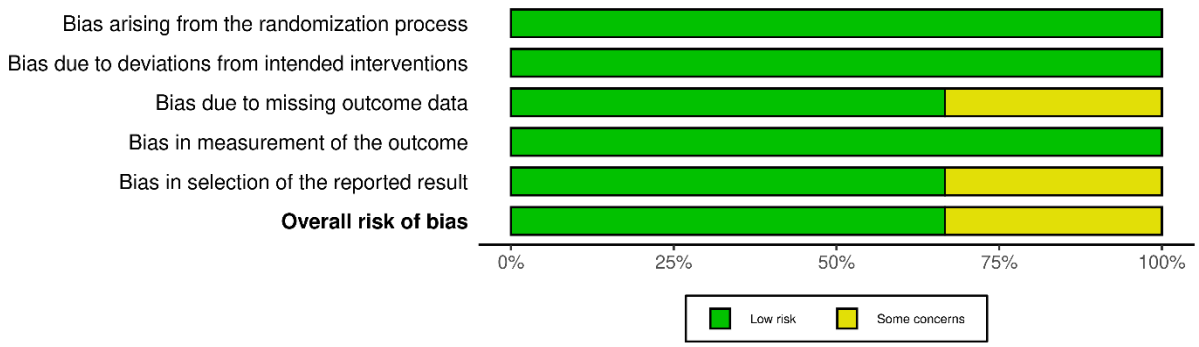


Figure PS7 3 Risk of bias summary for clinical effectiveness and safety outcomes in the RCTs (updated literature search)



7.3.4 Applicability of evidence to Switzerland

In accordance with the characteristics described in ***Section 7.2.2.4*** a few notable attributes of the newly identified RCTs from the updated literature search deserve mention.

Firstly, the included studies were mostly consistent with Swiss practice. The dose, administration technique, administration frequency and brand (when specified) of erenumab, eptinezumab and galcanezumab were the same as those listed on the Spezialitätenliste.

Secondly, 2 of the RCTs included from the updated literature search (DRAGON 2022 and PERSIST 2022) were conducted solely in Asia.[1,2] These trials may be less representative of the Swiss population, as the prevalence of migraine has been reported to be lower in Asian populations.[5,6] The one RCT with centres in Europe had no study centres in Switzerland, but is likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. broadly following European Headache Federation guidelines)[7] and healthcare systems.

Finally, none of the RCTs allowed the use of concomitant preventive migraine medications. To be eligible for inclusion in the DELIVER 2022 trial, patients were required to have previously failed 2–4 migraine preventive medication categories in the past 10 years (see ***Appendix F, Table A21*** for further details). Trials that excluded those with treatment failures are less representative of the Swiss clinical context.

7.3.5 Findings

Results are summarised per trial for each relevant PICO outcome.

7.3.5.1 DRAGON 2022

DRAGON 2022[1] sought to investigate the use of erenumab 70 mg compared to placebo in chronic migraine patients. This RCT was assessed to pose some concerns for RoB. The effectiveness and safety results were generally consistent with the findings summarised in ***Section 7.2.3.1*** and ***Section 7.2.4.1.*** One other RCT in the original analysis reported results that investigated the use of erenumab 70 mg in chronic migraine patients at 3 months.[8] Both trials showed a similar direction of effect in effectiveness and safety outcomes reported at this timepoint.[1,8]

7.3.5.1.1 Effectiveness outcomes

- **MMDs** were significantly less frequent in patients randomised to erenumab 70 mg compared to placebo at week 4 (MD -2.53, 95% CI: -3.54 to -1.52, p < 0.001), week 8 (MD -1.96, 95% CI: -3.10 to -0.82, p = 0.001) and week 12 (MD -1.57, 95% CI: -2.83 to -0.30, p = 0.01).
- No significant differences in **MHDs with acute medication use** were reported between those randomised to erenumab 70 mg or placebo at week 12 (MD -0.67, 95% CI: -1.76 to 0.41, p = 0.223).
- The **response rate (50%)** was significantly greater in patients randomised to erenumab 70 mg compared to placebo at week 4 (OR 2.19, 95% CI: 1.48 to 3.25, p < 0.001), week 8 (OR 1.72, 95% CI: 1.21 to 2.45, p = 0.002) and week 12 (OR 1.54, 95% CI: 1.09 to 2.17, p = 0.014).
- No significant differences in **mMIDAS** scores were reported between those randomised to erenumab 70 mg or placebo at week 12 (MD -1.74, 95% CI: -5.06 to 1.58, p = 0.305).

7.3.5.1.2 Safety outcomes

- No significant differences in the number of **AEs** were reported between erenumab 70 mg and placebo at week 12 (OR 0.92, 95% CI: 0.66 to 1.29, p = 0.64).
- No significant differences in the number of **TRAEs** were reported between erenumab 70 mg and placebo at week 12 (OR 0.96, 95% CI: 0.59 to 1.58, p = 0.88).
- No significant differences in the number of **SAEs** were reported between erenumab 70 mg and placebo at week 12 (OR 1.00, 95% CI: 0.34 to 2.88, p = 0.99).
- No significant differences in the number of **AEs leading to discontinuation** were reported between erenumab 70 mg and placebo at week 12 (OR 1.00, 95% CI: 0.14 to 7.12, p = 0.99).

7.3.5.2 DELIVER 2022

DELIVER 2022[3,4] sought to investigate the use of eptinezumab 100 mg and eptinezumab 300 mg compared to placebo in episodic and chronic migraine patients with 2–4 prior treatment failures. This RCT was assessed to pose a low RoB. The effectiveness and safety results published by this RCT fill a gap in the original analyses (***Section 7.2.3.1*** and ***Section 7.2.4.1***) as none of the included RCTs in this HTA reported results on eptinezumab 100 mg or eptinezumab 300 mg in this specific population of interest.

7.3.5.2.1 Effectiveness outcomes

- At 1–12 weeks, **MMDs** were significantly less frequent in patients randomised to eptinezumab 100 mg (MD -2.7, 95% CI: -3.4 to -2.0, p < 0.0001) and eptinezumab 300 mg (MD -3.2, 95% CI: -3.9 to -2.5, p < 0.0001) compared to placebo. At 13–24 weeks, **MMDs** were significantly less frequent in patients randomised to eptinezumab 100 mg (MD -3.0, 95% CI: -3.8 to -2.2, p < 0.0001) and eptinezumab 300 mg (MD -3.7, 95% CI: -4.5 to -3.0, p < 0.0001) compared to placebo.
- At 1–12 weeks, **MHDs** were significantly less frequent in patients randomised to eptinezumab 100 mg (MD -2.6, 95% CI: -3.3 to -1.9, p < 0.0001) and eptinezumab 300 mg (MD -3.0, 95% CI: -3.7 to -1.9, p < 0.0001) compared to placebo. At 13–24 weeks, **MHDs** were significantly less frequent in patients randomised to eptinezumab 100 mg (MD -3.0, 95% CI: -3.8 to -2.3, p < 0.0001) and eptinezumab 300 mg (MD -3.6, 95% CI: -4.4 to -2.9, p < 0.0001) compared to placebo.
- At 1–12 weeks, significant reduction in **MHDs with acute medication use** were reported between those randomised to eptinezumab 100 mg (MD -2.5, 95% CI: -3.2 to -1.9, p < 0.0001) and eptinezumab 300 mg (MD -3.0, 95% CI: -3.6 to -2.4, p < 0.0001) compared to placebo. At 13–24 weeks, **MHDs with acute medication use** were significantly less frequent in patients

randomised to eptinezumab 100 mg (MD -2.9, 95% CI: -3.6 to -2.2, p < 0.0001) and eptinezumab 300 mg (MD -3.5, 95% CI: -4.2 to -2.8, p < 0.0001) compared to placebo.

- At 1–12 weeks the **response rate (50%)** was significantly greater in patients randomised to eptinezumab 100 mg (OR 4.9, 95% CI: 3.3 to 7.5, p < 0.0001) and eptinezumab 300 mg (OR 6.6, 95% CI: 4.4 to 10.0, p < 0.0001) compared to placebo. At 13–24 weeks, the **response rate (50%)** was significantly greater in patients randomised to eptinezumab 100 mg (OR 3.56, 95% CI: 2.50 to 5.10, p < 0.0001) and eptinezumab 300 mg (OR 4.69, 95% CI: 3.29 to 6.75, p < 0.0001) compared to placebo.
- At 1–12 weeks, the **response rate (75%)** was significantly greater in patients randomised to eptinezumab 100 mg (OR 9.2, 95% CI: 4.2 to 24.4, p < 0.0001) and eptinezumab 300 mg (OR 11.4, 95% CI: 5.2 to 30.2, p < 0.0001) compared to placebo. At 13–24 weeks, the **response rate (75%)** was significantly greater in patients randomised to eptinezumab 100 mg (OR 3.8, 95% CI: 2.2 to 6.6, p < 0.0001) and eptinezumab 300 mg (OR 5.3, 95% CI: 3.20 to 9.20, p < 0.0001) compared to placebo.
- At 12 weeks, significant improvements were reported for all **MSQ** domains in patients randomised to eptinezumab 100 mg (**RFR:** MD 11.3, 95% CI: 8.0 to 14.7, p < 0.0001; **RFP:** MD 11.1, 95% CI: 8.0 to 14.3, p < 0.0001; **EF:** MD 11.1, 95% CI: 7.5 to 14.6, p < 0.0001) and eptinezumab 300 mg (**RFR:** MD 15.0, 95% CI: 11.6 to 18.3, p < 0.0001; **RFP:** MD 13.5, 95% CI: 10.4 to 16.6, p < 0.0001; **EF:** MD 13.5, 95% CI: 10.0 to 17.0, p < 0.0001) compared to placebo. At 24 weeks, significant improvements were reported for all **MSQ** domains in patients randomised to eptinezumab 100 mg (**RFR:** MD 15.1, 95% CI: 11.7 to 18.5, p < 0.0001; **RFP:** MD 12.6, 95% CI: 9.4 to 15.8, p < 0.0001; **EF:** MD 14.1, 95% CI: 10.5 to 17.7, p < 0.0001) and eptinezumab 300 mg (**RFR:** MD 15.0, 95% CI: 11.6 to 18.4, p < 0.0001; **RFP:** MD 13.2, 95% CI: 10.1 to 16.4, p < 0.0001; **EF:** MD 14.1, 95% CI: 10.6 to 17.7, p < 0.0001) compared to placebo. At week 12 and week 24, the between-group MDs for all MSQ domains (RFR, RFP and EF) were greater than the reported MIDs in ***Appendix E***.
- At 4 weeks, mean **HIT-6** score was significantly reduced in patients randomised to eptinezumab 100 mg (MD -4.9, 95% CI: -6.0 to -3.7, p < 0.0001) and eptinezumab 300 mg (MD -5.1, 95% CI: -6.2 to -3.9, p < 0.0001) compared to placebo. At 12 weeks, mean **HIT-6** score was significantly reduced in patients randomised to eptinezumab 100 mg (MD -3.8, 95% CI: -5.0 to -2.5, p < 0.0001) and eptinezumab 300 mg (MD -5.4, 95% CI: -6.7 to -4.2, p < 0.0001) compared to placebo. At 24 weeks, mean **HIT-6** score was significantly reduced in patients randomised to eptinezumab 100 mg (MD -5.0, 95% CI: -6.3 to -3.7, p < 0.0001) and eptinezumab 300 mg (MD -6.0, 95% CI: -7.3 to -4.7, p < 0.0001) compared to placebo.

- At 4 weeks, significant improvements in **EQ-5D-5L** were reported in patients randomised to eptinezumab 100 mg (MD 4.7, 95% CI: 1.9 to 7.6, p ≤ 0.05) and eptinezumab 300 mg (MD 5.2, 95% CI: 2.4 to 8.0, p ≤ 0.05) compared to placebo. At 12 weeks, significant improvements in **EQ-5D-5L** were reported in patients randomised to eptinezumab 100 mg (MD 5.1, 95% CI: 2.2 to 8.1, p ≤ 0.05) and eptinezumab 300 mg (MD 7.5, 95% CI: 4.5 to 10.4, p < 0.0001) compared to placebo. At 24 weeks, significant improvements in **EQ-5D-5L** were reported in patients randomised to eptinezumab 100 mg (MD 4.7, 95% CI: 1.8 to 7.7, p ≤ 0.05) and eptinezumab 300 mg (MD 8.0, 95% CI: 5.1 to 10.8, p < 0.0001) compared to placebo.

7.3.5.2.2 Safety outcomes

- No significant differences in the number of **TRAEs** were reported between eptinezumab 100 mg (OR 1.11, 95% CI: 0.8 to 1.54, p = 0.53) or eptinezumab 300 mg (OR 1.04, 95% CI 0.75 to 1.44, p = 0.83) and placebo at week 24.
- No significant differences in the number of **SAEs** were reported between eptinezumab 100 mg (OR 1.25, 95% CI: 0.33 to 4.7, p = 0.74) or eptinezumab 300 mg (OR 1.79, 95% CI: 0.52 to 6.19, p = 0.35) and placebo at week 24.
- No significant differences in the number of **AEs leading to discontinuation** were reported between eptinezumab 100 mg (OR 1.00, 95% CI: 0.06 to 16.01, p = 0.99) or eptinezumab 300 mg (OR 6.19, 95% CI: 0.74 to 51.71, p = 0.09) and placebo at week 24.

7.3.5.3 PERSIST 2022

PERSIST 2022[2] sought to investigate the use of galcanezumab 120 mg compared to placebo in episodic migraine patients. This RCT was assessed to pose a low RoB. The effectiveness and safety results were generally consistent with the findings summarised in ***Section 7.2.3.1*** and ***Section 7.2.4.1***. One other RCT in the original analysis reported results that investigated the use of galcanezumab 120 mg in episodic migraine patients at 1–3 months.[9] Both trials showed a similar direction of effect in the effectiveness outcomes reported at this timepoint.[2,9] Safety timepoints differed between these 2 RCTs; PERSIST reported SAEs and adverse events leading to discontinuation at 3 months, whereas Skljarevski et al 2018 reported SAEs and adverse events leading to discontinuation at 1–12 weeks and 12–24 weeks.[2,9]

7.3.5.3.1 Effectiveness outcomes

- **MMDs** were significantly less frequent in patients randomised to galcanezumab 120 mg (MD - 1.82, 95% CI: -2.32 to -1.32, p < 0.0001) compared to placebo at 1–3 months.

- **MHDs with acute medication use** were reported to be significantly less frequent in patients randomised to galcanezumab 120 mg (MD -1.78, 95% CI: -2.25 to -1.31, p < 0.0001) compared to placebo at 1–3 months.
- **Response rate (50%)** was significantly greater in patients randomised to galcanezumab 120 mg (OR 2.48, 95% CI: 1.87 to 3.29, p < 0.0001) compared to placebo at 1–3 months.
- **Response rate (75%)** was significantly greater in patients randomised to galcanezumab 120 mg (OR 2.82, 95% CI: 2.01 to 3.97, p < 0.0001) compared to placebo at 1–3 months.
- **Response rate (100%)** was significantly greater in patients randomised to galcanezumab 120 mg (OR 3.31, 95% CI: 1.99 to 5.50, p < 0.0001) compared to placebo at 1–3 months.
- Significant improvements were reported for all **MSQ** domains in patients randomised to galcanezumab 120 mg (**RFR:** MD 7.07, 95% CI: 5.20 to 8.95, p < 0.0001; **RFP:** MD 6.03, 95% CI: 4.10 to 7.95, p < 0.0001; **EF:** MD 4.16, 95% CI: 2.00 to 6.32, p = 0.0002) compared to placebo at 1–3 months. Significant improvements in **MSQ total** were also reported in patients randomised to galcanezumab 120 mg (MD 6.17, 95% CI: 4.39 to 7.95, p < 0.0001) compared to placebo at 1–3 months. At 1–3 months, the between-group MD for MSQ RFR was greater than the MID of 3.2 points, and the between-group MD for MSQ RFP was greater than the MID of 4.6 points (***Appendix E***).
- Mean **MIDAS** score was significantly reduced in patients randomised to galcanezumab 120 mg (MD -12.43, 95% CI: -18.81 to -6.05, p = 0.0001) compared to placebo at 3 months. This trial reported an MD greater than the MIC of 4.5 points (***Appendix E***).

7.3.5.3.2 Safety outcomes

- No significant differences in the number of **TRAEs** were reported between galcanezumab 120 mg and placebo at 3 months (OR 1.3, 95% CI: 0.92 to 1.84, p = 0.13).
- No significant differences in the number of **SAEs** were reported between galcanezumab 120 mg and placebo at 3 months (OR 0.49, 95% CI: 0.09 to 2.71, p = 0.42).
- No significant differences in the number of **AEs leading to discontinuation** were reported between galcanezumab 120 mg and placebo at 3 months (OR 6.07, 95% CI: 0.73 to 50.78, p = 0.09).

7.3.6 Postface references

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8 Costs, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

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A Markov model was developed to quantify the cost-utility of CGRP antagonists using incremental quality-adjusted life years (QALY) with univariate, scenario and probabilistic sensitivity analyses evaluating uncertainties in the model. The results have been presented as incremental cost-utility ratios (ICUR) and as a series of cost-effectiveness acceptability curves to show the probability that a given intervention can be considered cost-effective under a range of willingness-to-pay thresholds (WTPs).

CGRP antagonists are reimbursed for patients in Switzerland who have failed 2 prior preventive migraine treatments. The clinical results from trials that specifically included this patient population, or presented subgroup analyses, were used as assumptions in the modelling. The cost-effectiveness of CGRP antagonists versus best supportive care (BSC) ranged from CHF134,152 to CHF318,982 per QALY gained over an analysis period of one year among episodic migraine patients, and CHF53,067 to CHF84,033 per QALY gained among chronic migraine patients. CGRP antagonists appear to be more cost-effective among chronic migraine patients. Analyses were also conducted at 5 and 10 years. The results of this report are similar to some reviewer analyses of models submitted to the Canadian Agency for Drugs and Technologies in Health (CADTH) for reimbursement. As there were no eptinezumab trials that included patients who had failed 2 prior preventive therapies, this is not included in this range but as a sensitivity analysis in the main report.

BSC in the economic modelling section refers to the placebo arms of trials outlined in the clinical evidence section. Patients in the placebo arms were permitted to use concomitant medications, which reflects clinical practice. Only one trial was found that compared a CGRP antagonist to a preventive therapy (topiramate). Given the paucity of data, this comparison is included as a sensitivity analysis.

Univariate, probabilistic and scenario sensitivity analyses were used to explore a range of different model assumptions. Specifically, differing doses, medicine costs, Swiss-Diagnosis-related group (DRG) cost weights for health states, structural assumptions and estimated health state utilities were included in sensitivity analyses. The analyses indicated the ICUR was most sensitive to the medicine cost assumptions used in the model. Scenario analysis including the reduction in MMDs experienced by those discontinuing treatment, response rates and estimated utilities were the most important assumptions driving modelling results. Utilities were a very uncertain factor as no information on utilities was systematically collected across the clinical studies. A mapping function was used in the economic model for this report, which increases the uncertainty.

A budget impact analysis was undertaken to determine the current additional cost of CGRP antagonists. The cost of CGRP antagonists was estimated to be CHF19.3 million in 2021 and CHF25.5 million in 2022. Given the high uncertainties associated with uptake and the sensitivity of economic modelling results to medicines prices, a range of hypothetical uptake and price scenarios were included in the budget impact analysis. The net cost of CGRP antagonists increases to CHF79.9, CHF199.8 and CHF400.9 million by 2026 at current prices assuming 10%, 25% and 50% hypothetical uptake, respectively, among eligible patients.

8.1 Methodology costs, cost-effectiveness and budget impact

8.1.1 Review of economic literature

The systematic literature searches outlined in the ***HTA Protocol*** were used to identify studies assessing the economics of the CGRP antagonists for patients diagnosed with episodic and chronic migraine. The search included the listed databases (See ***HTA Protocol***), HTA agency websites (listed in ***Appendix K***) and reference lists of recent systematic reviews hand-searched for economic studies not captured in the database searches. Economic evaluations published within the last 10 years (i.e. cost-effectiveness, cost-utility, cost or cost-benefit analyses) and meeting the PICO criteria were included.

Identified economic studies that met the inclusion criteria were reviewed to inform the methodology for this HTA. The review focused on model characteristics and relevance to the evaluation (i.e. country, treatment regimen, costing year, model time horizon, study perspective, patient characteristics, type of model, included health states, nature of sensitivity analysis, discount rate, QoL measure, evaluation outcome). Data extraction was completed by one reviewer (RM). The extraction template and data are presented in ***Table 151***. Several studies—such as reviews, real-world costing analyses and migraine patient utility estimates that did not meet the review inclusion criteria but could inform the economic evaluation—were included in ***Appendix J***.

8.1.2 Methodology for the cost-effectiveness analysis

Because published economic studies identified during the search were insufficient to answer the research questions posed in this HTA, a de novo Markov model was developed to quantify the cost-utility analysis of CGRP antagonists (erenumab, fremanezumab, galcanezumab and eptinezumab) for treatment of migraine versus BSC. An overview of the modelling methodology is provided in ***Table 150***. A Markov model was used, as this structure allows longer term extrapolations included in sensitivity analyses. The model incorporates results from the clinical evaluations, which have been used as input parameters for the transition of a hypothetical cohort of patients through the included health states.

The model was developed using TreeAgePro (TreeAge Software, Inc, 1 Bank Street Williamstown, MA, 01267 USA).[133] ICURs were calculated using base case unit costs and health outcomes were reported as QALYs at 1, 5 and 10 years. Costs and QALYs were discounted at 3% per annum in the base analysis and a half-cycle correction was applied to both costs and health outcomes.

Table 150 Summary of the proposed economic evaluation methodology

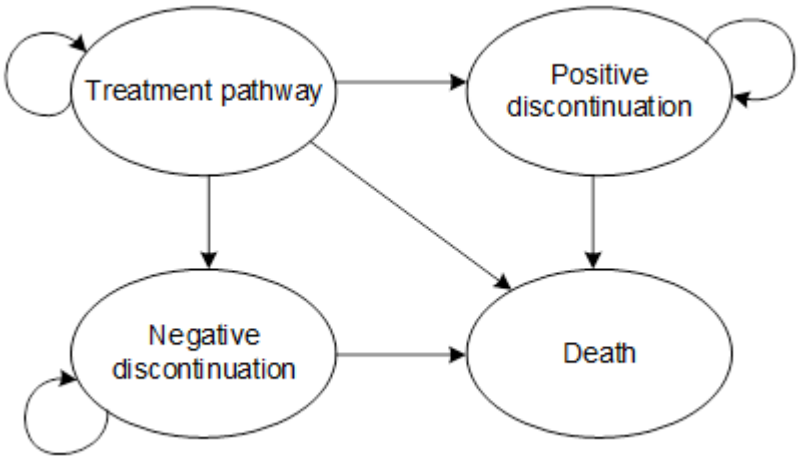
Perspective	Swiss healthcare payer
Patient population	Swiss patients diagnosed with episodic migraine for at least 1 year who did not respond or who insufficiently responded to at least 2 other prevention therapies and patients experiencing chronic migraine for at least 1 year who insufficiently responded to at least 2 other prevention therapies
Intervention	• Erenumab (Aimovig®) • Fremanezumab (Ajovy®) • Galcanezumab (Emgality®) • Eptinezumab (Vyepti®)
Comparator	BSC (i.e. placebo arm of key RCTs, as these RCTs allowed use of concomitant migraine medications)
Type of economic evaluation	CUA
Time horizon	1, 5 and 10 years
Sources of inputs	Published meta-analyses, RCTs, observational studies, Spezialitätenliste, TARMED, Swiss DRG, Swiss clinical expert opinion
Costs	Direct medical costs (CHF) (Pharmaceutical costs, outpatient and inpatient medical care costs)
Effect measure	QALYs
Discount rate	3.0% p.a. for both costs and QALYs

Abbreviations
BSC = best supportive care, **CHF** = Swiss francs, **CUA** = cost-utility analysis, **DRG** = diagnosis-related group, **RCT** = randomised controlled trial, **p.a.** = per annum, **QALYs** = quality-adjusted life years.

The structure of the Markov model is presented in ***Figure 39***. The model includes 4 states: treatment pathway (CGRP antagonist or BSC), positive discontinuation, negative discontinuation and death. Patients can transition from CGRP antagonists to negative discontinuation as part of clinical assessments and because of patient preference or AEs. Swiss patients need to demonstrate some reduction in MMDs at 3 months and at least 50% reduction in baseline MMDs at 6 months during clinical assessments to continue reimbursed treatment to 12 months.

A negative discontinuation transition probability at 6 months is included in the model to reflect the 50% MMD reduction stopping rule. Trials did not comprehensively report the proportion of patients who showed some MMD reduction at 3 months, so the model includes a negative discontinuation probability associated with clinical assessment at 6 months. Assumptions are derived from 50% response rates reported in key clinical trials. After 6 months, patients may discontinue as a result of AEs or due to patient preference. A >6 month transition probability is included from 6 months onward to account for longer-term CGRP antagonist negative discontinuation.

Figure 39 Markov model structure



All Swiss patients cease being eligible for treatment reimbursement at 1 year and are assumed to recommence using CGRP antagonists after 3 months, following clinical guidance. This stopping rule is included in the 5- and 10-year models. Responding patients remain in the CGRP antagonist treatment pathway state but return to baseline MMDs for 3 months during the period that they are assumed not to use CGRP antagonists. They return to longer-term treatment MMDs once treatment recommences, along with longer-term (>6 month) CGRP antagonist negative discontinuation assumptions. There is some uncertainty associated with this assumption, as some re-uptake patients may experience increased headache days during the first month after the break. Consequently, modelling projections longer than 1 year are included as sensitivity analyses.

Some models submitted to HTA agencies allow patients to transition to a positive discontinuation state from the on-treatment state. Patients in this state are assumed to experience on-treatment QoL without using CGRP antagonists. This possibility is included as a sensitivity analysis. Patients can transition to death from all states and this transition is derived from Swiss life tables. Non-responding patients cannot transition from discontinuation states back to the on-treatment state.

The analysis took the perspective of a healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance have been included, irrespective of the actual payer (mandatory health insurer, other social insurer, government [federal, cantons, communities] or out-of-pocket). The analysis does not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs. Costs for health states were taken from Swiss DRG costs.[134] The Spezialitätenliste was used for medicine costs, and TARMED for general doctor and neurologist costs. Probabilistic sensitivity analysis was performed to account for uncertainty in input parameters. The analysis involved 10,000 iterations, which were used to calculate 95% CI.

Sensitivity of the results to different model assumptions was explored in univariate and scenario sensitivity analyses.

8.1.3 Methodology for budget impact analysis

8.1.3.1 Patient numbers

Swiss Tarifpool data for CGRP antagonist packs sold in Switzerland from 2018 to 2021 has been used to estimate current patient numbers.[28] Translating pack sales into number of patients using CGRP antagonists is difficult, as adherence, rate of real-world response and the distribution of patients using various CGRP antagonist regimes across Switzerland are unknown. The literature was reviewed and response rates from trials outlined in the clinical evidence were used to derive average numbers of doses per CGRP antagonist treated patient. These are outlined in the budget impact section.

8.1.3.2 Budget impact analysis

Projected costs to the payer for CGRP antagonist treatment of migraine over the next 5 years have been calculated as part of the budget impact analysis. This is conducted from the perspective of a Swiss healthcare payer using an epidemiological approach and market share of the 4 CGRP antagonists currently reimbursed in Switzerland.

Hypothetical uptake scenarios among the current eligible population are estimated for current CGRP antagonist sales, using an assumed number of doses per average patient, along with projections of future uptake scenarios (10%, 25%, and 50% uptake by 2026), based on uptake growth assumptions using the current market shares of CGRP antagonists.

CGRP antagonists were introduced in Switzerland as a preventive treatment for patients who failed ≥2 preventive treatments, so the introduction is not assumed to substitute for other therapies and instead represents an additional cost.

8.2 Results of the literature review

8.2.1 Included studies

The literature search conducted in the clinical section (***Section 7.2.1***) identified 39 studies from databases and reference lists in the systematic reviews of Ruggeri et al 2020 and Mahon et al 2020.[135,136] Data were extracted from 6 published economic studies[137-142] that met the inclusion criteria and 6 HTA agency reviews[143-148] of sponsor-submitted models (***Table 151***). Rationales for inclusion and exclusion of studies are presented in ***Appendix I***. The most frequent reasons for exclusion were the intervention being onabotulinumtoxinA or topiramate rather than CGRP antagonists or the study being a general study about migraine burden of disease, QoL or treatment costs.

In total, 4 of the 6 included published economic studies were prepared by authors employed by or receiving payment from pharmaceutical companies for study publication (see ***Table 151***). HTA agency websites were also searched, with results presented in ***Appendix K***. Reviews of sponsor-submitted models by CADTH and the UK National Institute for Health and Care Excellence (NICE) are summarised in ***Appendix L***.

Table 151 Data extraction template of cost and cost-effectiveness studies

Health economic evaluation summary													
Study and Declarations	**Country**	**Treatment regimen,**	**Costing Year**	**Model time horizon**	**Study Perspective**	**Patient characteristics**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Mahon et al 2021[137] Some authors were employees of Novartis	Sweden	-Erenumab administered at 4-week intervals, base case 140 mg dose -Best supportive care, acute treatment (triptans, analgesics, etc.)	2019	10 years	Societal	-At least 4 MMDs per month -2 or more previous preventive treatments failed	Hybrid decision and Markov model	-Responder -Non-responder -On-treatment -Negative discontinue -Re-evaluation -Positive discontinue	-Dose -Time -Line of therapy -Trials included -Response -Treatment effect -Proportion CM	3%	Randomised controlled trials, NCT02066415,[79] STRIVE,[48] ARISE[75] and LIBERTY[49]	MSQ-mapped EQ-5D values	Cost per QALY gained
Irimia et al 2021[138] Some authors received fees from Teva Spain for manuscript presentation	Spain	-Fremanezumab -Erenumab -Galcanezumab -OnabotulinumtoxinA	2017	12 weeks	Payer	-EM and/or CM -Treatment duration of 12 weeks	Cost model	Treated patient	-Patients with EM or CM -Duration of CGRP antagonist treatment	Nil	Fremanezumab, HALO EM/CM[86,89] and FOCUS[91] Erenumab, STRIVE,[48] ARISE[75] Galcanezumab, EVOLVE-1[92] and 2,[93] REGAIN[50] OnabotulinumtoxinA, PREEMPT,[149] COMPEL[150]	Nil	Cost per patient
Giannouchos et al 2019[139]	Greece	-Erenumab -OnabotulinumtoxinA	2019	1 year	Societal	Patients with CM	Decision model	0–3 migraine days/month to 24–30 migraine days/month	-Co-pay -QALYs -Adherence -Effectiveness -Triptan use -Utilisation	Nil	Controlled clinical trials and a pooled analysis of the 2 trials for OnabotulinumtoxinA	EQ-5D	Cost per QALY gained
Porter et al 2019[140] Some authors were employees of Amgen	Global	-Erenumab -Placebo	2018	1 month	Societal	-4–14 headache days, -≥15 days, of which ≥8 were migraine	Cost model	Arms of trial	NA	NA	STRIVE[48] and ARISE[75] trials for EM patients, trial NCT02066415[79] for CM patients. Trials data converted to monthly estimates of costs	NA	Cost per migraine day and month

Health economic evaluation summary													
Study and Declarations	**Country**	**Treatment regimen,**	**Costing Year**	**Model time horizon**	**Study Perspective**	**Patient characteristics**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Sussman et al 2018[141] Study sponsored by Amgen	USA	-Erenumab 140 mg -OnabotulinumtoxinA -No preventive treatment	2017	2 years	Societal and payer	Adult, EM and CM failed preventive therapy	Markov model	0–3 migraine days/month to 24–30 migraine days/month	-Utilities -Costs -Attack rate	3%	EM and CM clinical trials and onabotulinumtoxinA CM clinical trial	EQ-5D	Cost per QALY gained
Lipton et al 2018[142]	USA	-Erenumab 140 mg -standard of care, acute cases -Scenario onabotulinumtoxinA	2017	10 years	Societal and payer	EM and CM failed preventive therapy	Markov model	MMD continuous	-Discount -Utilities -Discontinuation -Costs -Productivity	3%	-Network meta-analysis of discontinuation in 9 clinical studies -Previous model	MSQ-mapped EQ-5D values	Cost per QALY gained
NICE Sponsor-submitted model for Erenumab[143]	UK	-50% of patients initiated on 70 mg dose and 50% on 140 mg dose -Placebo arms from clinical trials. - onabotulinumtoxinA also considered	2018	10 years	NHS and Social Services	-≥3 prior failed prophylactic treatments ->4 MMDs per month	Hybrid decision and Markov model	-Responder -Non-responder -On-treatment -Negative discontinue -Re-evaluation -Positive discontinue	-Dose -Time -Line of therapy -Trials included -Response -Treatment effect -Proportion CM	3.5%	Randomised controlled trials, NCT02066415,[79] STRIVE,[48] ARISE[75] and LIBERTY[49]	MSQ-mapped EQ-5D values	Cost per QALY gained
NICE Sponsor-submitted model for Fremanezumab[144]	UK	-Single injection monthly (225 mg) or 3 injections every 3 months (675 mg). -Best supportive care informed by the placebo control arm of FOCUS	2019	10 years	NHS and Personal Social Services	-≥3 prior failed prophylactic treatments ->4 MMDs per month	Decision tree before a state transition model	-Responder -Non-responder -MMD health states	-Tornado diagrams redacted	3.5%	Randomised controlled trial, FOCUS	MSQ-mapped EQ-5D values	Cost per QALY gained

Health economic evaluation summary													
Study and Declarations	**Country**	**Treatment regimen,**	**Costing Year**	**Model time horizon**	**Study Perspective**	**Patient characteristics**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
NICE Sponsor-submitted model for Galcanezumab[143,145]	UK	-Loading dose of 240 mg followed by a single monthly injection - Galcanezumab at a dose of 120 mg -Best supportive care, acute treatment (triptans, analgesics, etc.) -OnabotulinumtoxinA in CM patients	2020	25 years	NHS and Social Services	-4 migraine days per month -Failed ≥ 3 prior prophylactic treatments	Hybrid decision and Markov Model	-Responder -Non-responder -On-treatment -Off treatment -Death	-Tornado diagrams redacted	3.5%	EVOLVE-1 and EVOLVE-2 and REGAIN trials	MSQ-mapped EQ-5D values	Cost per QALY gained
CADTH [146] Sponsor-submitted model for Erenumab[143]	Canada	-Erenumab 70 mg or 140 mg administered subcutaneously, once monthly -Best supportive care, acute treatment (triptans, analgesics, etc.) -OnabotulinumtoxinA in CM patients only	2019	5 years	Canadian publicly funded health care payer	-At least 4 MMDs per month -8 migraine days per month and previously failed at least 2 migraine preventive therapies	Hybrid decision and Markov model	-Responder -Non-responder -On-treatment -Negative discontinue -Re-evaluation -Positive discontinue	-Dose -Time -Line of therapy -Trials included -Response -Treatment effect -Proportion CM	3%	Randomised controlled trials, NCT02066415,[79] STRIVE,[48] ARISE[75] and LIBERTY[49]	MSQ-mapped EQ-5D values	Cost per QALY gained
CADTH [147] Sponsor-submitted model for Fremanezumab	Canada	-Fremanezumab, 225 mg subcutaneous injection: 225 mg monthly or 675 mg quarterly -Placebo, erenumab, galcanezumab, onabotulinumtoxinA	2019	10 years	Canadian publicly funded health care payer	-At least 4 MMDs per month	Markov model	-On-treatment -Off-treatment -Death	-Time horizon -Discount rate -Societal perspective -Utilities -Stopping rules -Alternative comparators -<2 prior therapies	1.5%	HALO CM, HALO EM, and FOCUS	MSQ-mapped EQ-5D values	Cost per QALY gained

Health economic evaluation summary													
Study and Declarations	**Country**	**Treatment regimen,**	**Costing Year**	**Model time horizon**	**Study Perspective**	**Patient characteristics**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
CADTH [148] Sponsor-submitted model for Galcanezumab	Canada	-Galcanezumab. 240 mg (administered as 2 consecutive injections of 120 mg), followed by once monthly doses of 120 mg -Best supportive care, consisting of acute medication for migraine as permitted in the CONQUER trial	2021	20 years	Canadian publicly funded health care payer	-Adults at least 4 migraine days per month and -Failed 2 prior preventive treatments	Semi-Markov model	-On-treatment, -Off-treatment due to nonresponse -Off-treatment due to AEs -Death	-Discount rate -Time horizon -Response definition -Treatment-waning assumption -MMD distribution -Removing hospitalisations -Incorporating all-cause discontinuation -Societal perspective	1.5%	CONQUER trial	MSQ-mapped EQ-5D values	Cost per QALY gained

Abbreviations

AEs = adverse events, **CGRP** = calcitonin gene-related peptide, **CM** = chronic migraine, **EM** = episodic migraine, **EQ-5D** = EuroQol-5D, **MMD** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life Questionnaire 2.1, **NA** = not applicable, **NHS** = National Health Service, **QALY** = quality-adjusted life year, **QoL** = quality of life, **UK** = United Kingdom, **USA** = United States of America.

The 12 economic studies[137-148] included in this review are outlined in the following description, which includes assessment using elements of the Drummond criteria for determining the quality of economic evaluations.[151] Each description outlines patient characteristics, intervention, comparator, modelling approaches, outcomes and costs.

Existing published evidence was assessed for applicability to the HTA key questions relating to cost-effectiveness analyses (CEA). No evidence directly answering this HTA key question within the Swiss context was identified, therefore a de novo economic evaluation has been conducted. Evaluation methods employed in previous cost-effectiveness studies have been used to inform the modelling strategies for a de novo evaluation.

8.2.1.1 Patient characteristics

Following ***HTA Questions 7 and 8***, the economic evaluation considers Swiss episodic and chronic migraine patients who did not respond or insufficiently responded to ≥2 other prevention therapies.

Economic studies identified in the review (see ***Table 151***) varied in the types of included patients. The economic evaluation by Porter et al 2019 was based on clinical evidence from the STRIVE and ARISE trials, which recruited episodic migraine patients with 4–14 MMDs and MHDs, and the NCT02066415 trial, which recruited chronic patients with more than 15 MHDs.[48,75,79,140] Mahon et al 2021 included patients from the trials NCT02066415, STRIVE, ARISE and LIBERTY with at least 4 MMDs per month and patients who had failed 2 previous preventive treatments due to insufficient treatment response or AE-related discontinuation.[48,49,75,79,137] Patients seeking specialist care by a neurologist or headache expert were also included.

The Sussman et al 2018 economic model incorporated chronic migraine and episodic migraine cohorts, with all patients having failed at least one previous preventive treatment.[141] Patients in the episodic migraine cohort had 4–14 MMDs, while patients in the chronic migraine cohort must have had at least 15 MMDs.[141] The average ages and gender balances from the clinical trials used in the Sussman et al 2018 study were similar for episodic migraine (40.9 years, 85.6% female) and chronic migraine (41.9 years, 84.0% female) patients.[141]

The Lipton et al 2018 (see ***Table 151***) evaluation included subgroups of patients who had previously failed preventive therapy.[142] Failure was reported for those who had discontinued treatment due to limited efficacy or intolerability. Because chronic patients are more likely to seek treatment, the overall migraine patient population was modelled from a composition of 33% episodic migraine and 67% chronic migraine patients.[142]

The erenumab model submitted to CADTH included a base case intervention for adult patients who have at least 4 MMDs and a reimbursement request analysis for adult patients who have at least 8 MMDs and previously failed at least 2 migraine preventive therapies.[146] The comparator was BSC, which included treatment with acute medications and medical management involving general practice (GP) and emergency department visits. Both populations were stratified for episodic migraine and chronic migraine patients, with episodic migraine being <15 monthly headache days, of which 4 to 15 are MMDs, and for chronic migraine patients, ≥15 monthly headache days, of which 8 or more are MMDs. The base case analysis assumed 46% and 54% of patients experienced episodic and chronic migraine, respectively (derived from the CHORD study), and 68% and 32% had episodic and chronic migraine, respectively, in the reimbursement request analysis. The model starting population was 82.8% female with a mean age of 42 years, which was derived from the STRIVE clinical trial.

The model submitted to NICE (outlined in committee papers) in the UK was similar to that assessed by CADTH.[143] CADTH noted the structure included a decision tree for the 12-week assessment period (classifying patients as responders or non-responders), then a Markov model with 12-week cycle lengths. Erenumab was compared to standard of care in episodic migraine, and to onabotulinumtoxinA and standard of care in chronic migraine.

The economic model developed in this study includes episodic and chronic migraine patients. This distinction is consistent with the HTA questions of the study. Characteristics of patients in pivotal trials have been compared to the Swiss context. The comparison includes dimensions such as age, gender, experience of episodic or chronic migraine, and failure of prior preventive treatments.

8.2.1.2 Intervention

The identified economic models include a range of CGRP antagonists and dosing regimens (summarised in ***Table 151***). Mahon et al 2021 evaluated erenumab (140 mg) administered in 4-week intervals in their base case.[137] Studies by Porter et al 2019 and Lipton et al 2018 also included erenumab as the intervention.[140,142] Irimia et al 2021 compared fremanezumab with other CGRP antagonists to determine AE costs.[138]

The HTA questions for this HTA relate to erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®). As per COGE GmbH Tarifpool © SASIS AG sales data from 2022, erenumab is the most widely used CGRP antagonist in Switzerland, at 66% of all packs sold. The next most utilised is galcanezumab (19%), then fremanezumab (15%), and finally eptinezumab (0.5%).[28] Given the widespread utilisation of erenumab, this CGRP antagonist is presented as the first intervention modelled in the economic evaluation. Analyses are also undertaken for galcanezumab, fremanezumab and eptinezumab.

8.2.1.3 Comparator

Many of the identified economic studies in this review used acute care as the comparator (***Table 151***).[137,141,142] In the case of Mahon et al 2021,[137] this involved reported outcomes from the placebo arm of the RCTs NCT02066415, STRIVE, ARISE and LIBERTY, in which acute medication was allowed for placebo-treated patients.[48,49,75,79] Lipton et al 2018 noted that in clinical practice most patients are managed with acute treatments.[142] OnabotulinumtoxinA is used after the failure of prior preventive treatments but is only indicated for chronic migraine patients. Lipton et al 2018 included a scenario where erenumab was compared to onabotulinumtoxinA in a chronic migraine population.[142] Giannouchos et al 2019 used onabotulinumtoxinA as the comparator,[139] Porter et al 2019 used placebo,[140] and Irimia et al 2021 used placebo in a similar way to Mahon et al 2021.[137,138] Irimia et al 2021 used erenumab, galcanezumab and onabotulinumtoxinA as comparators for fremanezumab when costing AEs among CGRP antagonist treatments.[138]

The ***HTA protocol*** indicated that the comparator to be included in this economic study is BSC for migraine prevention, which includes beta blockers (propranolol, metoprolol), calcium antagonists (flunarizine), anticonvulsants (topiramate) and antidepressants (amitriptyline). OnabotulinumtoxinA is not reimbursed in Switzerland, so this medicine is not considered. Preventive treatment was only included in one identified RCT,[80] with most trials including a placebo comparison, which allowed acute treatment. Correspondingly, the placebo arms of trials in which acute care was allowed is the comparator used in this economic analysis and is referred to as BSC. The nature of acute care allowed in included trials is outlined in ***Appendix F***. Results of the preventive treatment comparator trial (erenumab versus topiramate) are included as a sensitivity analysis.

8.2.1.4 Modelling approaches

Modelling approaches are summarised for each of the included economic studies (***Table 151***).[151] Four published studies determined the cost-effectiveness of CGRP antagonists for the preventive treatment of migraine;[137,139,141,142] the other published studies present cost-per-patient treatment models.[138,140] Irimia et al 2021 compared the cost of AEs associated with preventive treatment of migraine with fremanezumab versus erenumab, galcanezumab and onabotulinumtoxinA.[138] Porter et al 2019 compared the costs of treatment and productivity losses associated with migraine.[140] All 6 studies submitted by sponsors for reimbursement in the UK and Canada determined the cost-effectiveness of CGRP antagonist treatments for the preventive treatment of migraine.

Nine studies employed Markov models.[137,141-148] Mahon et al 2021 and a number of the sponsor submitted models used a hybrid decision tree plus Markov model, Sussman et al 2018 used a hybrid

Monte Carlo patient simulation and Markov cohort model, and Lipton et al 2018 used a Markov health state-transition model.[137,141,142]

The nature of the health states included in the models varied. Mahon et al 2021 included responder and non-responder states for the assessment period, then on-treatment, negative discontinuation re-evaluation and positive discontinue states for the extrapolated Markov model projection.[137] Lipton et al 2018 included health states for patients on preventive treatment, off preventive treatment and dead.[142]

Sussman et al 2018 formulated MMD categories for the episodic and chronic migraine cohorts.[141] The migraine days per month for each state were 0–3, 4–9 and 10–14 MMDs for episodic migraine patients, and 15–19, 20–23 and 24–30 MMDs for the chronic migraine group. Porter et al 2019 developed a model that was linked to arms of trials, and Irimia et al 2021 calculated AE rates for fremanezumab versus erenumab, galcanezumab and onabotulinumtoxinA using trial data.[138,140]

8.2.1.5 Model time horizon

The time horizons of costs and benefits were stated for the modelling studies outlined in ***Table 151***. Mahon et al 2021 employed a 10-year time horizon, which the authors considered to be a conservative approach.[137] They noted the Martelletti 'My Migraine Voice' global study reported participants had migraine for an average of 11.6 years, although 27% had migraine for more than 20 years.[152] Lipton et al 2018 had a similar 10-year timeframe, with a model cycle length of 28 days.[142] Sussman et al 2018 included a similar cycle length of 1 month, but the timeframe of the analysis was 2 years.[141] The Porter et al 2019 study included trial data for up to 24 weeks for episodic migraine patients and 12 weeks for chronic migraine patients.[140] Trial data were used to calculate daily and monthly migraine costs. Irimia et al 2021 included trial data with a similar length of maximum follow-up of 12 weeks.[138]

The appropriate timeframe for economic models was a major consideration for the CADTH and NICE review groups when assessing sponsor-submitted models (see ***Appendix L***). Of the CADTH sponsor-submitted economic models, the erenumab model had a time horizon of 5 years, fremanezumab 10 years and galcanezumab 20 years.[146-148] In the case of NICE, the erenumab submitted model had a time horizon of 10 years, fremanezumab 10 years and galcanezumab 25 years.[143-145] The NICE fremanezumab review group concluded that, 'on balance a 10-year time horizon is reasonable, given the competing requirements of capturing long-term treatment effect and avoiding increasing uncertainty as extrapolation lengthens.' (p. 494).[144]

CGRP antagonists are reimbursed for a maximum of one year in Switzerland, after which a patient is assessed and can then recommence treatment following clinical guidance.[2] The base model for the current evaluation has a timeframe of 1 year. Two longer extrapolations are included, being 5 years (in line with the CADTH evaluated models) and 10 years. Treatment discontinuations at 6 months and 12

months are included in this model, following stopping rules in Switzerland, along with an on-going on-treatment discontinuation associated with patient preference and AEs. A cycle length of 1 month is used, as this is the time between intervention administrations for a number of widely used CGRP antagonists.

It should be noted that the first stopping rule in Switzerland is at 3 months, where a patient can continue if some improvement is observed.[2] The proportion of patients reporting some improvement at 3 months was not systematically reported across the included trials. The proportion experiencing a 50% reduction in MMDs was commonly reported. This proportion is included at 6 months in the model. Correspondingly, modelling results are subject to uncertainty.

8.2.1.6 Discount rate

The discount rate was stated in modelling studies, generally being 3% (***Table 151***). This rate was justified by the model authors as being consistent with guidelines. In Mahon et al 2021 costs and outcomes were discounted at this rate as recommended in current Swedish Dental and Pharmaceutical Benefits Agency (TLV) guidance.[137] Lipton et al 2018 used published USA recommendations.[142,153] A 3% discount rate is included in the current economic model. It should be noted that the discount rate in economic modelling is applied to future costs and benefits to generate a present value. The discount is not related to pricing.

8.2.1.7 Sensitivity analyses

Approaches to sensitivity analyses were outlined in modelling studies along with the choice of variables for sensitivity analysis being justified (***Table 151***). Analyses were conducted for parameters such as dose, time, line of therapy, trials included, response, treatment effect on MMDs and proportion of chronic migraine patients in studies such as Mahon et al 2021.[137] These parameters vary in the current economic model. Given that erenumab has the greatest uptake in Switzerland and the evidence base for this CGRP antagonist is the most substantial, the model for this medicine is used as an exemplar for sensitivity analyses.

8.2.1.8 Outcomes and costs

8.2.1.8.1 Sources of effectiveness assumptions

The sources of effectiveness estimates used in the modelling studies were stated (***Table 151***). Most studies used the results of clinical trials to model response and MMD outcomes. The Porter et al 2019 decision model used 3 RCTs: STRIVE and ARISE for episodic migraine patients and NCT02066415 for chronic migraine patients.[48,75,79,140] Mahon et al 2021 used 4 RCTs: NCT02066415, STRIVE, ARISE and LIBERTY.[48,49,75,79,137] Irimia et al 2021 used a range of studies, due to inclusion of a wider range of CGRP

antagonists.[140] For fremanezumab, the HALO EM, HALO CM and FOCUS RCTs were used;[86,89,91] for erenumab, STRIVE and ARISE RCTs were used;[48,75] for galcanezumab, EVOLVE-1 and EVOLVE-2 and REGAIN RCTs were used;[50,92,93] and for onabotulinumtoxinA, the PREEMPT RCT and COMPEL open label study were used.[149,150] The trials in the current economic model were selected based on patient inclusion criteria of failure of ≥2 prior preventive treatments (outlined in the treatment effectiveness section). Sensitivity analyses are included for trials where these inclusion criteria were not applied.

8.2.1.8.2 Modelling treatment effectiveness

Treatment effectiveness was captured by transition between health states and MMD days in many of the modelling studies outlined in ***Table 151***. Sussman et al 2018 assigned costs and utilities based on the number of MMDs at the end of the first cycle, which were held constant across the model's timeframe due to limited long-term efficacy data.[141] In Lipton et al 2018,[142] patients on treatment were subject to a rate of discontinuation taken from the clinical evidence.

Mahon et al 2021 included a decision tree for the 12-week clinical trial assessment phase.[137] The model captured patient baseline MMD distributions, along with the proportion of responders at week 12, and associated MMD distributions for responders and non-responders. The Mahon et al 2021 Markov model covered a post-trial period, where non-responders discontinued treatment and transitioned to a negative discontinuation state.[137] A proportion of positive responders moved to a positive discontinuation state. Patients in the negative discontinuation state were assumed to receive acute medications and experience baseline utility, while those in the positive discontinuation state stopped CGRP antagonist treatments, but experienced on-treatment utilities.

8.2.1.8.3 Utility outcomes

Quality of life measures for each of the included studies are presented in ***Table 151***. Lipton et al 2018 and Mahon et al 2021 used patient responses to the MSQ and mapped these to the EQ-5D instrument using previously published algorithms for episodic and chronic migraine patients outlined by Gillard et al 2012.[137,142,154] These authors reported algorithms for mapping using datasets collected by the International Burden of Migraine Study survey.[155] The sponsor-submitted erenumab models for CADTH and NICE outlined in ***Table 151*** also estimated utility values as a function of MMDs, derived from MSQ data collected from key trials mapped to EQ-5D.[143,146]

Sussman et al 2018 used results from the International Burden of Migraine Study survey for EQ-5D estimates.[141] Giannouchos et al 2019 employed preferences using a UK real-world setting.[136,139] The type of treatment also impacted utility, so predicted values were specified for treated (erenumab,

onabotulinumtoxinA) and untreated patients. Mahon et al 2021 predicted utility based on MMD alone and no adjustment was made for treatment impact (***Table 151***).[137]

8.2.1.8.4 Cost estimation approach

Economic modelling studies included in the current review (see ***Table 151***) examined intervention and comparator direct cost and resource use implications, which were largely specified as a function of MMDs. Quantities of resource use were generally reported separately from unit costs. Methods for estimating the quantities and unit costs were described, and currency and price data recorded for each of the identified modelling studies. For example, Mahon et al 2021 calculated costs for a given health state by multiplying the cost associated with each MMD frequency by the proportion of patients experiencing that MMD frequency in a health state.[137] Lipton et al 2018 included health services costs in their model for primary care doctor, emergency room visits, hospitalisations and specialist neurologist consultations based on published unit costs.[142] The Sussman et al 2018 study included probabilities of physician visits (0.000698), emergency department visits (0.003663) and hospitalisation (0.009985) per MMD.[141]

Relevant unit costs sourced from the Swiss Tariff System TARMED for outpatient care and DRGs for inpatient care have been included in the current model. Health service utilisation has been estimated as a function of MMDs using algorithms derived from the European wellness survey outlined by Doane et al 2020, and applied to these unit costs.[156]

8.2.1.8.5 Adverse event costs

AE disutility and costs were not generally included in identified economic models. Most of the sponsor-submitted models did not explicitly consider AEs, while Mahon et al 2021 included AEs in the discontinuations rate.[137] Sussman et al 2018 discussed AE-related costs, noting the most common types of AEs reported in erenumab trials were nasopharyngitis, upper respiratory tract infection, sinusitis, constipation, arthralgia and injection-site pain.[141] These were not thought to significantly impact healthcare resource utilisation and were not included in their model. They suggested this approach was consistent with other published migraine models that considered onabotulinumtoxinA and topiramate.[157,158] AE costs are not included in the current economic model as the safety profile of CGRP antagonists and BSC do not significantly differ in key trials. Safety is described in the clinical evaluation section of this report (***Section 7.2.4.1***) and is summarised for included trials in relevant CGRP antagonist treatment effectiveness sections of the economic analysis.

8.2.1.8.6 Indirect cost estimates

Indirect costs, such as reduced work productivity, were included in several other studies. Economic cost studies (see ***Appendix J***) by Badia et al 2004 in Spain and Pradalier et al 2004 in France found these costs to be substantial.[159,160] The cost–benefit study of Seddik et al 2021 in Germany and results of the Migraine Background Questionnaire© self-administered by patients at a screening visit for 3 phase-III clinical trials of rizatriptan reported by Gerth 2001 identified significant days lost from work.[161,162]

Productivity benefits are not included in cost-utility analysis (CUA) studies for the Swiss FOPH as the perspective chosen by the FOPH is direct medical costs covered according to mandatory social health insurance law (KVG). These have not been captured in the current model.

8.2.1.8.7 Costs of comorbidities

The costs of comorbidities (depression, anxiety etc) and clinical outcomes associated with medication overuse or headache rehabilitation have not been taken into consideration in the current economic modelling, as these outcomes were not systematically reported in the identified clinical evidence and could not be translated into QALYs.

8.2.1.8.8 Medicine costs

CGRP antagonist medicine costs associated with the intervention arm of the model are calculated by combining unit costs from the Spezialitätenliste along with dosages reported in each of the key trials.[2] Medication costs for other medicines were specified as a function of MMDs in the identified modelling studies. For example, Mahon et al 2021 specified medication usage rates as a function of migraine frequency for triptans and other acute medications.[137] Regressions were fitted to pooled NCT02066415 and STRIVE data and used to estimate the number of medication days per month for MMD days.[48,79] Usage has been specified as a function of MMDs for other medicines in the current model; unit costs were sourced from the Spezialitätenliste.[2]

8.2.1.8.9 Model results

Results of the key Markov models that estimated costs per QALY gained are summarised in this section. Limitations of the sponsor-submitted models highlighted by review groups are presented in ***Appendix L***.

Erenumab

The Mahon et al 2021 model calculated erenumab treatment resulted in incremental cost-effectiveness ratio (ICERs) of EUR3,310 (CHF3,152) and EUR28,769 (CHF27,401) per QALY gained in the total migraine and episodic migraine populations, and was dominant among chronic migraine patients.[137]

Sussman et al 2018 calculated cost-effectiveness ratios for chronic migraine patients of USD23,079 (CHF20,205) and USD65,720 (CHF57,534) versus no preventive treatment and onabotulinumtoxinA, along with USD180,012 (CHF157,595) for episodic migraine patients versus no preventive treatment.[141] Lipton et al 2018 calculated incremental QALYs of 0.185 versus BSC and estimated cost offsets due to reduced MMD of USD8,482 (CHF7,426) over 10 years.[142]

The CADTH erenumab base-case analysis (46% of patients having chronic migraine) generated an ICUR of CAD89,773 (CHF59,234) for erenumab 70 mg versus BSC and CAD84,204 (CHF55,560) for erenumab 140 mg over 5 years. CADTH revised the base case in the episodic migraine population, meaning 140 mg had an ICUR of CAD153,635 (CHF101,372) whereas 70 mg was extendedly dominated in the sequential analysis.[146] A price reduction of 64% was required for 140 mg in the base analysis to attain a WTP threshold of CAD50,000 (CHF32,990) per QALY. For NICE,[143] the erenumab base-case model for the whole population (episodic and chronic migraine) had an ICUR of GBP22,309 (CHF24,990) per QALY gained versus BSC.

Fremanezumab

The CADTH sponsor submission estimated that the ICUR for episodic migraine (2 prior preventive therapies) was CAD138,122 (CHF91,127) per QALY gained compared with BSC, and for chronic migraine (≥ 2 prior preventive therapies) CAD102,184 (CHF67,194) per QALY gained.[147] The CADTH reanalysis resulted in CAD164,243 (CHF108,363) and CAD128,950 (CHF85,078) per QALY gained among episodic and chronic patients, respectively, compared with BSC. The NICE review group highlighted that the time horizon of the base-case analyses was 10 years.[144] The basis for this timeframe was that >99% of patients were estimated to have discontinued treatment by this time, given a positive stop rate of 20% annually.[163] The CADTH review noted that fremanezumab dominated erenumab and galcanezumab in the Sponsor's economic analysis. It was highlighted that the economic modelling was not based on head-to-head evidence and heterogeneity among included patients may bias the results in favour of fremanezumab. Correspondingly, results were not considered sufficient to conclude whether fremanezumab differed in effectiveness to other comparators.

Galcanezumab

The NICE review team estimated the ICUR for galcanezumab was GBP20,000–30,000 (CHF22,400–33,601) per QALY gained compared with BSC in episodic migraine, and GBP20,000–30,000 (CHF22,400–33,601) per QALY gained compared with onabotulinumtoxinA for chronic migraine.[145] Galcanezumab had an estimated ICUR of CAD39,010 (CHF25,737) per QALY gained for episodic migraine; 99.7% of iterations were cost-effective at a WTP threshold of CAD50,000 (CHF32,988) per

QALY in the CADTH reviewed model.[148] An ICUR of CAD16,594 (CHF10,948) per QALY gained was estimated for chronic migraine patients. The CADTH reanalysis resulted in CAD273,560 (CHF180,495) and CAD109,325 (CHF72,133) per QALY gained among episodic and chronic patients, respectively, compared with BSC. Key changes includes a reduced time horizon, removal of hospital costs, utilities and migraine day stratification.[148]

8.3 Results costs, cost-effectiveness and budget impact

8.3.1 Modelling inputs assumptions summary table

8.3.1.1 Population assumptions

The starting age, gender balance and number of MMDs for chronic and episodic patients are presented in ***Table 152*** as averages and mid-range estimates from key trials.

Table 152 Summary of population characteristics for the base economic evaluation

Assumptions	Values	Source
	Base	
Starting age (years)	42	Starting age of 42 years taken from erenumab submitted model to NICE. Average age from Tepper et al 2017, ARISE and STRIVE trials
Female (%)	85	Gender balance taken from erenumab submitted model to NICE. Proportion derived from Tepper et al 2017, ARISE and STRIVE trials
Chronic migraine patient starting MMDs (days)	18	Starting MMDs assumed from mid-range of clinical evidence
Episodic migraine patient starting MMDs (days)	9	Starting MMDs assumed from mid-range of clinical evidence

Abbreviations
MMD = monthly migraine days**, NICE** = National Institute for Health and Care Excellence (UK).

8.3.1.2 Costs and utilities

Model assumptions were derived for costs and QALY health outcomes. These are summarised in ***Table 153*** along with sources and the derivation of each assumption.

Table 153 Summary of cost and utility evidence for the base economic evaluation

Assumptions	Values		Source	Section of Report
Monthly cost medicines use, monitoring and doctor visits				
Unit cost (CHF)	**Base**	**PSA Distribution**		
Erenumab	517.6	-	Spezialitätenliste. Aimovig, 70 and 140 mg/ml, pen 1 ml	***Section 8.3.1.15.1***
Fremanezumab	527.4	-	Spezialitätenliste Ajovy, 225 mg/1.5 ml, pen 1.5 ml	***Section 8.3.1.15.1***
Fremanezumab	1523.1	-	Spezialitätenliste Ajovy, 225 mg/1.5 ml, 3 pen 1.5 ml	***Section 8.3.1.15.1***

Assumptions	Values		Source	Section of Report
Eptinezumab	1521.3*	-	Spezialitätenliste, Vyepti, 100 mg/ml, 1 ml	***Section 8.3.1.15.1***
Galcanezumab	532.3	-	Spezialitätenliste, Emgality, 120 mg/ml, 1 ml	***Section 8.3.1.15.2***
Rizatriptan	46.7	Triangular	Spezialitätenliste, Maxalt, 5 mg, 6 tablets	***Section 8.3.1.15.2***
Sumatriptan	35.8	Triangular	Spezialitätenliste, Sumatriptan Sandoz, 50 mg, 6 tablets	***Section 8.3.1.15.2***
Zolmitriptan	39.6	Triangular	Spezialitätenliste, Zolmitriptan Sandoz, 2.500 mg, 6 tablets	***Section 8.3.1.15.2***
Ibuprofen	8.0	Uniform	Spezialitätenliste, Ibuprofen Mylan, Filmtabl 400 mg, Blist 50 tablets	***Section 8.3.1.15.2***
Topiramate	77.2	-	Spezialitätenliste, Topiramat Sandoz, 100 mg, 60 tablets	***Section 8.3.2.1.4***
Medicines use				
Erenumab	Monthly	-	Spezialitätenliste	***Section 8.3.1.15.1***
Fremanezumab	Monthly, Quarterly	-	Spezialitätenliste	***Section 8.3.1.15.1***
Galcanezumab	Monthly and loading	-	Spezialitätenliste	***Section 8.3.1.15.1***
Eptinezumab	Quarterly	-	Spezialitätenliste	***Section 8.3.1.15.1***
Rizatriptan, Sumatriptan and Zolmitriptan use days per month by MMDs	Linear regression intercept and variables outlined in costs section of report	-	Monthly triptan use days per MMD derived from regression included in erenumab sponsor submitted model to NICE. Assumes 1 tablet used per use day at average cost of included products	***Section 8.3.1.15.2***
Ibuprofen l use days per month by MMDs	Linear regression intercept and variables outlined in costs section of report	-	Monthly other acute medicine use days per MMD derived from regression included in erenumab sponsor submitted model to NICE. Assumes 2 tablets used per use day at average cost of included products	***Section 8.3.1.15.2***
Topiramate	100 mg/day	-	Included as sensitivity analysis	***Section 8.3.2.1.4***
Health services for medicines				
CGRP monitoring and treatment commencement (CHF)	179	Triangular. Assumes high and low costs 20% above and below mean.	Follow-up neurologist visit cost. Derived from expert clinical feedback as part of model development.	***Section 8.3.1.15.3***
Health services unit costs for medicines for disease management				
General practitioner visit (CHF)	100	Triangular. Assumes high and low costs 20% above and below base.	GP consultation assumed to cost CHF100	***Section 8.3.1.15.3***
Neurologist visit (CHF)	277	Triangular. Assumes high and low costs 20% above and below base.	Patients availing neurologist services would receive a mix of first and follow-up consultations. An average cost of CHF272 is included. Derived from expert clinical feedback as part of model development.	***Section 8.3.1.15.3***
Emergency department visit (CHF)	1,411	Triangular. Minimum value does not include imaging.	An average cost of CHF1,411 is included. The assumption is based on clinical feedback during the evaluation	***Section 8.3.1.15.3***

Assumptions	Values		Source	Section of Report
Hospital visit (CHF)	5,729	Normal	Swiss DRG B77B (Headaches and age >15 years, more than 1 day of occupancy)	***Section 8.3.1.15.3***
Health services utilisation by MMD				
Monthly general practitioner, emergency department, hospital inpatient and neurologist visits by MHDs	Linear regression intercept and variables outlined in costs section of report	Normal distribution assumed for variable	6 month utilisation rate by MHD from Doane[156] converted to monthly cycle and linear regression conducted	***Section 8.3.1.15.3***
Utility				
EQ-5D utility by MMD	Linear regression intercept and variables outlined in utility section of report	Normal distribution assumed for variable	Erenumab sponsor-submitted regression model to NICE included in committee papers based on the results of Tepper et al 2017 and mapping algorithm of Gillard et al 2012	***Section 8.3.1.14***

Abbreviations
CHF = Swiss francs, **DRG** = Diagnosis-Related Group, **EQ-5D** = EuroQol- 5 Dimension, **MHD** = monthly headache**, MMD** = monthly migraine days**, NA** = not applicable, **NICE** = National Institute for Health and Care Excellence (UK), **PSA** = probabilistic sensitivity analysis.
Notes
***** The public price of eptinezumab reduced to CHF1396 on 1 May 2023. The previous price of CHF1521 was used in the economic model. The lower price will not significantly change the ICER.
Source
Spezialitätenliste[2] 1/9/2022, for medicines.

8.3.1.3 Reduction in migraine frequency (MMDs)

Baseline MMDs for chronic and episodic patients were derived from key trials. These align with frequencies for migraine patients in Europe reported in surveys. Assumptions are outlined in ***Table 154***. Reductions in migraine frequency were included in the current economic model as MMD reductions from those at baseline, in a series of steps reflecting outcomes reported in trials. A reduction was estimated for the first 3 months, then at months 4 to 6 and in subsequent cycles.

Base case treatment effectiveness assumptions are summarised in ***Table 154*** for erenumab, ***Table 155*** for fremanezumab, and ***Table 156*** for eptinezumab and galcanezumab. Reductions in MMDs are specified for episodic and chronic migraine patients who have failed ≥2 preventive treatments across each of the CGRP antagonists.

Table 154 Summary of erenumab base case effectiveness assumptions

Assumption	Erenumab				Source
	CM		EM		
	140 mg	70 mg	140 mg	70 mg	
CGRP antagonist MMD reduction, 0-3 months	-7.0	-5.4	-2.3	-1.7	LIBERTY, STRIVE and Tepper et al 2017 trials, ***Table 161*** and ***Table 162***
CGRP antagonist MMD reduction, 4-6 months	-7.0	-5.4	-2.9	-1.5	3-month reduction from the above trials assumed for 6 months for CM group
BSC MMD reduction, 0-3 months	-2.7	-2.7	-0.3	-0.5	LIBERTY, STRIVE and Tepper et al 2017 trials, ***Table 161*** and ***Table 162***
BSC MMD reduction 4-6 months	-2.7	-2.7	-0.3	-0.3	3-month reduction from the above trials assumed for 6 months for CM group
CGRP antagonist negative discontinuation, 6 months	58.7%	64.4%	64.0%	73.5%	The discontinuation proportion is calculated as 1 minus the CGRP responder proportion from the trials listed below.
BSC negative discontinuation, 6 months	85.8%	85.8%	88.9%	88.9%	The discontinuation proportion is calculated as 1 minus BSC responder proportion from the trials listed below
CGRP antagonist negative discontinuation per month >6 months	1.0%	1.0%	1.0%	1.0%	From LIBERTY open label extension for erenumab reported by Ferrari[164]
BSC negative discontinuation, >6 months	0.0	0.0	0.0	0.0	Assumed to be 0 after 6 months. Evidence outlining longer term discontinuation was not available.
CGRP antagonist 50% responder proportion, 6 months	41.3%	35.6%	36.2%	26.5%	LIBERTY, STRIVE and Tepper et al 2017 trials, ***Table 163*** and ***Table 164***
BSC responder 50% responder proportion, 6 months	14.2%	14.2%	11.1%	11.1%	LIBERTY, STRIVE and Tepper et al 2017 trials, ***Table 163*** and ***Table 164***
Positive discontinuation	NA	NA	NA	NA	Not included as base case.

Abbreviations

BSC = best supportive care, **CGRP** = calcitonin gene-related peptide antagonists, **CM** = chronic migraine, **EM** = episodic migraine, **MMD** = monthly migraine days, **NA** = not applicable, **RCT** = randomised control trial.

Table 155 Summary of fremanezumab base case effectiveness assumptions

Assumption	Fremanezumab				Source
	CM		EM		
	625mg	225 mg	625mg	225 mg	
CGRP antagonist MMD reduction, 0-3 months	-3.9	-4.5	-3.7	-3.8	FOCUS trial, ***Table 165***
CGRP antagonist MMD reduction, 4-6 months	-3.9	-4.5	-3.7	-3.8	3-month reduction from trial listed above assumed for 6 months.
BSC MMD reduction, 0-3 months	-0.7	-0.7	-0.7	-0.7	FOCUS trial, ***Table 165***
BSC MMD reduction 4-6 months	-0.7	-0.7	-0.7	-0.7	3-month reduction assumed for 6 months. FOCUS trial, ***Table 165***
CGRP antagonist negative discontinuation, 6 months	66%	66%	66%	66%	The discontinuation proportion is calculated as 1 minus the CGRP responder proportion from the trials listed below.
BSC negative discontinuation, 6 months	91%	91%	91%	91%	The discontinuation proportion is calculated as 1 minus BSC responder proportion from the trials listed below
CGRP antagonist negative discontinuation per month >6 months	1.0%	1.0%	1.0%	1.0%	LIBERTY open label extension for erenumab reported by Ferrari[164]
BSC negative discontinuation, >6 months	0.0	0.0	0.0	0.0	Assumed to be 0 after 6 months. Evidence outlining longer term discontinuation was not available.
CGRP antagonist responder, 6 months	34.0%	34.0%	34.0%	34.0%	3-month response assumed for 6 months. FOCUS trial, ***Table 166***
BSC responder, 6 months	9.0%	9.0%	9.0%	9.0%	3-month response assumed for 6 months. FOCUS trial, ***Table 166***
Positive discontinuation	NA	NA	NA	NA	Not included as base case. Evidence outlining longer term discontinuation was not available.

Abbreviations

BSC = best supportive care, **CGRP** = calcitonin gene-related peptide antagonists, **CM** = chronic migraine, **EM** = episodic migraine, **MMD** = monthly migraine days, **NA** = not applicable, **RCT** = randomised control trial**.**

Table 156 Summary of eptinezumab and galcanezumab base case effectiveness assumptions

Assumption	Galcanezumab		Eptinezumab		Source
	CM	EM	CM	EM	
CGRP antagonist MMD reduction, 0-3 months	-5.7	-2.9	-7.7	-4.3	Galcanezumab derived from CONQUER and REGAIN trials (***Table 165***) and Eptinezumab, PROMISE 1-2, Dodick et al 2019 (***Table 169***)
CGRP antagonist MMD reduction, 4-6 months	-5.7	-2.9	-8.3	-4.5	Galcanezumab 3-month reduction derived from CONQUER and REGAIN trials and assumed for 6 months (***Table 165***) and Eptinezumab, PROMISE 1-2, Dodick et al 2019 (***Table 169***)
BSC MMD reduction, 0-3 months	-1.5	-0.3	-5.6	-3.6	Galcanezumab derived from CONQUER and REGAIN trials (***Table 165***) and Eptinezumab, PROMISE 1-2, Dodick et al 2019 (***Table 169***)
BSC MMD reduction 4-6 months	-1.5	-0.3	-6.4	-3.8	Galcanezumab 3-month reduction derived from CONQUER and REGAIN trials and assumed for 6 months (***Table 165***) and Eptinezumab, PROMISE 1-2, Dodick et al 2019 (***Table 169***)
CGRP antagonist negative discontinuation, 6 months	69.0%	58.2%	39.0%	43.4%	The discontinuation proportion is calculated as 1 minus the CGRP responder proportion from the trials listed below.
BSC negative discontinuation, 6 months	91.0%	82.9%	56.0%	54.9%	The discontinuation proportion is calculated as 1 minus BSC responder proportion from the trials listed below
CGRP antagonist negative discontinuation per month >6 months	1.0%	1.0%	1.0%	1.0%	LIBERTY open label extension for erenumab reported by Ferrari[164]
BSC negative discontinuation, >6 months	0.0	0.0	0.0	0.0	Assumed to be 0 after 6 months. Evidence outlining longer term discontinuation was not available.
CGRP antagonist responder, 6 months	31%	42%	61.0%	56.6%	Galcanezumab derived from CONQUER and REGAIN trials (***Table 168***) and Eptinezumab, PROMISE 1-2, Dodick et al 2019 (***Table 170***)
BSC responder, 6 months	9.2%	17.1%	44.0%	45.1%	Galcanezumab derived from CONQUER and REGAIN trials (***Table 168***) and Eptinezumab, PROMISE 1-2, Dodick et al 2019 (***Table 170***)
Positive discontinuation	NA	NA	NA	NA	Not included as base case.

Abbreviations
BSC = best supportive care, **CGRP** = calcitonin gene-related peptide antagonists, **CM** = chronic migraine, **EM** = episodic migraine, **MMD** = monthly migraine days, **NA** = not applicable, **RCT** = randomised control trial**.**

Responders are assumed to maintain full treatment effect throughout the time horizon for the remainder of the year or death in the 1-year model analysis. Most blinded RCTs had limited weeks of follow-up of around 12 weeks. Eptinezumab had the longest reported follow-up of 37 to 48 weeks. On-treatment MMD reductions at 3 or 6 months reported in RCTs were assumed to continue over the remainder of projection periods in the current base model. The sustained longer-term MMD reduction assumption was derived from data reported in open label extensions of the blinded phases of trials. The nature of the extensions varied for each CGRP antagonist.

For erenumab chronic migraine patients, results of the open label extension reported by Tepper et al 2017 indicated sustained treatment benefit.[165] The average change from baseline MMDs was -8.5 days to 9.4 days for the 70 mg dose against parent study baseline and -10.5 days to 7.3 days for the 140 mg dose at week 52. In the open label phase of the LIBERTY trial, Ferrari et al 2022 reported MMD

reductions from baseline at 112 weeks among erenumab episodic migraine patients.[164] Ferrari et al 2022 reported that patients receiving 140 mg in the continuous erenumab group had an average reduction in MMDs of -3.9; those who switched from placebo to erenumab in the extension had a reduction of -4.6 MMDs. MMD reductions in the extension were greater than those in the blinded trial. An MMD reduction of -1.8 was reported at the end of the 12-week blinded RCT for the erenumab group.[49]

In the case of galcanezumab, Pozo-Rosich et al 2021 undertook a post hoc analysis of clinical trial data from episodic (EVOLVE-1, EVOLVE-2; both 6-month duration) and chronic (REGAIN; 3-month duration) migraine patient trials.[166] The authors found that once-monthly galcanezumab had consistent efficacy throughout the dosing intervals in all trials; there was no evidence that the effect of galcanezumab dissipates at the conclusion of the dosing interval. The open label phase of REGAIN among chronic migraine patients reported that from a baseline of 19.4 MMDs at the beginning of the double-blind period, patients at month 12 in the previous placebo and galcanezumab (120 mg and 240 mg) groups had MMD reductions of -8.5, -9.0 and -8.0, respectively.[167] These MMD reductions were higher than those reported at the end of the blinded RCT at 3 months.[167]

Increases in MMD reductions were also reported for eptinezumab with increasing weeks of follow-up. Smith et al 2020 reported mean reductions for both approved eptinezumab doses (100 and 300 mg) during weeks 1–12, 13–24, 25–36 and 37–48. The 100 mg dose reported mean reductions of -3.9, -4.5, -4.7 and -4.5 days, respectively, compared to placebo for episodic migraine patients in the PROMISE-1 trial. The 300 mg dose reported mean reductions of -3.2, -3.8, -4.0 and -4.0 days, respectively, compared to placebo for episodic migraine patients in the PROMISE-1 trial.[107]

Longer-term projections have considerable uncertainty, as follow-up in blinded RCTs and open label extensions was limited compared to the 5- and 10-year model projections in this report. Open label studies are also subject to greater bias compared to blinded RCTs. Treatment waning effects are included as sensitivity scenarios to examine the impact of longer-term MMD reductions on the current model results.

8.3.1.4 Negative discontinuation

Transition probabilities for negative discontinuation were sourced from trials for the proportion of non-responders, those experiencing AEs and patient preferences. Swiss reimbursement requires that patients demonstrate a reduction in MMDs at 3 months and a 50% reduction at 6 months to continue to access reimbursed treatment. The proportion of patients having a ≥50% reduction in MMDs was a primary endpoint in numerous trials. This was generally reported at 3 months. If reported, a 6-month proportion was used; however, in the absence of data for this timepoint, the 3-month response was included and subjected to sensitivity analysis.

Similarly to MMD reductions, observations from open label extensions were used to support longer-term response and treatment continuation (>6 months) assumptions. The open label phase of REGAIN among chronic migraine patients reported a ≥50% response among those who previously took placebo, galcanezumab 120 mg or 240 mg as 57%, 57% and 53%, respectively, at 12 months.[167] These rates are higher than those reported at 3 months.[167]

Rates of continuation are governed by factors in addition to clinical response. For erenumab, in an open label extension, Ferrari et al 2022 reported continuation at around 2 years (112 weeks).[164] The ≥50% responder rate was 57.2% at 112 weeks. Of these responders, 69.2% remained responders at ≥50% and 13% of the non-responders had converted to ≥50% responders by the end of the 12-week RCT. The authors noted that 181 participants entered the open label phase of the trial and 75.4% of these reached 112 weeks, representing 24.6% discontinuation. Reasons for discontinuation included lack of efficacy (44%), participant decision (37%) and AEs (12%). A long-term discontinuation probability of 1% is included for all CGRP antagonist in the current models, by converting 24.6% at 112 weeks to a monthly probability.

All CGRP antagonist non-responders transition to the negative discontinuation state in the current model and are assumed to receive BSC. A non-responder is defined as a patient who does not experience a 50% reduction in MMDs compared to that at baseline. Non-responders are assumed to experience QoL consistent with that calculated using baseline MMDs. Patients on BSC who discontinue are also assigned monthly MMDs at baseline. Those who respond are assumed to sustain MMD reductions estimated from the last timepoint of follow-up from the included trials.

8.3.1.5 Adverse events

AEs are captured in the overall negative discontinuation rate outlined above but do not directly impact utilities.

8.3.1.6 Positive discontinuation

A proportion of patients who respond to treatment may sustain treatment benefits following discontinuation. Some submitted models to HTA agencies included a positive stopping rule, which assumes sustained full effect without treatment costs. This assumption is not included in the base model in this report. A sensitivity analysis is included where 20% of patients transition to a positive discontinuation state each year after annual re-evaluation.

8.3.1.7 Mortality

Death is an absorbing state to which patients in all other states can transition. Background general population mortality rates are age-dependent and drawn from Swiss life tables. Migraine is not assumed to elevate background mortality.

8.3.1.8 Applicability of Trials

This section addresses how the characteristics of patients in the clinical evidence compare with circumstances of use in Switzerland.

8.3.1.8.1 Baseline and clinical characteristics

The clinical evidence evaluation noted that the patient population receiving CGRP antagonists for migraine across the included trials appears to be similar to the general Swiss and European population of migraine patients. It was indicated that several trials were conducted outside of Europe, which include patients less representative of the Swiss population. The base model uses an average age of 42 years with 85% of participants being women. Chronic migraine patients are assumed to have baseline MMDs of 18; episodic migraine patients 9.

Comparators specified in the HTA protocol are standard of care for migraine prevention, each intervention compared to the other, and placebo. Medications for migraine prevention approved for use in Switzerland include beta blockers (i.e. propranolol and metoprolol), calcium antagonists (i.e. flunarizine), anticonvulsants (i.e. topiramate) and antidepressants (i.e. amitriptyline). Only one RCT was identified that included topiramate as the comparator. Most trials involved placebo arms where use of acute medications was allowed. Consequently, this comparator is used in the base model and a sensitivity analysis is included for the CGRP antagonist versus topiramate economic analysis.

8.3.1.8.2 Erenumab trials

Most of the trials enrolled adult patients age 18 to 65 years with a history of migraine with or without aura. Patients were excluded if they were older than 50 years or if they experienced cluster or hemiplegic migraine headaches. The average age was 41 to 44 years in most trials, with 85% to 90% being female. These demographic characteristics are in line with Swiss and European migraine surveys. For example, the cohort study of 4,547 people in the canton of Zurich, found prevalence of migraine with aura was estimated to be higher in females at 3.9% (males 2.1%).[10] Swiss migraine prevalence was highest in these age groups (15–49 years) in the global burden of disease study.[4] The starting age of the erenumab model submitted to NICE was 42.3 years, based on average ages from Tepper et al 2017, STRIVE, ARISE and LIBERTY.[48,49,75,103] The percentage of females in the model submitted to NICE was 84.51%, which was derived from these trials.[143]

LIBERTY was the major trial where prior preventative treatment failures was an inclusion criterion for episodic patients;[49] a subgroup analysis was conducted for the STRIVE trial.[48] These trials form the basis for MMD frequency reduction and response assumptions in the current erenumab episodic migraine model. The Tepper et al 2017 trial was used for chronic migraine patients.[79] Patients were treated with both erenumab 70 mg and 140 mg in Tepper et al 2017 and STRIVE, and with 140 mg in LIBERTY.[48,49,79] Analyses were undertaken in the current economic analyses for both these dosing regimens, as they account for 66% of CGRP antagonist use in Switzerland in 2022.[28] The remaining trials presented in ***Table 157*** were used to source assumptions for sensitivity analyses for patients without failed previous treatment.

Table 157 Features of patient populations and clinical usage in erenumab trials

Parameter	Overview
Chronic migraine	
Tepper et al 2017 [79] (NCT02066415)	
Demographics	-Average patient age was 42.1 years and females accounted for 79% of the study population -67.9% of patients had failed 1 preventative treatment and 49% at least 2 prior treatments. -MMDs at baseline were 17.2-18.2
Clinical usage	-Erenumab 70 mg, erenumab 140 mg or placebo -The trial involved sites in North America (Canada and the USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, and the UK). -The trial involved an initial screening phase (up to 3 weeks), a baseline phase (4 weeks), a double-blind treatment phase (12 weeks), and a safety follow-up phase (12 weeks).
Episodic migraine	
LIBERTY [49] (NCT03096834)	
Demographics	-Average patient age was 44.4 years and females accounted for 81.3% of participants. -Average starting MMDs of 9.3 days in both the erenumab 140 mg and placebo groups. -38.6% had failed 2 prior prophylactic treatments, 37.8% failed 3, and 22.8% failed 4 prior prophylactic treatments
Clinical usage	-Erenumab 140 mg or placebo administered subcutaneously -The trial included a screening phase (0–2 weeks), baseline phase (4 weeks), double-blind treatment phase (12 weeks), open label treatment phase (156 weeks), and a follow-up phase (12 weeks)
STRIVE [48] (NCT02456740)	
Demographics	-Average age was 40.9 years and 85.2% were women. -Baseline MMDs were 8.23, 8.29 and 8.34 days in the placebo, erenumab 70 mg and erenumab 140 mg arms. -The study noted baseline characteristics were comparable between the ITT population and the patients for whom ≥3 prior prophylactic treatments had failed.
Clinical usage	-Erenumab 70 mg, erenumab 140 mg or placebo administered subcutaneously monthly for 6 months -The trial included 121 sites across North America, Europe, and Turkey -The timing involved screening (≤3 weeks of initial screening and a 4-week baseline phase); double-blind treatment phase (24 weeks); the active-treatment phase, repeat randomisation over 28 weeks; and a safety follow-up phase (12 weeks)
ARISE [75] (NCT02483585)	

Parameter	Overview
Demographics	-Average age was 42 years and 85.3% were women with disease duration of 21 years. -Baseline MMDs were 8.4 and 8.1 days in the placebo and erenumab 70 mg arms. -The trial noted baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed were reported and characteristics for this subgroup were consistent with those in the full trial population -The trial included 69 sites across North America and Europe
Clinical usage	-Erenumab 70 mg or placebo administered subcutaneously
EMPOwER [76] (NCT03333109)	
Demographics	-Average age was 37.5 years, 81.9% were women and MMDs were 8.2 at baseline -53.2% patients had prior prophylactic medication treatment, whereas 46.8% were treatment naive.
Clinical usage	-Monthly placebo, erenumab 70 mg, or 140 mg during a 3-month treatment period followed by a 12-week (3-month) safety follow-up

Abbreviations
ITT = intension-to-treat, **MMD** = monthly migraine days, **UK** = United Kingdom, **USA** = United States of America.

8.3.1.8.3 Fremanezumab trials

A range of trials are provided in the clinical evaluation, with starting ages and gender balances consistent with those in the erenumab trials outlined above. The clinical section noted that 6 identified trials excluded participants who had failed 2–4 prior preventative treatments. Only one trial (FOCUS) included patients with prior preventative treatment failures.[91] This trial is used to derive assumptions for the current fremanezumab economic model. Details of the trial are presented in ***Table 158***. Average ages and gender balances were similar to those in trials of other CGRP antagonists.

The large HALO EM and HALO CM trials excluded patients who had previous treatment failure with 2 classes of migraine-prevention medication.[86,89] This trial and others that excluded patients with failed treatment history were used for modelling assumptions as part of sensitivity analyses. Fremanezumab was modelled as a self-administered subcutaneous injection using a prefilled syringe, as either a single injection monthly (225 mg) or 3 injections every 3 months (675 mg). The base model included single injection monthly as this is the most widely used product in Switzerland. BSC was compared to fremanezumab, informed by the placebo control arm of the FOCUS trial.[91] The BSC arm precluded the use of active prophylactic treatment but did allow acute headache- and migraine-specific medication.

Table 158 Features of patient populations and clinical usage in fremanezumab trials

Parameter	Overview
Episodic migraine	
HALO EM [86]	
Demographics	-Average ages were 41.1–42.9 years and most participants were female (84.8%) -21.3% of participants had received 1–3 preventative therapies. -Baseline MMDs were 8.9–9.2 migraine days for the 28 days run in -Patients who had previous treatment failure with 2 classes of migraine-preventive medication were excluded.
Clinical usage	-One 225 mg fremanezumab injection (1.5 mL) and 2 x 1.5 mL placebo injections at baseline; 1 x 225 mg fremanezumab injection (1.5 mL) at weeks 4 and 8 -Fremanezumab quarterly involved 675 mg (3 x 225 mg injections at baseline; 1 x 1.5 mL placebo injection at weeks 4 and 8)
Chronic migraine	
HALO CM [89]	
Demographics	-Baseline 11.4 MMDs -Participants reported using medication 10.4-9.8 days per month baseline
Clinical usage	-One 225 mg fremanezumab injection (1.5 mL) and 2 x 1.5 mL placebo injections at baseline; 1 x 225 mg fremanezumab injection (1.5 mL) at weeks 4 and 8 -Fremanezumab quarterly involved 675 mg (3 x 225 mg injections at baseline; 1 x 1.5 mL placebo injection at weeks 4 and 8)
Episodic and chronic migraine	
FOCUS [91]	
Demographics	-Average age 46.2 and most were female (84%). -More participants had chronic migraine (61%) than episodic migraine (39%). -50% of participants had not responded to 2 migraine preventive medications, 32% to 3, and 18% to 4
Clinical usage	-One 225 mg fremanezumab injection (1.5 mL) and 2 x 1.5 mL placebo injections at baseline; 1 x 225 mg fremanezumab injection (1.5 mL) at weeks 4 and 8 -Fremanezumab quarterly involved 675 mg (3 x 225 mg injections at baseline; 1 x 1.5 mL placebo injection at weeks 4 and 8 -104 sites across Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, UK, and USA
Sakai et al 2021a [90]	
Demographics	-The authors noted demographic and other baseline characteristics were similar among groups, including proportion of female subjects, age and weight/body mass index -Lack of efficacy of at least 2 of 4 clusters of preventive medications was an exclusion criteria
Clinical usage	-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 -Trial conducted in Japan and Korea

Abbreviations
MMD = monthly migraine days, **UK** = United Kingdom, **USA** = United States of America.

8.3.1.8.4 Galcanezumab trials

The clinical evaluation noted that 7 trials excluded participants who had no therapeutic response to >2 or ≥3 prior preventative treatments (see ***Appendix F***).[50,92-97] The economic model uses evidence from the CONQUER trial that evaluated the efficacy and safety of galcanezumab in patients who experienced 2–4 migraine preventive failures.[98] Analyses were conducted for episodic and chronic migraine patients. Patients in the placebo arm of the CONQUER trial used acute treatments, including sumatriptan, ibuprofen, paracetamol, eletriptan, rizatriptan and naproxen.[98] A subgroup analysis of patients who had failed 2 treatments was included as part of the REGAIN trial.[50] Results of this trial are combined with those from CONQUER for chronic migraine patients.[98]

Other major identified trials include EVOLVE, which recruited episodic migraine patients who had not failed 2 preventive treatments.[95] This trial included a population of average age 41.9 years; 85.4% females.[95] Camporeale et al 2018 included episodic and chronic migraine patients who had not failed >3 preventive medications.[97] Sakai et al 2020a included episodic migraine patients who had not failed ≥3 classes of migraine preventive treatments.[94] Most patients were female (84.3%) and mean patient age was 44.1 years. These studies were used in a sensitivity analysis in the economic modelling for this report. Details of the trials are presented in ***Table 159***.

Table 159 Features of patient populations and clinical usage in galcanezumab trials

Parameter	Overview
Episodic or chronic migraine	
CONQUER [98] (failed 2–4 preventive medications)	
Demographics	-Average age of 46 years and mostly female (86%), -58% of patients had episodic migraine and 42% of patients had chronic migraine and MHDs at baseline were 13.2
Clinical usage	-Galcanezumab 120 mg following a loading dose of 240 mg. -64 sites in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, UK, and USA)
Camporeale [97] (not failed >3 preventive medications)	
Demographics	-Average age of 42 years and most female (83%) -episodic migraine (79%), and 10.6 monthly MHD.
Clinical usage	-Galcanezumab 120 mg involved initial loading dose of 240 mg (2 injections of 120 mg each); following doses were self- or caregiver-administered as a single injection of 120 mg monthly. -Galcanezumab 240 mg received 2 injections of 120 mg at each monthly dosing visit
Episodic migraine	
EVOLVE-1 [92] (not failed). Patients with a history of failure to respond to ≥3 classes of migraine preventive treatments excluded.	
Demographics	-Average age of 40.7 years and mainly women (83.7%) -MHDs were 9.1 at baseline and MMDs 5.6-5.8 -60.0% reported using prior migraine preventive treatment

Parameter	Overview
Clinical usage	-90 sites in North America with treatment period (month 1, 2, 3, 4, 5 and 6); and a 4-month post-treatment period (month 7, 8, 9 and 10). -Galcanezumab dose regimen (120 mg or 240 mg) monthly during office visits
EVOLVE-2 [93] (not failed). Patients with a history of failure to respond to ≥3 classes of migraine preventive treatments excluded.	
Demographics	-Average age was 41.9 years and the population was largely female (85.4%), - -66.9% of patients had 8 or more MHDs per month. -65.5% had prior experience with migraine preventive treatments and 14.3% of them had previously failed 2 or more preventive medications
Clinical usage	-Nine study sites in USA, UK, the Netherlands, Spain, Czech Republic, Germany, Argentina, Israel, Korea, Taiwan and Mexico. -6-month double-blind treatment phase. Patients were excluded if they had failed treatment with ≥3 migraine prevention drugs
Sakai et al 2020a [94] (not failed). Patients with a history of failure to respond to ≥3 classes of migraine preventive treatments excluded.	
Demographics	-Average age was 44.1 years, most patients were female (84.3%) and baseline MHDs were 8.7. -60.6% reported using migraine preventive treatment previously. 33.8% had no preventive treatment failures and 66.2% had failed one or more preventive treatments.
Clinical usage	-Galcanezumab 120 mg or 240 mg once per month -6-month, phase 2, randomised, double-blind, placebo-controlled study of galcanezumab in Japanese outpatients with episodic migraine from 40 sites
Chronic migraine	
REGAIN [50] (not failed). Patients with a history of failure to respond to ≥3 classes of migraine preventive treatments excluded.	
Demographics	-Demographic and baseline characteristics similar across treatment groups
Clinical usage	-Monthly galcanezumab 120 mg (with 240 mg loading dose) or galcanezumab 240 mg -Patients must not have previously failed to respond to >3 different medication classes -Patients required to have 15 MHDs, of which at least 8 were migraine

Abbreviations
MHD = monthly headache days, **MMD** = monthly migraine days, **UK** = United Kingdom, **USA** = United States of America.

8.3.1.8.5 Eptinezumab trials

None of the eptinezumab trials explicitly stated whether patients who had failed 2 previous treatments were included. A comparison between eptinezumab and BSC is included in the economic model, although the subgroup is not specifically defined for trials of this medicine. The episodic patient group was included in the PROMISE-1 trial;[82] with a mean number of MMDs of 8.6 across treatment groups. Adults with episodic migraine were randomised to eptinezumab 30 mg, 100 mg, 300 mg or placebo for up to 4 IV doses administered every 12 weeks. Chronic migraine patients included in the PROMISE-2 trial had ≥15 to ≤26 headache days and ≥8 migraine days during the 28-day screening period.[84] They received IV eptinezumab 100 mg, eptinezumab 300 mg or placebo. Details of the trials are presented in ***Table 160***.

Table 160 Features of patient populations and clinical usage in eptinezumab trials

Parameter	Overview
Episodic migraine	
PROMISE-1 [82]	
Demographics	-Average age of 39.8 years and most female (84.3%) -Average MMDs was 8.6 across treatment groups.
Clinical usage	-Four treatments of eptinezumab or placebo (administered IV day 0, week 12, week 24 and week 36) -Adults with episodic migraine were randomised to eptinezumab 30 mg, 100 mg, 300 mg, or placebo for up to 4 intravenous doses administered every 12 weeks.
Chronic migraine	
PROMISE-2 [84] (≥15 to ≤26 headache days and ≥8 migraine days during the 28-day screening period)	
Demographics	-Average age was 40.5 years and most patients were female (88.2%), -Average age at migraine diagnosis was 22.5 years
Clinical usage	-Eptinezumab 100 mg, 300 mg or placebo administered on day 0 and week 12 -13 countries (USA, Spain, Ukraine, Russian Federation, UK, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark and Belgium)

Abbreviations
IV = intravenous, **MHD** = monthly headache days**, MMD** = monthly migraine days, **UK** = United Kingdom, **USA** = United States of America.

8.3.1.9 Erenumab treatment effectiveness

8.3.1.9.1 Reduction in migraine frequency

Economic models submitted to NICE (outlined in committee papers) included patient-level trial data that allowed the proportion of patients experiencing a given MMD frequency to be captured by treatment group and timepoint. Economic modelling for CGRP antagonist and placebo arms in the current HTA report used average reductions in MMDs and response rate (≥50% MMD reduction) from results reported in the publicly available published literature. The results of key trials used to estimate changes in baseline MMDs for erenumab (140 mg and 70 mg) and BSC among episodic and chronic migraine patients are summarised in ***Table 161*** and ***Table 162***.

The LIBERTY trial recruited episodic migraine patients who had failed previous treatment.[49] Episodic migraine patients using the erenumab 140 mg and 70 mg regimes had more substantial reductions in MMDs at all reported timepoints over 12 weeks when compared to placebo.[49] MMD reductions from baseline were greater for those receiving erenumab in the STRIVE subgroup of patients with prior treatment failure.[48] The reductions in MMDs from these trials are presented as weighted averages from the STRIVE and LIBERTY trials for the episodic migraine population in ***Table 161***.[48,49]

A sensitivity analysis using outcomes reported in trials that excluded patients who had failed preventive treatment was also undertaken. These trials (outlined in ***Table 161***) reported significantly greater changes in MMDs from baseline for erenumab compared to placebo. Results from Tepper et al 2017

were used to estimate MMD change among chronic migraine patients.[79] The erenumab 70 mg and 140 mg groups had a greater reduction in MMDs from baseline during the last 4 weeks of the double-blind treatment phase compared with placebo. Data from this trial were the sole source of MMD change assumptions among chronic migraine patients in the current economic model.

Table 161 Erenumab 140 mg reduced MMDs from baseline

	Erenumab (140 mg)			Best supportive care		
	Value	SE/SD	N	Value	SE/SD	N
Episodic migraine (failed)						
LIBERTY [49] (Failed 2 treatments)						
Weeks 1–4	-1.80	0.40	119	0.10	0.30	124
Weeks 5–8	-2.30	0.40	119	0.10	0.40	124
Weeks 9–12	-1.80	0.40	118	-0.20	0.40	120
Week 12	-1.80	0.60	76	-0.50	0.50	69
STRIVE [48] (Subgroup who failed ≥2 prior treatments)						
1 month	-2.50	NR	58	-0.30	NR	54
2 months	-3.00	NR	58	-0.40	NR	54
3 months	-3.50	NR	58	-0.90	NR	54
4 months	-2.70	NR	58	0.00	NR	54
5 months	-3.00	NR	58	-0.70	NR	54
6 months	-3.10	NR	58	-0.10	NR	54
Average						
0–3-month average for episodic migraine base model	-2.33			-0.26		
4–6-month average for episodic migraine base model	-2.93			-0.27		
Chronic migraine (Failed)						
Tepper et al 2017 [103] (Failed 2 treatments)						
0–3-month average for chronic migraine base model	-7.00	NR	92	-2.7	NR	142
Episodic migraine (Not failed)						
EMPOwER [76] (Not failed)						
1 month	-3.12	0.28	214	-1.69	0.23	324
2 months	-3.88	0.29	205	-2.48	0.24	318
3 months	-4.79	0.3	199	-3.1	0.25	310
Sakai et al 2019 [77] (Not failed)						
4–6 months	-1.83	NR	136	0.06	NR	136
Average						
0–3 months for episodic migraine sensitivity analysis	-3.93			-2.42		
4–6 months for episodic migraine sensitivity analysis	-1.83			0.06		

Abbreviations
MMD = monthly migraine days, **N** = number, **NR** = not reported, **SD** = standard deviation, **SE** = standard error.

Table 162 Erenumab 70 mg reduced MMDs from baseline

	Erenumab (70 mg)			Best supportive care		
	Value	SE/SD	N	Value	SE/SD	N
Episodic migraine (Failed >2 previous treatments included)						
STRIVE [48]						
1 month	-1.60	NR	49	-0.30	NR	54
2 months	-1.80	NR	49	-0.40	NR	54
3 months	-1.80	NR	49	-0.90	NR	54
4 months	-2.00	NR	49	0.00	NR	54
5 months	-1.40	NR	49	-0.70	NR	54
6 months	-1.20	NR	49	-0.10	NR	54
0–3 months for episodic migraine base model	-1.73			-0.53		
4–6 months for episodic migraine base model	-1.53			-0.27		
Chronic migraine (Failed >2 previous treatments included)						
Tepper et al 2017 [103]						
3 months for chronic migraine base model	-5.40	0.40	188	-2.70	0.40	93
Episodic migraine (Failed >2 previous treatments excluded)						
EMPOwER [76]						
1 month	-2.66	0.23	325	-1.69	0.23	324
2 months	-3.68	0.24	316	-2.48	0.24	318
3 months	-4.2	0.25	306	-3.1	0.25	310
Sakai et al 2019 [77]						
4–6 months	-2.25	NR	135	0.06	NR	135
Sun et al 2016 [78]						
12 weeks	-3.40	0.40	104	-2.30	0.30	153
ARISE [75]						
3 months	-2.90	0.20	282	-1.80	0.20	288
Average						
0–3 months for episodic migraine sensitivity analysis	-3.25			-2.16		
4–6 months for episodic migraine sensitivity analysis	-2.25			0.06		

Abbreviations
MMD = monthly migraine days, **N** = number, **NR** = not reported, **SD** = standard deviation, **SE** = standard error.

8.3.1.9.2 Response assessment

Patients are required to demonstrate a reduction in MMDs at 3 months and ≥50% reduction in MMDs at 6 months to continue to access reimbursed treatment in Switzerland. The proportion of patients having ≥50% reduction in MMDs was reported in numerous trials, but generally at 3 months of follow-up. Where possible, the 6-month responder proportion is used in the economic model. In the absence of data at this timepoint, the 3-month response is included and subject to sensitivity analysis.

STRIVE reported response at 4–6 months of 36.2% for 140 mg erenumab versus 11.1% for placebo.[48] This estimate is used for the 6-month response in the economic model for 140 mg erenumab use among

episodic patients (outlined in ***Table 163***). Similar trials were used for the 70 mg erenumab analysis (presented in ***Table 164)***. A sensitivity analysis was included using data from trials that did recruit patients with a history of failed prevention. Significant differences were also evident in the other included trials. The chronic migraine response rates drawn from Tepper et al 2017 (***Table 163*** and ***Table 164***), appeared to have higher absolute differences between arms than among the episodic migraine patient group.[103]

Table 163 Erenumab 140 mg >50% MMD reduction response at 3 and 6 months

	Erenumab 140 mg		Best supportive care	
	Proportion % >50% MMD reduction	N	Proportion % >50% MMD reduction	N
Episodic migraine (Failed >2 previous treatments included)				
LIBERTY [49]				
Week 12	26.3	72	11.1	76
STRIVE [48]				
3 months	46.6	58	14.8	54
4–6 months used in episodic migraine base model	36.2	58	11.1	54
Average (140 mg)				
3 months	35.4		12.6	
Chronic migraine (Failed >3 previous treatments included)				
Tepper et al 2017 [103]				
3 months used in chronic migraine base model	41.3	92	14.2	142
Episodic migraine (Failed >2 previous treatments excluded)				
EMPOwER [76]				
3 months	63.9	219	44.8	330
Sakai et al 2019 [77]				
4–6 months	27.2	136	7.4	136

Abbreviations
MMD = monthly migraine days, **N** = number.

Table 164 Erenumab 70 mg >50% MMD reduction response at 3 and 6 months

	Erenumab 70 mg		Best supportive care	
	Proportion % >50% MMD reduction	N	Proportion % >50% MMD reduction	N
Episodic migraine (Failed >2 previous treatments included)				
STRIVE [48]				
3 months	26.5	49	14.8	54
4–6 months used in episodic base model	26.5	49	11.1	54
Chronic migraine (Failed >2 previous treatments included)				
Tepper et al 2017 [103]				
3 months used in chronic base model	35.6	93	14.2	142
Episodic migraine (Failed >2 previous treatments excluded)				
EMPOwER [76]				
3 months	55.3	329	44.8	330
ARISE [75]				
3 months	39.7	282	29.5	288
Average (70 mg) of EMPOwER [76] and ARISE [75]				
3 months	48.1		37.7	
Sakai et al 2019 [77]				
4–6 months used in episodic migraine sensitivity model	28.9	135	7.4	136

Abbreviations
MMD = monthly migraine days, **N** = number.

8.3.1.9.3 Adverse events

The safety profile of CGRP antagonists was found to be similar to that of BSC in the clinical evaluation. In the LIBERTY trials,[49] AEs reported in the erenumab group were similar to those reported in the placebo group, with no clinically meaningful differences in hepatic-function testing, creatinine concentrations, total neutrophil counts, vital signs or electrocardiogram findings.[49] The EMPOwER trial reported SAEs for 0.6% of patients receiving placebo, 0.9% of those receiving erenumab 70 mg and 0% of those receiving erenumab 140 mg.[76]

Discontinuation rates because of AEs were low, with no chronic migraine patients in the erenumab 70 mg group of Tepper et al 2017 and only 2 patients in the placebo (<1%) and erenumab 140 mg (1%) groups discontinuing.[79] In the ARISE trial, 0.3% of patients in the placebo group and 1.8% in the erenumab group experienced AEs that led to treatment discontinuation.[75] AEs are not costed in the economic model. An overall negative discontinuation rate is included, which includes the small proportion of patients discontinuing due to AEs. A rate of 1% per month (after >6 months) was applied. Details are in ***Section 8.3.1.5***.

8.3.1.10 Fremanezumab treatment effectiveness

8.3.1.10.1 Reduction in migraine frequency

Patients who had failed 2 prior treatments were included in the FOCUS trial for both episodic and chronic migraine patients.[91] The RCT had a maximum follow-up of 3 months.[91] Results are presented in ***Table 165***. The estimate at this timepoint is used for longer-term MMD projections, which creates uncertainty. The assumption is subject to sensitivity analysis.

Several trials have been undertaken that exclude patients who have failed previous treatments (e.g. HALO EM, HALO CM, Sakai et al 2021a and Sakai et al 2021b).[86,87,89,90] These are included in the economic model as a sensitivity analysis.

Table 165 Fremanezumab reduced MMDs from baseline

	Fremanezumab (225 mg)			Fremanezumab (625 mg)			Best supportive care		
	Value	**SE/SD**	**N**	**Value**	**SE/SD**	**N**	**Value**	**SE/SD**	**N**
Episodic migraine (Failed >2 previous treatments included)									
FOCUS [91]									
3 months	-3.80	NR	110	-3.70	NR	107	-0.70	NR	112
Chronic migraine (Failed >2 previous treatments included)									
FOCUS [91]									
3 months	-4.50	NR	177	-3.90	NR	169	-0.70	NR	167
Episodic migraine (Failed >2 previous treatments excluded)									
HALO EM [86]									
4 weeks	-3.50	NR	287	-3.30	NR	288	-1.70	NR	290
12 weeks	-3.70	NR	287	-3.40	NR	288	-2.20	NR	290
Sakai et al 2021b[87]									
12 weeks	-4.00	0.40	121	-4.00	0.40	117	-1.00	0.40	116
Episodic migraine average, where patients failed >2 previous treatments excluded. Average from HALO EM [86] and Sakai et al 2021b [87]									
3 months	-3.79			-3.57			-1.86		
Chronic migraine (Failed >2 previous treatments excluded)									
HALO CM [89]									
4 weeks	-4.50	0.30	375	-4.40	0.30	375	-2.10	0.30	375
12 weeks	-5.00	0.40	375	-4.90	0.40	375	-3.20	0.40	371
Sakai et al 2021a[90]									
12 weeks	-4.90	0.50	187	-4.10	0.50	189	-2.80	0.50	190
Chronic migraine average, where patients failed >2 previous treatments excluded. Average from HALO CM [89] and Sakai et al 2021a [90]									
3 months	-4.97			-4.63			-3.06		

Abbreviations
MMD = monthly migraine days, **N** = number, **NR** = not reported, **SD** = standard deviation, **SE** = standard error.

8.3.1.10.2 Response assessment

The proportions of participants of both episodic and chronic migraine patients in FOCUS reporting ≥50% reduction in MMDs were higher versus placebo over 12 weeks with quarterly fremanezumab or monthly fremanezumab.[91] These proportions are used in the economic model. A sensitivity analysis is included for patients who had not failed 2 prior treatments (based on the HALO EM and Sakai et al 2021 reported trials). Results are presented in ***Table 166***.[75,90]

Table 166 Fremanezumab 50% response

	Fremanezumab (225 mg)		Fremanezumab (625 mg)		Best supportive care	
	Proportion % >50% MMD reduction	N	Proportion % >50% MMD reduction	N	Proportion % >50% MMD reduction	N
Chronic and episodic migraine (Failed >2 previous treatments included)						
FOCUS [91]						
3 months	34.00	283	34.00	276	9.00	278
Chronic migraine (Failed >2 previous treatments excluded)						
HALO CM [89]						
12 weeks	44.50	345	40.50	350	18.10	342
Sakai et al 2021a [90]						
12 weeks	29.0	186	29.1	189	13.2	190
Chronic migraine average, where patients failed >2 previous treatments excluded. Average from HALO CM [89]and Sakai et al 2021a [90]						
3 months	39.07		36.50		16.35	
Episodic migraine (Failed >2 previous treatments excluded)						
HALO EM [86]						
12 weeks	51.20	263	49.00	269	37.20	268
Sakai et al 2021b [87]						
12 weeks	41.30	121	45.30	117	11.20	116
Episodic migraine average, where patients failed >2 previous treatments excluded. Average from HALO EM [86] and Sakai 2021b [87]						
3 months	48.08		47.88		29.35	

Abbreviations
MMD = monthly migraine days, **N** = number.

8.3.1.10.3 Adverse events

No cost allowance was included for AEs in the economic model for fremanezumab. SAEs were reported among 1% of participants receiving placebo, <1% receiving quarterly fremanezumab and 1% receiving monthly fremanezumab. AEs leading to discontinuation were reported for 1% of participants in the placebo group, <1% in the quarterly fremanezumab group and 1% in the monthly fremanezumab group.

In the placebo group, AEs leading to study discontinuation were chest discomfort, injection-site pain and vulval cancer. In the fremanezumab groups, AEs resulting in discontinuation were palpitations, fatigue, cholelithiasis, road traffic accidents and temporal arteritis. Similarly in HALO EM,[86] low SAEs (<2%)

were reported for both arms of the trial. The same overall negative discontinuation rate as that assumed for erenumab is included in the economic model for fremanezumab.

8.3.1.11 Galcanezumab treatment effectiveness

8.3.1.11.1 Reduction in migraine frequency

CONQUER[98] is the key trial used to estimate galcanezumab effectiveness among episodic and chronic migraine patients who have failed 2 or more previous preventive treatments. A subgroup analysis from the REGAIN trial was also used for chronic migraine patients.[50] The included RCTs had a maximum follow-up of 3 months and results at this timepoint were used for longer-term projections. Results are presented in ***Table 167***. No sensitivity analysis was undertaken for the group of patients who had not failed 2 or more preventive treatments.

Table 167 Galcanezumab reduced MMDs from baseline

	Galcanezumab (120 mg)			Galcanezumab (240 mg)			Best supportive care		
	Value	SE/SD	N	Value	SE/SD	N	Value	SE/SD	N
Episodic migraine (Failed >2 previous treatments included)									
CONQUER [98]									
3 months used as base assumption	-2.90	0.30	137	-	-	-	-0.30	0.30	132
Chronic migraine (Failed >2–3 previous treatments included)									
CONQUER [98]									
3 months	-6.00	0.70	95	-	-	-	-2.20	0.30	132
REGAIN [50]									
3 months	-5.35	0.71	72	-2.77	0.66	104	-1.01	0.54	174
Chronic migraine average, where patients included if failed >2 treatments									
3 months used as base assumption	-5.72			-			-1.52		

Abbreviations
MMD = monthly migraine days, **N** = number, **SD** = standard deviation, **SE** = standard error.

8.3.1.11.2 Response assessment

Clinical trial data at 3 months were used to inform the proportion of patients who had a ≥50% reduction in MMD response. Using data from the CONQUER trial,[98] the percentage of patients with ≥50% reduction from baseline MMDs was significantly greater in the galcanezumab group compared with placebo. In the REGAIN trial,[50] the mean percentage of chronic migraine patients with ≥50% reduction in MHD from baseline was also higher for galcanezumab compared with placebo. Results are outlined in ***Table 168***. The 3-month estimate is used for response at the 6-month stopping point in the economic model.

Table 168 Galcanezumab 50% response

	Galcanezumab (120 mg)		Galcanezumab (240 mg)		Best supportive care	
	% >50% MMD reduction	N	% >50% MMD reduction	N	% >50% MMD reduction	N
Episodic migraine (Failed >2 previous treatments included)						
CONQUER [98]						
3 months for base episodic model	41.8	137	-	-	17.1	132
Chronic migraine (Failed >2–3 previous treatments included)						
CONQUER [98]						
3 months	32.0	95	-	-	8.9	98
REGAIN [50]						
3 months	29.6	72	18.70	104	9.4	174
Chronic migraine average, where patients excluded if failed >2 treatments. Average from ARISE [75] and REGAIN [50]						
3 months for base chronic model	31.0		-		9.2	

Abbreviations
MMD = monthly migraine days, **N** = number.

8.3.1.11.3 Adverse events

As for other CGRP antagonists, the type and number of AEs were similar between galcanezumab and placebo. Most were mild or moderate in severity in the CONQUER trial.[98] No deaths were reported in the EVOLVE-2 trial;[93] the percentages of SAEs were 1.1%, 2.2% and 3.1% for the placebo, galcanezumab 120 mg and galcanezumab 240 mg groups, respectively, and did not differ significantly. The same overall negative discontinuation rate as that assumed for erenumab is included in the economic model for galcanezumab. A rate of 1% per month (after >6 months) was applied (***Section 8.3.1.3***).

8.3.1.12 Eptinezumab treatment effectiveness

8.3.1.12.1 Reduction in migraine frequency

None of the identified eptinezumab trials had specific inclusion or subgroup analyses for patients who had failed 2 prior treatments. The comparison between eptinezumab and BSC is modelled using data from the PROMISE trials,[82,109] although it is uncertain whether patients had previous exposure to preventive treatment. The PROMISE-2 trial included chronic migraine patients; the PROMISE-1 trial included episodic migraine patients.[82,84] Eptinezumab 100 mg demonstrated statistically significant reductions in MMDs during weeks 1–12 compared to placebo and the reductions were maintained until 48 weeks.[107] Results are outlined in ***Table 169***.

Table 169 Eptinezumab reduced MMDs from baseline

	Eptinezumab (100 mg)					
	Value	SE/SD	N	Value	SE/SD	N
Chronic migraine						
PROMISE-2 [109]						
1–12-week average	-7.70	NR	356	-5.60	NR	366
13–24-week average	-8.30	7.03	356	-6.40	7.16	366
Episodic migraine						
PROMISE-1 [82]						
1–12-week average	-3.90	-	221	-3.20	-	222
13–24-week average	-4.50	-	221	-3.80	-	222
25–36-week average	-4.70	-	221	-4.0	-	222
37–48-week average	-4.50	-	221	-4.1	-	222
Dodick et al 2019 [83]						
1 months	-5.60	3.30	76	-3.90	3.50	80
2 months	-5.60	3.00	78	-4.60	3.60	80
3 months	-5.60	4.00	73	-4.60	3.50	78
Episodic migraine average						
3 months	-4.32			-3.56		

Abbreviations
MMD = monthly migraine days, **N** = number, **NR** = not reported, **SD** = standard deviation, **SE** = standard error.

8.3.1.12.2 Response assessment

The PROMISE-1 episodic migraine and PROMISE-2 chronic migraine responder rates are summarised in ***Table 170***.[82,84] Dodick et al 2019 also reported response for episodic migraine patients who had failed 2 previous treatments, but only at 3 months.[83]

Table 170 Eptinezumab 50% response

	Eptinezumab (100 mg)		Best supportive care	
	Proportion % ≥50% MMD reduction	N	Proportion % ≥50% MMD reduction	N
Chronic migraine				
PROMISE-2 [109]				
1–12-week average	57.6	356	39.3	366
13–24-week average for model	61.0	356	44.0	366
Episodic migraine				
PROMISE-1 [82]				
1–12-week average	49.8	221	37.4	222
13–24-week average for model	62.0	221	51.4	222
Dodick et al 2019 [83]				
3 months	77.0	73	67.0	78

Abbreviations
MMD = monthly migraine days, **N** = number.

8.3.1.12.3 Adverse events

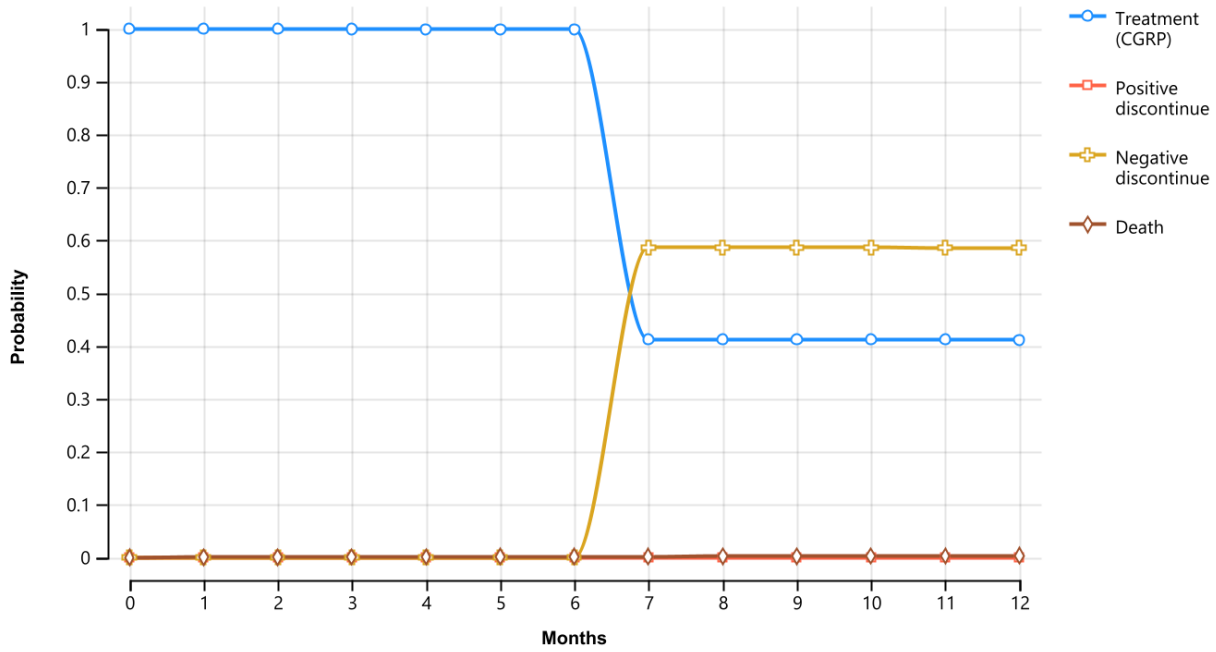
The safety profile is similar to those of other CGRP antagonists. No specific AE costs were included in the economic model.

8.3.1.13 Markov traces

8.3.1.13.1 Base case (1-year)

The short-term trace for the CGRP antagonist and BSC arms of the economic model are presented in ***Figure 40*** and ***Figure 41*** using erenumab 140 mg among chronic migraine patients as an example. This CGRP antagonist accounts for 66% of CGRP antagonist reimbursements in Switzerland in 2022 and there were many identified trials from which to derive effectiveness data. It is evident that discontinuation commences at 6 months following assessment of response (≥50% reduction in MMDs). For the following 6 months, patients discontinue at 1% per month for CGRP antagonists. Death is an absorbing state equally applied across all states in both arms of the model.

Figure 40 Erenumab 140 mg, 1-year model, chronic migraine

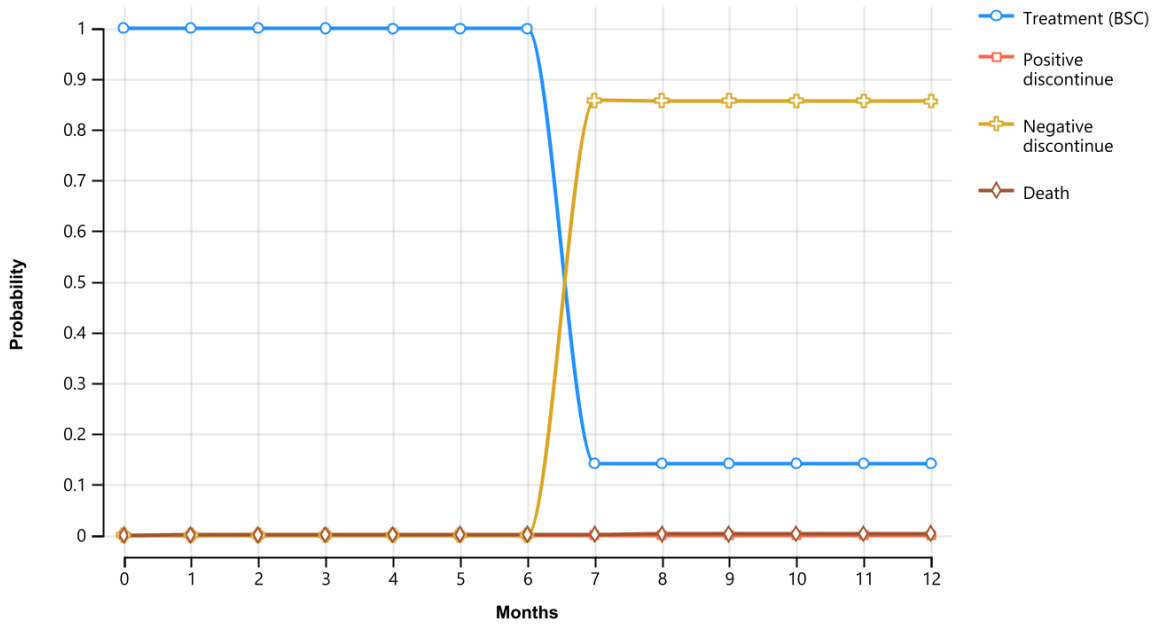


Abbreviations
CGRP = calcitonin gene-related peptide.

The response rate is lower in the BSC arm. Non-responding patients are assumed to move to the negative discontinuation state where they experience baseline MMDs and corresponding utility. The small proportion of responders is assumed to sustain treatment benefit and thus remain in the treatment state. This assumption is uncertain. The NICE committee paper appraisal of the submitted fremanezumab model indicates that the placebo response observed during clinical trials would not be

evident in clinical practice.[144] Correspondingly, a sensitivity analysis is included where both responders and non-responders return to baseline MMDs and utility.

Figure 41 BSC, 1-year model, chronic migraine



Abbreviations
BSC = best supportive care.

8.3.1.14 Utility measures

Limited studies were found that outlined QoL estimates for migraine patients. A study by Matza et al 2019 that elicited EQ-5D utilities using time trade-off interviews for migraine QoL among UK patients was identified in the literature review (**Appendix J**). EQ-5D reported directly by patients during trials is the preferred measure of QoL in economic studies.[168] Only a limited number of studies employed EQ-5D-5L questionnaires.

Sponsors highlighted in NICE committee papers that EQ-5D-5L questionnaires reflect a patient's self-assessment at a single timepoint—such as at the time of treatment appointments—and may not reflect migraine-related QoL over a representative period.[143] For example, it was noted that patients may delay treatment appointments in the event they are experiencing migraine.

The migraine specific QoL questionnaire (MSQ) collects data over a longer period. MSQ is a 14-item QoL instrument that measures migraine-related functional status, role prevention, role restriction and emotional function. The clinical evaluation noted that data reporting for MSQ was not comprehensive across all included trials.

Given the lack of comprehensive MSQ and EQ-5D data, the sponsor-derived functions for mapping EQ-5D utilities for each MMD frequency are used in the economic model. The approach used results of the MSQ surveys in erenumab trials (Tepper et al 2017, STRIVE and ARISE) and EQ-5D-3L mapping algorithms outlined by Gillard et al 2012.[48,75,79,154] The formulas were EQ-5D utility = 0.1768 (0.0034) + 0.0140 (0.0004) x MMD for episodic migraine patients using data from STRIVE and ARISE, and EQ-5D utility = 0.1353 (0.0062) + 0.0206 (0.0005) x MMD based on the results of Tepper et al 2017.[48,75,79]

CADTH guidelines do not recommend using mapped utility values.[169] The CADTH review of submitted models using the mapping algorithm established by Gillard et al 2012 noted it used a UK value set and generated values that may not reflect Canadian preferences.[154] It was further noted that trials incorporated in the Gillard et al 2012 algorithm used different numbers of headache days for episodic migraine classification.[154] Despite these shortcomings, the Gillard et al 2012 mapping algorithm is used in the current economic model given limited use of EQ-5D-5L questionnaires across trials.[154] Variables in the algorithm are subject to sensitivity analysis to determine the robustness of results to assumptions.

8.3.1.14.1 Erenumab

Utility results for the erenumab economic analysis using the episodic and chronic migraine equations based on sponsor algorithms developed using Gillard et al 2012 are presented in ***Table 171***.[154] Starting MMDs at baseline of 9 and 18 are based on trial MMD reduction data presented in ***Table 162*** and ***Table 161***.

Individual patient data outlining average MMDs for those having a ≥50% reduction in MMD response are not publicly available across included trials. On-treatment utility in the longer term (>6 months) is assumed to be 50% of baseline MMDs for all CGRP antagonists, given a response is defined as 50% reduction in baseline MMDs. Sponsor-submitted models generally used a higher estimate than this assumption. These estimates from NICE committee papers are included in ***Table 171***.[143] For example, in the case of erenumab 140 mg, episodic migraine patients on treatment were assumed to have a utility of 0.760 in the current model rather than 0.779 used by the sponsor in the model submitted to NICE committee papers.[143] The estimate of 0.760 used in the current report is driven by a 50% improvement in the number of MMDs, which is translated to utility using the Gillard et al 2012 function outlined in the sponsor-submitted model outlined in the NICE committee papers.[143,154] Differences were greater in the chronic migraine analysis. The sponsor assumptions are included as sensitivity analyses. Negative discontinuing patients are assumed to return to baseline utility values.

Table 171 Erenumab utilities

	Erenumab 70 mg			Erenumab 140 mg			Best supportive care*		
	MMD	Mapped Utility	Sponsor Utility in NICE [143] committee papers	MMD	Mapped Utility	Sponsor Utility	MMD	Mapped Utility	Sponsor Utility in NICE [143] committee papers
Episodic migraine									
Baseline	9.0	0.697	0.688	9.0	0.697	0.688	9.0	0.697	0.688
Treatment 0-3-month	7.3	0.721	0.769-0.695	6.7	0.730	0.784-0.686	8.7	0.701	0.77-0.685
Treatment 4-6-month	7.5	0.719	NR	6.1	0.738	NR	8.7	0.701	NR
Treatment >6 months	4.5	0.760	0.760	4.5	0.760	0.779	4.5	0.760	0.756
Negative discontinue	9.0	0.697	0.688	9.0	0.697	0.688	9.0	0.697	0.688
Positive discontinue		0.760	NR		0.760	NR		NA	NA
Chronic migraine									
Baseline	18.0	0.494	0.466	18.0	0.494	0.466	18.0	0.494	0.466
Treatment 0-3-month	12.6	0.605	0.735-0.491	11.0	0.638	0.752-0.512	15.3	0.550	0.731-0.495
Treatment 4-6-month	12.6	0.605	NR	11.0	0.638	NR	15.3	0.550	NR
Treatment >6 months	9.0	0.679	0.735	9.0	0.679	0.752	9.0	0.679	0.731
Negative discontinue	18.0	0.494	0.466	18.0	0.494	0.466	18.0	0.494	0.466
Positive discontinue	9.0	0.679	NR	9.0	0.679	NR	NA	NA	NA

Abbreviations
MMD = monthly migraine days, **NA** = not applicable**, NR** = not reported.
* Standard care presented for 140 mg model. Utilities are included in the models for BSC arms associated with 140 mg and 70 mg trials.

8.3.1.14.2 Fremanezumab

The model submitted to NICE[144] and outlined in committee papers used QoL data from the FOCUS trial,[91] which included patients who had failed ≥2 prior prophylactic therapies. The sponsor's model for erenumab outlined in NICE committee papers preferenced data from the disease-specific MSQ questionnaire over EQ-5D data because QoL was captured over the previous 4 weeks rather than the day of the clinic visit.[143] Utility values were redacted in publicly available versions of the sponsor's submission.

The NICE reviewers of the sponsor's model were concerned that utilities represent underestimates, particularly for chronic migraine patients.[144] They were noted as being aligned with the NICE-reviewed erenumab model at low MMD values, with slightly reduced utilities at the highest MMD states.[143] As the values for fremanezumab were redacted in the submitted dossiers, utility algorithms per MMD outlined for erenumab were used for fremanezumab in the current analysis. MMDs from key fremanezumab trials

outlined in ***Table 165*** were mapped to the utility values at baseline, 0–3 and 4–6 months, and longer-term on-treatment (***Table 172***). The same assumptions as outlined earlier are used for discontinuation utilities.

Table 172 Fremanezumab utilities

	Fremanezumab (225 mg)		Fremanezumab (625 mg)		Best supportive care	
	MMD	Mapped Utility	MMD	Mapped Utility	MMD	Mapped Utility
Episodic migraine						
Baseline	9.0	0.697	9.0	0.697	9.0	0.697
Treatment 0-3-month	5.2	0.750	5.3	0.749	8.3	0.707
Treatment 4-6-month	5.2	0.750	5.3	0.749	8.3	0.707
Treatment >6 months	4.5	0.760	4.5	0.760	4.5	0.760
Negative discontinuation	9.0	0.697	9.0	0.697	9.0	0.697
Positive continuation	4.5	0.760	4.5	NA	NA	NA
Chronic migraine						
Baseline	18.0	0.494	18.0	0.494	18.0	0.494
Treatment 0-3-month	13.5	0.587	14.1	0.574	17.3	0.508
Treatment 4-6-month	13.5	0.587	14.1	0.574	17.3	0.508
Treatment >6 months	9.0	0.679	9.0	0.679	9.0	0.679
Negative discontinuation	18.0	0.494	18.0	0.494	18.0	0.494
Positive continuation	9.0	0.679	9.0	NA	NA	NA

Abbreviations
MMD = monthly migraine days, **NA** = not applicable.

8.3.1.14.3 Galcanezumab

The EVOLVE-1, EVOLVE-2, REGAIN and CONQUER studies collected data using the MSQ.[50,92,93,98] The EQ-5D-5L QoL instrument was only administered in the CONQUER study.[98] Utilities were derived using a previously published mapping algorithm by Gillard et al 2012.[154] MMDs from key galcanezumab trials outlined in ***Table 167*** were mapped to the utility values at baseline, 0 to 3 and 4 to 6 months, and longer-term on-treatment (***Table 173***).

Table 173 Galcanezumab utilities

	Galcanezumab (120 mg)		Best supportive care	
Episodic migraine	**MMD**	**Mapped Utility**	**MMD**	**Mapped Utility**
Baseline	9.0	0.697	9.0	0.697
Treatment 0-3-month	6.1	0.738	8.7	0.701
Treatment 4-6-month	6.1	0.738	8.7	0.701
Treatment >6 months	4.5	0.760	4.5	0.760
Negative discontinuation	9.0	0.697	9.0	0.697
Positive continuation	4.5	0.760	NA	NA
Chronic migraine				
Baseline	18.0	0.494	18.0	0.494
Treatment 0-3-month	12.3	0.612	16.5	0.525
Treatment 4-6-month	12.3	0.612	16.5	0.525
Treatment >6 months	9.0	0.679	9.0	0.679
Negative discontinuation	18.0	0.494	18.0	0.494
Positive continuation	9.0	0.679	NA	NA

Abbreviations
MMD = monthly migraine days, **NA** = not applicable.

8.3.1.14.4 Eptinezumab

The comparison between eptinezumab and BSC is modelled using MMD data from the PROMISE trials and Dodick et al 2014.[82,84,96] MMDs were mapped using the previously described approach (***Table 174***).

Table 174 Eptinezumab utilities

	Eptinezumab (100 mg)		Best supportive care	
Episodic migraine	**MMD**	**Mapped Utility**	**MMD**	**Mapped Utility**
Baseline	9.0	0.697	9.0	0.697
Treatment 0-3-month	4.7	0.758	5.4	0.747
Treatment 4-6-month	4.5	0.760	5.2	0.750
Treatment >6 months	4.5	0.760	4.5	0.760
Negative discontinuation	9.0	0.697	9.0	0.697
Positive continuation	4.5	0.760	NA	NA
Chronic migraine				
Baseline	18.0	0.494	18.0	0.494
Treatment 0-3-month	10.3	0.653	12.4	0.609
Treatment 4-6-month	9.7	0.665	11.6	0.626
Treatment >6 months	9.0	0.679	9.0	0.679
Negative discontinuation	18.0	0.494	18.0	0.494
Positive continuation	9.0	0.679	NA	NA

Abbreviations
MMD = monthly migraine days, **NA** = not applicable.

8.3.1.15 Costs input

Costing studies identified as part of this literature review suggest differing treatments have differing medicines costs and associated health services costs (see ***Appendix J***). Costs were found to be higher for patients who had failed greater numbers of preventive treatments. For example, Amin et al 2021,[170] Foster et al 2021[171] and Chandler et al 2021[172] compared direct and healthcare resource utilisation costs for preventive migraine medication-naïve patients and those with ≤3 preventive migraine medication switches before initiating CGRP antagonists (using the IBM® MarketScan® database, USA). Results suggest that direct and health services costs increased significantly with increasing use of prior medicines. McAllister et al 2021[173] found significant reductions in headache frequency and health services use after fremanezumab initiation in patients with migraine in the USA (using the Midwest component of EMRClaims+®, an integrated health services database). Given costs vary based on migraine severity, they are applied to each health state in the model on a monthly basis. Costs include medicines and services associated with the intervention, along with disease management costs based on MMDs calculated for each state.

8.3.1.15.1 Medicine costs

The cost of CGRP antagonist treatment includes the cost of the medicine and training in self-administration at commencement. These costs are assumed to be additional visits that CGRP antagonist-treated patients would undertake in addition to acute migraine management costs. Monitoring costs were applied at 3 and 6 months in the 1-year modelling timeframe to align with Swiss treatment regulations. Training for treatment commencement and monitoring were assumed to be undertaken by a neurologist. Treatment with CGRP antagonists may normally only be continued based on a review by a board-certified neurologist in Switzerland.

Further consultations are required for longer modelling timeframes. CGRP antagonist therapy must be discontinued no later than 1 year after the start of therapy. If the patient experiences a relapse within 6 months of discontinuing therapy (at least 8 MMDs), a resumption of CGRP receptor antagonist or CGRP inhibitor therapy can be requested via a renewed cost approval for 12 months. This can be continued if the therapy is still necessary and effective. Based on these considerations, additional neurologist visits are included at 15 months, then at 3 and 5 months following treatment commencement. This pattern is followed over the 5- and 10-year projections.

Dosage and unit costs for the intervention and acute medication costs are presented in ***Table 175***.

Table 175 Unit costs for medicines and associated services (CHF)

Medicine costs		
Medicine	**Unit cost (CHF, public)**	**Source and dosing**
Erenumab	517.6	Aimovig, 70 and 140 mg/ml, pen 1 ml, monthly
Fremanezumab	527.4	Ajovy, 225 mg/1.5 ml, pen 1.5 ml, monthly
Fremanezumab	1523.1	Ajovy, 225 mg/1.5 ml, 3 pen 1.5 ml, quarterly
Eptinezumab	1521.3	Vyepti, 100 mg/ml, 1 ml, quarterly
Galcanezumab	532.3	Emgality, 120 mg/ml, 1 ml, monthly (starting dose of 240 mg/ml, 2 pre-filled pens)
Rizatriptan	46.7	Maxalt, 5 mg, 6 tablets. One tablet per migraine day
Sumatriptan	35.8	Sumatriptan Sandoz, 50 mg, 6 tablets. One tablet per migraine day
Zolmitriptan	39.6	Zolmitriptan Sandoz, 2.500 mg, 6 tablets. One tablet per migraine day
Ibuprofen	9.75	Ibuprofen 400 mg, Blist 50 tablets. One tablet per migraine day
Topiramate	77.2	Topiramat Sandoz, 100 mg, 60 tablets. One tablet per migraine day
Migraine-specific medication related services		
Therapy initiation (CHF)	179	In Switzerland, CGRP antagonist prescriptions and follow-up controls must be carried out by a board-certified specialist in neurology. Training for self-administration of patients is usually carried out by a neurologist. Since a detailed description including pictograms is included in each CGRP antagonist's package, the therapy initiation session usually takes 20 minutes or less. Expert opinion provided during the assessment indicated follow-up consultations ("Konsultation") of up to 20 minutes (patients over 6 years of age and up to 75 years of age, 65,14 Tax points) or up to 30 minutes (patients below 6 years of age and above 75 years of age, 102.36 Tax points) for focused neurological examination (Neurostatus B, 94.77 Tax points) and written report (40.93 Tax points) may be included. For example, for patients over 6 years of age and below 75 years of age could access a follow-up consultation for a patient with migraine costs of up to (65.14 + 94.77 + 40.93) x 0.89 = 179CHF.
CGRP Monitoring (CHF) visits	179	In Switzerland, the diagnosis, the prescription of CGRP antagonists and the follow-up control may only be carried out by a board-certified specialist in neurology. Monitoring occurs at 3 and 6 months.

Abbreviations
CHF = Swiss francs, **CGRP** = calcitonin gene-related peptide.
Source
Spezialitätenliste,[174] 1/9/2022, for medicines.

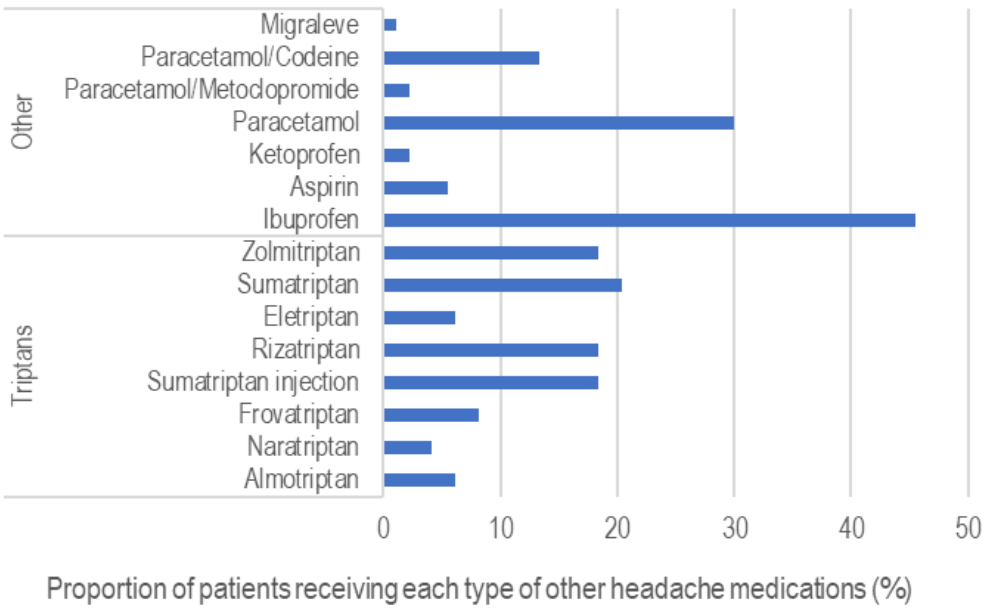
8.3.1.15.2 Other medicines

Acute medicine costs were added to the CGRP antagonist and BSC arms of the current economic model based on MMDs. Medication-related frequencies of resource utilisation were derived from Tepper et al 2017,[175] STRIVE,[102] ARISE[75] and LIBERTY[49] in the erenumab model submitted to NICE.[143] A simple linear regression was developed to predict the number of migraine days with triptans and other medications (assumed to be analgesics), providing estimates of average days of medication use for each frequency of MMDs.

Results of the NICE analysis were provided in Table 59 (p. 158) of the committee papers as resource use frequency (per 12-week cycle) for each MMD.[143] These estimates were converted to monthly rates and linear regression conducted for the current study. The resulting algorithms are triptan use days per month: -0.1726 + 0.4926 x MMDs (R^2=0.99) and other medicines use days per month: -1.1078 + 0.2163 x MMDs (R^2=0.99).

The cost per day of triptans was GBP2.55 (CHF2.85) and of other medicines was GBP0.27 (CHF0.30) in the NICE-reviewed models submitted in the UK.[143] The most frequently used medicines were identified using National Health and Wellness Survey (NHWS) data from 2017, where 22% of respondents had prescriptions for triptan medications and 41% had prescriptions for analgesic medications. Vo et al 2018 found a similar utilisation profile using a retrospective, cross-sectional analysis of 3,900 users of the Migraine Buddy© smartphone application across 17 European countries.[11]

Figure 42 Proportion of patients receiving each type of headache medication



Source
NHWS data from 2017 presented in NICE[143] committee papers

Most patients (47.5%) reported use of 1 medication per migraine attack, 28.5% reported use of ≥2 medications and 15.9% reported no medication use. Triptans (31.9%) were the most frequently used acute medication, followed by nonsteroidal anti-inflammatory drugs (28.7%), acetaminophen (18.9%) and opioids (8.4%) Weights from the NHWS survey for both headache medications and triptans are presented in ***Figure 42***, using data presented in the NICE[143] appraisal of sponsor-submitted modelling committee papers. Based on the average cost of 6-tablet packs of rizatriptan (CHF46.65), sumatriptan

(CHF35.75) and zolmitriptan (CHF39.55), a triptan cost per day of CHF6.78 was included in the current model. For other medicines, an average cost of ibuprofen of CHF0.2 per day was included.

8.3.1.15.3 Costs of migraine management

Other healthcare resources include GP visits, emergency department visits, hospitalisations and neurologist consultations associated with disease management. These costs were not reported across included trials in the clinical evidence section as they vary with migraine severity. They are included in the model based on modelled MMDS and unit costs for these services. Unit costs were obtained from the most recent Swiss DRG weights and TARMED positions, provided as part of clinical feedback when developing the model. The DRG weight is multiplied by the average Swiss hospital tariff of CHF9,628 to generate the hospital unit cost (***Table 176***).

Table 176 Unit costs (CHF) for health services costs

Cost item	Unit cost	Assumptions for Swiss context
Costs of migraine management		
General practitioner visit	100	A consultation in the UK was assumed to last 9.22 minutes and cost GBP37, or CHF41. Clinical feedback was sought to obtain detailed information on what length of time and appropriate tariff (CHF) is relevant for a typical migraine-related visit for a GP in Switzerland. Based on the clinical feedback provided, a GP consultation was assumed to cost CHF100 in the economic analysis. The cost is varied by 20% in the sensitivity analysis.
Neurologist visit	277	A consultation in the UK was assumed to last 30 minutes. Disease management consultations are costed as an average between an initial and follow-up visit in our model. The first consultation ("Konsiliarische Beratung / Konsilium") is assumed to last up to 60 minutes (5 minutes = 18.6 tax points, 60 minutes = 12 x 18.6 = 223.32 Tax points). The consultation time depends on the examiner. A full neurological examination (Neurostatus A) (208.49 Tax points) may be added. Tax point values are canton specific. An average Swiss tax point value of 0.89 is used. Migraine patients costs up to (223.32 + 208.49) x 0.89 = 375CHF. A follow-up visit would be CHF179. Patients availing neurologist services would be a mix of first and follow-up consultations. An average cost of CHF277 is included.
Emergency department visit	1,411	The UK model included the UK HRG code VB09Z. Category 1 investigation with Category 1–2 treatment costs GBP130 or CHF143. TARMED positions were provided as part of clinical feedback during the evaluation. Costs included consultation magnetic resonance imaging and diagnostic components. An average cost of CHF1,411 is included and varied by 20% in the sensitivity analysis.
Hospital inpatient visit	5,729	In the UK a weighted average of HRG codes AA31C, AA31D and AA31E, which relate to Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 11+, Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 7-10, Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-6 were used for this cost of GBP574 or CHF632. Swiss DRG B77B (Headaches and age >15 years, >1 day of occupancy) was used for a hospital cost of CHF5,729 in our model and varied by 20% in the sensitivity analysis.

Abbreviations
CHF= Swiss francs, **DRG** = diagnostic reference group, **GBP** = British pound, **GP** = general practice.

Healthcare resource consumption estimates are derived from the NHWS,[156] based on MHDs. The 2017 survey included 62,000 respondents in 5 European countries (France, Germany, Italy, Spain and UK). Service utilisation reported in the NHWS was analysed by Doane.[156] Resource uses were compared between migraine groups using generalised linear modelling after adjusting for covariates. Results over 6 months were adjusted for a cycle length of 1 month (***Table 177***). Linear regression was performed to calculate service utilisation per month based on MMDs. Intercept and variable terms, along with goodness of fit (R^2) are provided (***Table 178***, ***Figure 43***).

Table 177 Frequency of monthly health service utilisation, by MHDs

MHDs	Hospital	Emergency	GP	Neurologist
6 months				
1 to 3	0.150	0.280	2.250	0.090
4 to 7	0.160	0.380	2.710	0.160
8 to 14	0.170	0.420	3.060	0.210
>15	0.210	0.510	3.500	0.340
Monthly equivalent				
1 to 3	0.025	0.047	0.375	0.015
4 to 7	0.027	0.063	0.452	0.027
8 to 14	0.028	0.070	0.510	0.035
>15	0.035	0.085	0.583	0.057
Linear regression				
Intercept	0.023	0.044	0.353	0.009
Variable	0.001	0.003	0.015	0.003
Goodness of fit (R^2)	0.858	0.946	0.983	0.941

Abbreviations
GP = general practice, **MHD** = monthly headache days.
Source
Doane[156]

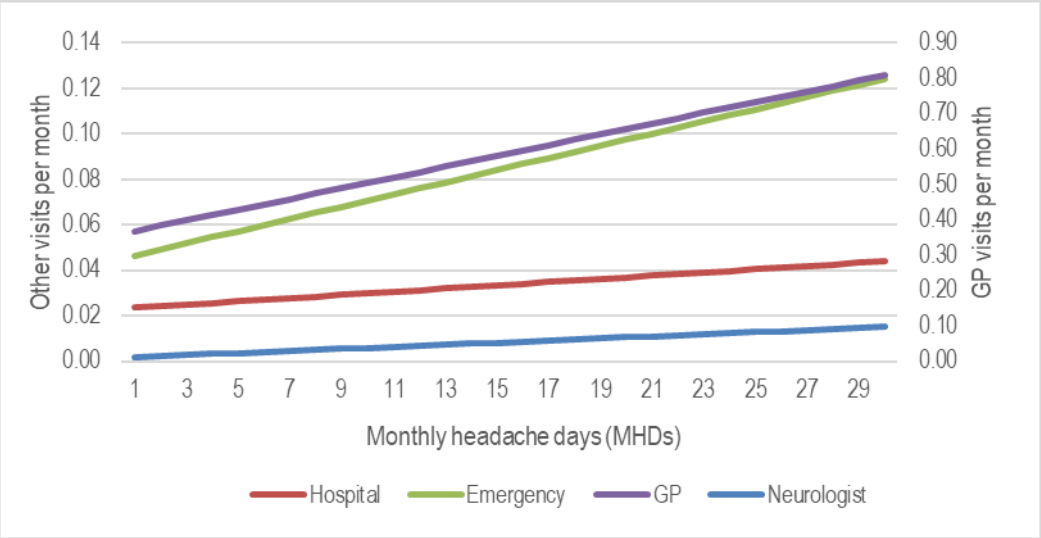
Reviewers of submitted models noted that healthcare resource consumption estimates from the NHWS (analysed by Doane[156]) were based on MHDs rather than MMDs. Measurement of MHDs may lead to underestimation of resource use and thereby favour the least effective treatment strategies. Costs are subject to sensitivity analysis given this uncertainty. Clinical feedback during model development indicated that migraine patients in Swiss rehabilitation settings may be hospitalised in Switzerland, especially in the case of a medication-overuse headache. Migraine patients from other settings may also be hospitalised in an acute care hospital, although this is not generally the case. As discussed above, hospital costs are subject to sensitivity analysis.

Table 178 Linear regressions for health service utilisation

Monthly health service utilisation by MHDs	Intercept and variable for linear regression	Source
Monthly GP visits by MHDs	Intercept, 0.353 Variable 0.015	6-month utilisation rate by MHD from Doane[156] converted to monthly cycle and linear regression conducted
Monthly neurologists visit by MHDs	Intercept, 0.009 Variable, 0.003	6-month utilisation rate by MHD from Doane[156] converted to monthly cycle and linear regression conducted
Monthly emergency department visit by MHDs	Intercept, 0.044 Variable, 0.003	6-month utilisation rate by MHD from Doane[156] converted to monthly cycle and linear regression conducted
Monthly hospital inpatient visit by MHDs	Intercept, 0.023 Variable, 0.001	6-month utilisation rate by MHD from Doane[156] converted to monthly cycle and linear regression conducted

Abbreviations
GP = general practice, **MHD** = monthly headache day.

Figure 43 Health services use per month, by MHDs



Abbreviations
GP = general practice, **MHD** = monthly headache days.
Source
Doane[156]

8.3.2 Results: cost-effectiveness

Cost-effectiveness modelling is included for patients that have failed >2 previous treatments, as this is a subpopulation of relevance for the policy maker. Results are first presented for erenumab, as this product is most widely used in Switzerland. Analyses are presented for chronic and episodic patients at different dosages. Univariate, probabilistic and scenario sensitivity analyses are also presented for erenumab, given its widespread use. Analyses are then presented for other CGRP inhibitors.

8.3.2.1 Erenumab

The incremental cost and effectiveness values of erenumab 70 mg and 140 mg versus BSC at 1 year are presented for chronic migraine patients (***Table 179***). The ICUR was CHF84,033 for 70 mg and CHF53,067 for 140 mg patients.

Table 179 Erenumab versus best supportive care (BSC) cost-effectiveness, chronic migraine patients that failed >2 previous treatments, 1 year

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
70 mg					
Erenumab	11,567		0.63		
Best supportive care	7,179	4,388	0.58	0.05	84,033
140 mg					
Erenumab	11,249		0.66		
Best supportive care	7,179	4,070	0.58	0.08	53,067

Abbreviations
CHF = Swiss francs, **ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

The incremental cost and effectiveness values of erenumab 70 mg and 140 mg versus BSC at 1 year are presented below for episodic migraine patients (***Table 180***). The ICUR was CHF318,982 for 70 mg and CHF173,174 for 140 mg patients.

Table 180 Erenumab versus best supportive care (BSC) cost-effectiveness, episodic migraine patients that failed >2 previous treatments, 1 year

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
70 mg					
Erenumab	8,559		0.78		
Best supportive care	3,844	4,715	0.76	0.01	318,982
140 mg					
Erenumab	8,545		0.79		
Best supportive care	3,882	4,663	0.76	0.03	173,714

Abbreviations
CHF= Swiss francs**, ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

Additional analyses were conducted using results from trials outlined in ***Table 161*** to ***Table 164*** for episodic migraine patients who had not failed 2 prior preventive treatments. These analyses are in line with the broader patient group outlined in the HTA research question presented in ***Section 2***. The ICURs were CHF233,089 for a 70 mg dose and CHF237,914 for 140 mg.

8.3.2.1.1 Sensitivity analyses

Probabilistic, univariate and scenario sensitivity analysis were undertaken to gauge the robustness of results to modelling assumptions. Given that erenumab has the most comprehensive evidence base and this medicine is the most widely used CGRP antagonist in Switzerland, it was used as an example for sensitivity analyses.

Univariate analysis involved 20% changes in base assumptions (outlined in ***Table 181***). Results of the analysis are presented as a tornado graph (***Figure 44***). Probabilistic sensitivity analysis was conducted using Monte Carlo simulation, with 10,000 iterations. Assumptions underpinning distributions used for key assumptions are presented in ***Table 181***. Scenarios were also constructed to test structural assumptions of the models including modelling timeframe, inclusion of positive discontinuation, revision to baseline MMDs upon negative discontinuation and waning of treatment effect.

Table 181 Sensitivity analyses

Sensitivity Analyses	Probabilistic distribution	Univariate	Scenarios
Modelling assumptions			
Patients who had not failed 2 preventive treatments	NA	NA	Data from trials who included this population was included in the economic model.
MMD reduction from baseline	Normal	±20%	Pooled analysis of trials who excluded patients with 2 or more prior failed preventive treatments detailed in model results section
Responders have on-treatment MMD reduction equivalent to 50% of baseline	NA	NA	Sponsor submitted long-term on-treatment utilities included in the model.
CGRP antagonist responders are assumed to have no waning in treatment effect	NA	NA	Waning applied. 5-year linear wane of effect to baseline for those on treatment and positive stoppers
CGRP antagonist non-responders assumed to experience BSC MMDs and utilities	NA	NA	Following the assessment period, non-responders are assumed to lose MMD benefits after 6 months and return to average MMDs
BSC responders are assumed to maintain treatment effect	NA	NA	Responders are assumed to return to baseline MMDs and corresponding utility after 6 months
Response at 6 months	NA	±20%	Pooled analysis of trials who excluded patients with ≥2 prior failed preventive treatments detailed in model results section
Long-term negative discontinuation of 1%	NA	±20%	NA
Apply positive discontinuation	NA	NA	20% of responders discontinue treatment at 12 months and sustain on-treatment MMD reduction benefits
Utilities equation, variable	Normal	±20%	NA
Topiramate included as comparator	NA	NA	Results of the HER-MES trial[80] and monthly cost (CHF39) of topiramate included.
Time and discount			
Time horizon	NA	NA	The time horizon for the model is changed to 5 and 10 years
Discount rate	NA	0, 5%	NA
Baseline characteristics (age)	Triangular	±20%	NA
Costs			

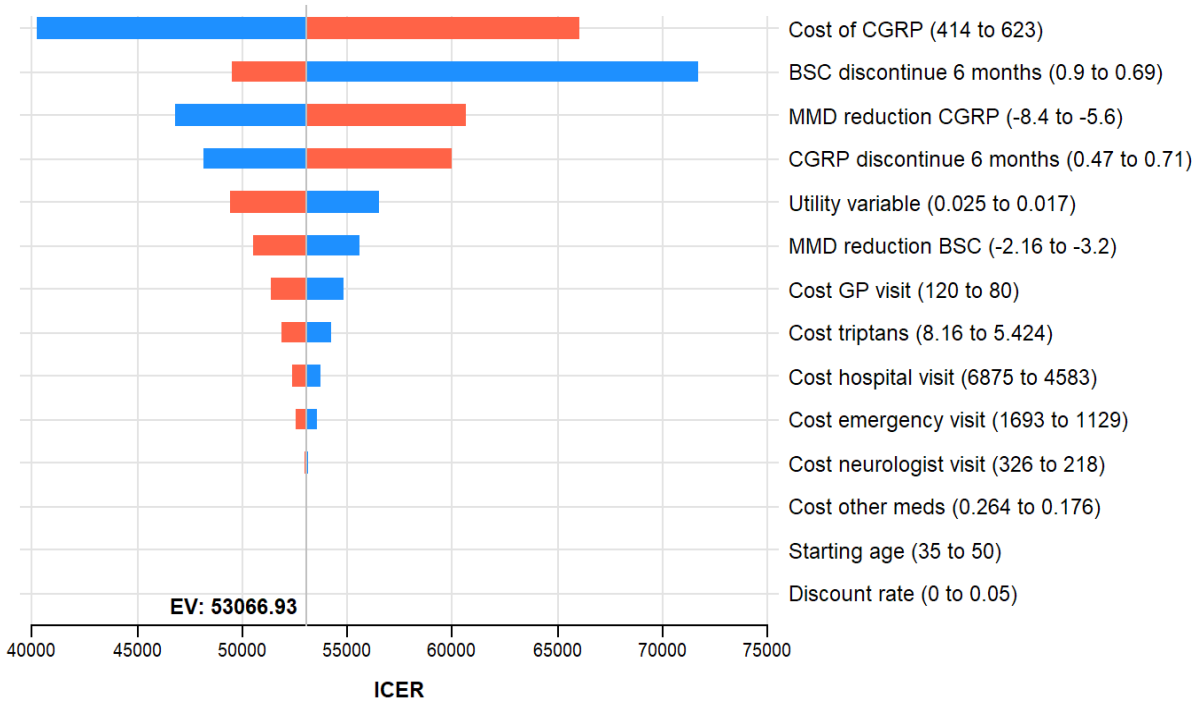
Sensitivity Analyses	Probabilistic distribution	Univariate	Scenarios
Drug acquisition cost	NA	±20%	NA
Self-administration training	NA	±20%	10% of CGRP antagonist-treated patients require neurologist support for monthly drug administration
Triptan and other acute medications	Triangular for triptans and uniform for other medicines	±20%	NA
Unit costs of GP, emergency, neurologist, hospital	Triangular for all except normal for hospital	±20%	NA
Resource use equation variable	Normal	±20%	NA

Abbreviations
BSC = best supportive care, **CGRP** = calcitonin gene-related peptide, **CHF** = Swiss francs, **GP** = general practitioner, **MMD** = monthly migraine days, **NA** = not applicable.

8.3.2.1.2 Univariate sensitivity analysis

Figure 44 illustrates which ICUR estimates were most affected by 20% variations in base assumptions. The analysis was performed using the erenumab 140 mg chronic migraine patient 1-year model. Variations in CGRP antagonist costs, utility estimates, MMD reduction and proportions responding had the largest impacts.

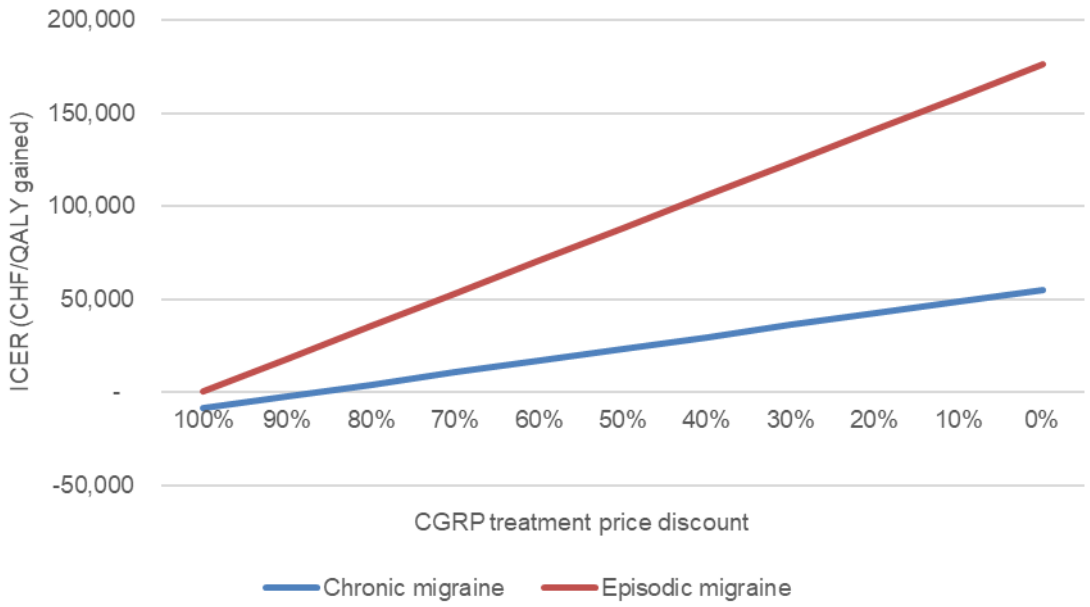
Figure 44 Erenumab 140 mg chronic migraine 1- year model tornado graph



Abbreviations
BSC = best supportive care, **CGRP** = calcitonin gene-related peptide, **CHF** = Swiss francs, **EV** = expected value, **GP** = general practice, **MMD** = monthly migraine day, **ICER** = incremental cost-effectiveness ratio.

A univariate sensitivity analysis on CGRP antagonist treatment price is presented in ***Figure 45*** to illustrate how ICUR estimates vary due to price reductions. The analysis was performed using the erenumab 140 mg chronic and episodic migraine patients 1-year model. A 50% reduction in CGRP antagonist price resulted in the episodic migraine model generating an ICUR of less than CHF100,000 per QALY gained.

Figure 45 Erenumab 140 mg chronic and episodic migraine 1-year model sensitivity to CGRP antagonist treatment price discount



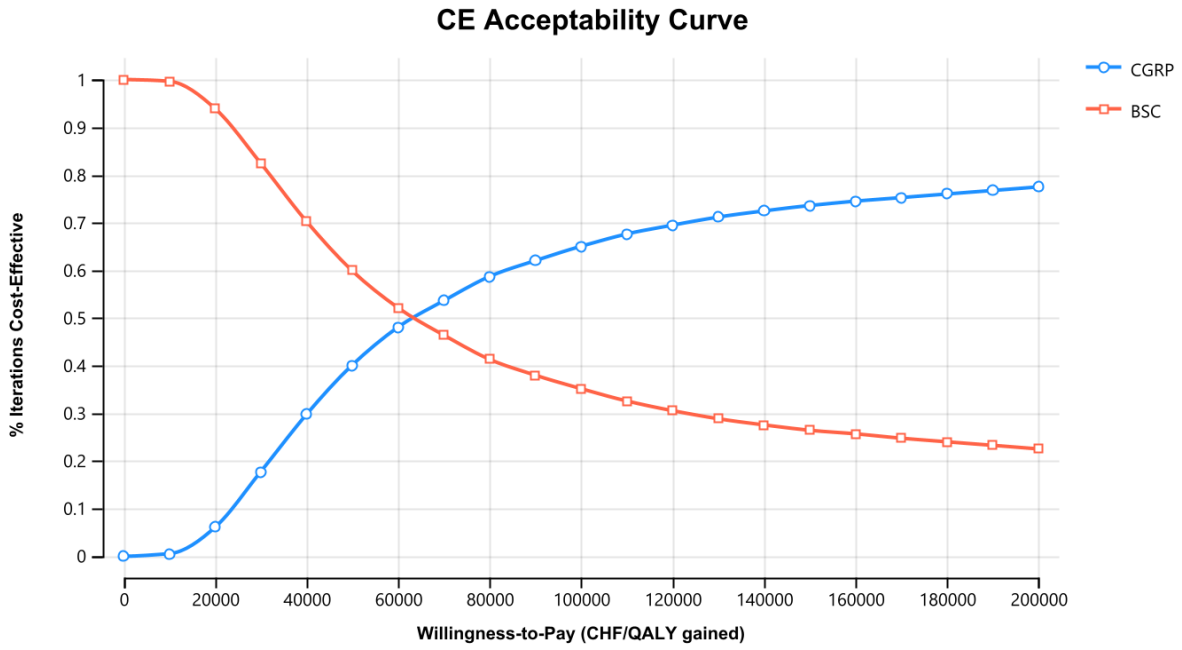
Abbreviations

CGRP = calcitonin gene-related peptide, **CHF** = Swiss francs**, ICER** = incremental cost-effectiveness ratio, **QALY** = quality-adjusted life year.

8.3.2.1.3 Probabilistic sensitivity analysis

Inputs were specified as distributions in the 1-year projection erenumab 140 mg versus BSC model for chronic migraine patients. A mean expected ICUR of CHF59,442 per QALY (95% CI from probabilistic sensitivity analysis CHF40,173 to CHF79,089) was estimated for chronic migraine patients. Cost-effectiveness acceptability curves are presented for chronic migraine patients (***Figure 46***). When considering cost-effectiveness thresholds of CHF50,000, CHF100,000 and CHF150,00 per QALY gained, erenumab had probabilities of cost-effectiveness of 40%, 65% and 74%, respectively, against BSC for chronic migraine patients.

Figure 46 Cost-effectiveness acceptability curve, erenumab 140 mg chronic migraine 1-year model (CHF/QALY gained)



Abbreviations
BSC = best supportive care, **CE** = cost-effectiveness**, CGRP** = calcitonin gene-related peptide antagonist **CHF** = Swiss francs, **QALY** = quality-adjusted life year.

8.3.2.1.4 Scenario analysis

A series of scenarios using results from the erenumab 140 mg in chronic migraine patients model over 5 years is presented (***Table 182***). Given uncertainty in the efficacy results of the open label studies, treatment waning is examined using a scenario where treatment effectiveness is reduced linearly over the model timeframe. The model is extended to 10 years, along with changing discontinuation and response assumptions. Topiramate is also included as a comparator. Scenarios having a moderate impact on the estimated ICURs included those in which the assumed MMDs experienced by CGRP antagonist non-responders was changed (i.e. BSC MMDs rather than baseline MMDs used for non-responders) and in which topiramate was included as a comparator.

Table 182 Scenario sensitivity analyses, erenumab 140 mg vs best supportive care (BSC) in chronic migraine, 5 years

Sensitivity Analyses	ICUR	Comments
Base	39,970	
Sponsor submitted long term on-treatment utilities included in the model.	29,540	Sponsor-submitted long-term on-treatment utility was 6% higher than that estimated by assuming the on-treatment group had MMDs equivalent to half of starting MMDs.
Waning applied. 5-year linear wane of effect to baseline for those on treatment and positive stoppers	40,233	The base model assumed treatment effectiveness was sustained through MMDs reported at months 3 or 6 would be observed for the rest of the projection.
CGRP antagonist non-responders are assumed to experience BSC MMDs and associated utility	14,480	Following the assessment period, non-responders are assumed to lose MMD benefits after 6 months and move to BSC on-treatment MMDs rather than baseline MMDs.
BSC responders are assumed to experience baseline MMDs and associated utility	25,909	Some of the BSC benefit is likely to be placebo and may not be sustained throughout the modelling period. Moving all BSC patients back to baseline MMDs removes the placebo impact over the long-term
20% of responders discontinue treatment at 12 months and sustain on-treatment MMD reduction benefits	32,013	20% of responders discontinue treatment and retain QoL experienced (i.e. MMD reduction and associated utility) when on-treatment
The time horizon for the model is changed to 10 years	37,502	The time horizon for the model is changed from 5 to 10 years.
Self-administration support	42,702	10% of CGRP antagonist-treated patients require neurologist support for monthly drug administration. The unit cost is increased by 5%.
Topiramate included as comparator	69,135	Results of the HER-MES trial[80] indicate the CGRP antagonist comparison with BSC is more cost-effective than with topiramate. The HER-MES trial included episodic and chronic patients, less than 10% of patients had failed 2 or more preventive treatments and, correspondingly, results are difficult to generalise to the Swiss context.

Abbreviations
BSC = best supportive care, **CE** = cost-effectiveness**, CGRP** = calcitonin gene-related peptide antagonists, **ICUR** = incremental cost utility ratio, **MMD** = monthly migraine days, **QoL** = quality of life.

8.3.2.2 Fremanezumab

The incremental costs and effectiveness of fremanezumab versus BSC at 1 year among chronic migraine patients are presented in ***Table 183***. The ICURs were CHF59,423 and CHF65,905 for chronic migraine patients being treated with 225 mg and 625 mg regimens, respectively.

Table 183 Fremanezumab vs best supportive care (BSC) cost-effectiveness, chronic migraine patients that failed >2 previous treatments, 1 year

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
225 mg					
Fremanezumab	11,847		0.62		
Best supportive care	7,761	4,086	0.55	0.07	59,423
625 mg					
Fremanezumab	11,818		0.61		
Best supportive care	7,761	4,057	0.55	0.06	65,905

Abbreviations
CHF = Swiss francs**, ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

Among episodic patients, the ICURs were CHF135,384 and CHF134,152 for those treated with 225 mg and 625 mg regimens, respectively. Sensitivity analyses for trial patients who had not failed previous treatments resulted in ICURs from CHF110,615 to CHF99,688 for chronic and CHF316,913 to CHF243,804 for episodic patients for 625 and 225 mg dosing.

8.3.2.3 Galcanezumab

The incremental costs and effectiveness of galcanezumab versus BSC at 1 year among episodic and chronic migraine patients are presented in ***Table 184***. The ICURs were CHF187,646 and CHF63,944 for episodic and chronic migraine patients, respectively.

Table 184 Galcanezumab vs best supportive care (BSC) cost-effectiveness, episodic and chronic migraine patients that failed >2 previous treatments, 1 year, 120 mg

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
Episodic migraine					
Galcanezumab	9,255		0.79		
Best supportive care	3,817	5,438	0.76	0.03	187,646
Chronic migraine					
Galcanezumab	12,088		0.63		
Best supportive care	7,562	4,526	0.56	0.07	63,944

Abbreviations
CHF = Swiss francs, **ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

8.3.2.4 Eptinezumab

The incremental costs and effectiveness of eptinezumab 100 mg versus BSC at 1 year among episodic and chronic migraine patients are presented in ***Table 185***. The ICURs were CHF825,236 and CHF108,104 for episodic and chronic migraine patients, respectively.

Table 185 Eptinezumab vs best supportive care (BSC) cost-effectiveness, 1 year, 100 mg

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
Episodic migraine					
Eptinezumab	8,759		0.81		
Best supportive care	2,681	6,078	0.80	0.01	825,236
Chronic migraine					
Eptinezumab	11,296		0.69		
Best supportive care	6,017	5,279	0.64	0.05	108,104

Abbreviations
CHF = Swiss francs**, ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

8.3.2.5 Key drivers of the economic model

Key drivers of the model are summarised in ***Table 186***. Univariate sensitivity analyses demonstrate that CGRP antagonist cost is a key deriver of model value. Assumptions about utilities and effectiveness also have a large impact on model results. Variations in the costs of most health states have a negligible impact on the estimated ICUR.

Table 186 Key drivers of the economic model

Description	Method/Value	Impact
Costs of CGRP antagonists	Costs of CGRP antagonists are the largest single cost component, accounting for more than half of the overall cost of the intervention. Changes in unit costs have a large impact on the estimated ICUR. Price reductions of 20% result in 140 mg erenumab having an ICUR of <CHF45,000 per QALY gained among chronic migraine patients.	**High** Sensitivity analysis indicated that 20% changes in unit costs had the largest impact on the estimated ICER.
Health services utilisation associated with costs of disease management	Costs of disease management were estimated as a function of MMDs. Studies have shown that MHDs are related to resource use,[176] and this approach was used in a range of submitted models to HTA agencies, in published literature and other interventions targeting migraine.[177] The Vo et al 2018[176] survey analysis of resource use among European migraine patients showed service use varies with MHDs. The rates of service utilisation may not reflect Swiss clinical practice. The clinical expert consulted as part of model development indicated migraine patients are rarely admitted to hospital for migraine outside of rehabilitation settings. Neurologists are required for on-going management so utilisation rates from the Vo et al 2018[176] analysis could underestimate the situation in Switzerland. The survey by Vo et al 2018[176] uses MHDs rather than MMDs. Sensitivity analysis of health services costs indicated ICUR results were moderately impacted by changes in these assumptions.	**Low** Sensitivity analysis of health services cost variables indicated ICUR results were moderately impacted by changes in these assumptions

Description	Method/Value	Impact
Costs of acute medication	The number of acute medication days were taken from sponsor-submitted models, using regression analysis in the key erenumab trials. Acute medications in the model consisted of NSAIDs/I and triptans. The cost of acute medication ranged from CHF0.2 for NSAIDS to CHF6.78 per day for triptans.	**Moderate** Sensitivity analysis of acute medication use variables indicated ICUR results were moderately impacted by changes in these assumptions
Health utilities calculated as a function of MMDs	EQ-5D utilities reported during trials are a preferred source of health quality estimates in economic modelling studies. These data were not comprehensively collected across trials, so this approach could not be used in our modelling study. Health-state utility values were derived from sponsor mapping of EQ-5D from MSQ data collected in trials. The current model does not account for migraine severity and utility is estimated as a function of MMDs. Sensitivity analysis indicated utility assumptions have a substantial impact on the estimated ICUR.	**High and unknown** The direction of the uncertainty associated with non-inclusion of severity in utility estimates is not clear.
Negative stopping rule applied at 6 months for patients who do not respond to treatment at ≥50% reduction in MMDs	Swiss clinical guidelines indicate patients being treated with CGRP antagonists have reduced MMDs at 3 months follow-up and a 50% reduction in MMDs at 6 months for treatment eligibility. Many blinded RCTs reported 50% response at 3 and 6 months, so there is uncertainty about response at longer periods of follow-up. Open label trial extensions suggest these responses were sustained; however, there are biases in extension phases. Model results are sensitive to the proportion of the CGRP antagonist arm deemed to be responsive and can continue treatment under Swiss guidance. CGRP antagonists are reimbursed for a maximum of one year in Switzerland, after which a patient is assessed and can then recommence treatment following clinical guidance. Base modelling assumed a 1-year time frame. Extending the modelling time frame to 5-years has a positive impact on cost-effectiveness.	**High** The response rate has a large impact on the estimated ICUR. Sensitivity analyses demonstrated the impact.
Positive stopping rules not included in the base model	Patients may discontinue treatment if they show a sufficient response to treatment. NICE reviewers of sponsor-submitted models noted that the proportion of patients who would stop under such a rule is not defined. A value of 20% was assumed and explored in scenario analyses. A similar scenario was included in the current erenumab 140 mg model for chronic migraine patients. All patients were assumed to stop treatment each year, and 20% of these patients would sustain treatment benefits in a positive discontinuation state for the remainder of the modelling projection.	**Moderate** Assuming a proportion of patients would gain treatment benefits without costs has a modest impact. The proportion of the patient population and treatment impact for this subpopulation is unclear.
Length of trial follow-up limits certainty about MMD reduction projections	There is uncertainty associated with long-term efficacy of CGRP antagonists on MMD reductions beyond the length of clinical trials. The justification for sustained response and MMD reduction assumptions is supported by data from open label trial extensions. The model does not consider longer-term changes in the frequency of migraine that are unrelated to treatment. For example, some patients may show a natural improvement or regression in MMDs over time.	**Moderate** The ICUR varied where treatment effect waned or increased over the modelling projection. The impact of natural migraine variation over time is unclear.
MMDs after treatment discontinuation are assumed to return to baseline MMDs	After a negative stop, non-responding CGRP antagonist and BSC patients were assumed to revert to their baseline MMD values. This is a conservative assumption as patients may maintain some treatment benefit. There is limited data about the migraine frequencies of patients once they have discontinued treatment. A sensitivity analysis was included where non-responders experience treatment benefits averaged between baseline MMDs and that on-treatment.	**High** Sensitivity analysis indicated that this assumption has a high impact on the estimated ICUR.

Description	Method/Value	Impact
Comparator did not include preventive migraine treatment	The economic model did not include all relevant comparators. Several other preventive medications, including calcium antagonists (flunarizine), anticonvulsants (topiramate), beta blockers and antidepressants are available for migraine prophylaxis in Switzerland. Only one trial was identified that compared erenumab verse topiramate (100 mg/day). A response of 55.4% vs 31.2% at 24 weeks and -5.86 MMD reduction over 4–6 months compared to-4.02 MMD in the HER-MES trial.[80]	**Uncertain** Sensitivity analysis indicated that economic analysis of erenumab verse topiramate (100 mg/day) rather than BSC had a moderate impact on the ICUR. This is only one preventive medicine available to Swiss patients. The impact of not including others is uncertain
The best supportive comparator in the economic model used the placebo arm of trials	The placebo arm of trials included in the clinical evidence section that included patients who had failed ≥2 preventive treatments was included as the comparative BSC arm of the economic model. The placebo arm allowed acute migraine medication use among participants, but it is unclear whether the nature of medicines used reflects BSC in Switzerland. It is difficult to attribute placebo and acute medicine use impacts on reported effectiveness.	**Uncertain** A proportion of patients in the comparator arm of key trials responded to treatment, despite following the placebo protocol. Modelling results are sensitive to the reduction in MMDS and responder proportions.

Abbreviations
BSC = best supportive care, **CGRP** = Calcitonin gene-related peptide antagonists, **CHF** = Swiss francs, **EQ-5D** = EuroQol- 5 Dimension, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **ICUR** = incremental cost utility ratio, **MHD** = monthly headache days, **MMD** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life Questionnaire 2.1, **NICE** = National Institute for Health and Care Excellence**, NSAID** = non-steroidal anti-inflammatory drugs, **QALY** = quality-adjusted life years, **RCT** = randomised controlled trial.

8.3.3 Results: budget impact

Projected costs to the payer for CGRP antagonist treatment of migraine over the next 5 years have been calculated as part of the budget impact analysis. CGRP antagonists are used in Switzerland as a preventive treatment for episodic and chronic migraine adult patients who have failed ≥2 preventive treatments. The use of CGRP antagonists is not assumed to substitute for other therapies and thus represents an additional cost. The target patient group is those who have failed 2 preventive treatments, so limited substitution for alternative preventive medicines could be expected. The economic modelling sensitivity analysis indicated that the reduction in acute migraine medications associated with fewer MMDs due to CGRP antagonist treatment had a moderate impact in the case of triptans and limited impact for other medicines on the calculated ICUR. These medicines have a relatively small cost when compared to CGRP antagonists. Although not including substitution in the budget impact analysis is a limitation, it is unlikely to have a large impact on projected net financial costs of CGRP antagonist uptake.

The budget impact is conducted from the perspective of a Swiss healthcare payer using an epidemiological approach and market share of the 4 CGRP antagonists currently reimbursed in Switzerland. In 2022, erenumab was the most widely used CGRP antagonist in Switzerland at 66% of

all packs sold. The next most utilised was galcanezumab (19%), then fremanezumab (15%) and finally eptinezumab (0.5%).[28] Eptinezumab was not introduced until 2022.

Hypothetical scenarios that reflect epidemiological assumptions have been developed to calculate the budget impact of CGRP antagonist uptake. This includes estimating the adult (≥18 years) population in Switzerland, the prevalence of migraine in the adult population, and the proportion of patients eligible for CGRP antagonist medicines based on failure of 2 prior preventive treatments. Hypothetical uptake scenarios among the current eligible population are estimated for current CGRP antagonist sales, an assumed number of doses per average patient, and future projections based on uptake growth assumptions using the current market shares of CGRP antagonists.

8.3.3.1 Approach and data sources

8.3.3.1.1 Eligible population in Switzerland

A range of studies has outlined the burden of migraine, such as the Chronic Migraine Epidemiology and Outcomes study,[178] the American Migraine Prevalence and Prevention study,[179] the International Burden of Migraine Study,[155] and the Euro light project.[180] It has been estimated that migraine effects approximately 1.6 million people in Switzerland, resulting in around 70,000 years of life lived with disability in 2016.[4] This study drew on global burden of disease migraine prevalence estimates for Switzerland of 21.4% for women and 10.9% for men.

There are some surveys of the Swiss population from which migraine prevalence can be drawn. A cohort study in Zurich found cumulative 30-year prevalence of migraine with aura to be 3% (2.1% in men; 3.9% in women), whereas the cumulative 30-year prevalence of migraine without aura was 36% (20.7% in men; 50.7% in women).[10] Across Europe, the Euro light project estimated the migraine prevalence rate among more than 170,000 adults was 14.7% (8% in men, 17.6% in women).[3] Using migraine prevalence estimates for Swiss adult females and males from the Global Burden of Disease Study results in around 1.2 million Swiss adults being estimated to experience migraine in 2021.

Migraine patients are further classified as chronic and episodic. The proportion of migraine patients in each of these categories is not clear. Economic models identified in the review included global estimates of episodic migraine and chronic migraine prevalence. For example, Sussman et al 2018[141] outlined general population estimates of episodic migraine and chronic migraine patients using the Stovner et al 2007[181] global burden of headache study. The study indicated 90% of all patients with migraine were classified as episodic migraine (0–14 MHDs) and 10% were chronic migraine patients experiencing an average of ≥15 MHDs. Mahon et al 2021 assumed chronic migraine affected 67% of people with migraine in the base case analysis.[182]

The base case analysis for Lipton et al 2018[142] assumed that 66.7% of patients had chronic migraine and 33.3% had episodic migraine, due to the health-seeking behaviour of those with more severe migraine. The cost-effectiveness analysis of fremanezumab submitted to CADTH [147] assumed episodic and chronic migraine prevalence of 91% and 9%, respectively, based on the baseline prevalence of episodic and chronic migraine in the Chronic Migraine Epidemiology and Outcomes study—a web-based study of migraine in the US.[183]

Some surveys have collected prevalence rates across Europe. A web-based survey was administered to panelists from 9 countries using a validated questionnaire including socio-demographics, clinical characteristics, migraine disability assessment, MSQ, patient health questionnaire and healthcare resource utilisation. Of the respondents, 5.7% were chronic migraine and 94.3% were episodic migraine patients.[184] It is difficult to quantify the proportions of chronic and episodic migraine patients in Switzerland, along with the proportions using preventive migraine medicines. The numbers of episodic patients are likely to be higher, however, the proportion of chronic migraine patients using preventive medicines is likely to be greater than episodic patients. Given this uncertainty, preventive treatment use is specified for all migraine patients in the budget impact analysis and a range of uptake scenarios included.

Only a proportion of migraine patients access preventive treatment; acute medication is most often sought. In Italy, a survey by Allena et al 2015[185] found only 16.6% of responders reporting headaches had received a diagnosis from a doctor, and 2.4% were using preventative medications. A self-administered headache questionnaire by Silberstein et al 2007 was mailed to a random sample of 120,000 US households to assess patterns of migraine treatment.[186] Most (97%) of migraineurs used acute treatments, half (52.8%) never used preventive treatment and around 7.9% were currently using preventive medication. The authors noted that prevention should be offered or considered by 28.4% of the migraine patients in the survey. Lipton et al 2007 concluded that 25.7% of migraineurs should be offered preventive therapy.[187] Based on a paucity of data, hypothetical scenarios are included in the budget impact analysis of this HTA report in which 10%, 25% and 50% of migraine patients would use preventive treatment when formulating potential uptake.

Swiss reimbursement requires patients to have failed 2 preventive treatments. The prevalence of this subpopulation is not supported by comprehensive evidence. The BECOME study is a prospective, non-interventional study conducted in 17 countries across Europe and Israel to determine the prevalence of failed treatment among patients visiting headache centres.[188] Of 20,837 patients in the study, around 62.2% reported ≥1 failed preventive treatment and 15.3% of patients reported ≥4. Among these patients, 41.6% had chronic migraine. 33.3% reported 4–7 MMD and 25.0% reported 8–14 MMDs. In the absence of data, our budget impact analysis included the hypothetical scenario that half of those accessing

preventive treatment would have failed 2 preventive treatments. These assumptions are combined to estimate the eligible Swiss population. It is estimated that around 143,000 Swiss patients would have been eligible for CGRP antagonists in 2021 under this hypothetical scenario.

8.3.3.1.2 CGRP antagonist use among the eligible population

Swiss Tarifpool data[28] has been sourced for past (i.e. 2018–2022) utilisation (i.e. packs sold). Data for 2022 were released after the preparation of the draft HTA. Given these data include utilisation estimates for eptinezumab, which was not introduced until 2022, these were incorporated into the budget impact analysis ad hoc. Averages prices per pack (per calendar year 2018–2022) were sourced from the Spezialitätenliste.

Under Swiss guidelines, CGRP antagonist treatment continuation is dependent on a 50% reduction in MMDs at 6 months after initiation of treatment. The proportion of 50% responders to CGRP antagonist treatment presented in the economic modelling effectiveness section varied from 40% among chronic patients to 35% for episodic patients, or an average of 38% across both patient groups (See ***Sections 8.3.1.11.2, 8.3.1.12.2, 8.3.1.9.2,*** and ***8.3.1.10.2***). Based on this responding proportion, the average number of doses per patient would be 8.3 in the first year of CGRP antagonist treatment (i.e. 6 doses over the first 6 months, then 2.3 doses for the remaining 6 months, based on 38% of patients being responders and continuing treatment). If all responding patients continue treatment in their second year, the average number of monthly doses would be 9, based on a 3-month period in which responding patients are required to discontinue. For the purposes of the hypothetical budget impact analysis, it is assumed that the average patient dosing per year is 9 for a CGRP antagonist that is administered monthly and 3 for quarterly administered treatments.

Sales of CGRP antagonist treatments and assumed numbers of patients are presented in ***Table 187***. Based on these assumptions, around 2.8% of eligible Swiss patients were using CGRP antagonists in 2021 (increasing to 3.7% in 2022). A series of linear uptake assumptions has been included as scenarios (10%, 25% and 50% uptake by 2026). Budget impact analysis has also been conducted to examine the financial implications of different pricing scenarios.

8.3.3.2 Assumptions for budgetary impact analysis

8.3.3.2.1 Number of patients currently treated with CGRP antagonists

The use of CGRP antagonists in Switzerland was provided by FOPH for major product types. The number of packs and estimated patients in 2021 are presented in ***Table 187***. Around 1.1 million Swiss adults were estimated to experience migraine in 2021 and 143,000 estimated to be eligible for treatment based on having failed ≥2 preventive treatments.

Table 187 CGRP antagonist usage in Switzerland 2018–2021

Description	2018	2019	2020	2021	Source
Swiss population					
Total population	8,544,500	8,606,000	8,670,300	8,738,800	Swiss Federal Statistics[189,190]
Adult population	6,921,045	6,970,860	7,022,943	7,078,428	80.1% of population >19 years
Female adults	3,488,207	3,513,313	3,539,563	3,567,528	Females 50.4% of population
Male adults	3,432,838	3,457,547	3,483,380	3,510,900	Males 49.6% of population
Migraine prevalence					
Female adults with migraine	744,837	750,198	755,803	761,774	Global Burden of Disease study 21.4% for women, and 10.9% for men (cited by Stovner [4])
Male adults with migraine	375,415	378,117	380,942	383,952	Global Burden of Disease study 21.4% for women, and 10.9% for men (cited by Stovner [4])
Total migraine patients	1,120,252	1,128,315	1,136,745	1,145,726	
Total eligible population	140,031	141,039	142,093	143,216	Assumes 25% use preventive treatment and 50% fail ≥2 treatments
Erenumab (Aimovig®)					
140 ml units	0	1,333	7,624	12,093	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
70 ml units	227	16,480	14,034	14,270	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF per 140ml	0	611	597	522	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF per 70ml	616	615	597	522	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
Cost per year, CHF	139,803	10,950,651	12,938,182	13,770,749	Sum volume and prices
Number of patients	25	1,979	2,406	2,929	9 doses per year
Fremanezumab (Ajovy®)					
225 mg/1.5 ml 3 pens 1.5 ml units			47	196	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
225 mg/1.5 ml pen 1.5 ml units			343	580	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
225 mg/1.5 ml s.c. 1.5 ml units			40	2,697	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF 225 mg/1.5 ml 3 pens			1,703	1,538	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF 225 mg/1.5 ml pen			589	538	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF 225 mg/1.5 ml s.c.			589	538	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
Cost per year, CHF			306,012	2,065,587	Sum volume and prices
Number of patients			58	430	3 and 9 doses per year
Galcanezumab (Emgality®)					
120 mg/ml pen 1 ml units		383	3,579	6,400	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF per 120 mg/ml pen 1 ml units		616	589	547	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
Cost per year, CHF		235,727	2,108,118	3,498,866	Sum volume and prices
Number of patients		38	358	640	10 doses per year (assume one loading dose)
Eptinezumab (Vyepti®)					

Description	2018	2019	2020	2021	Source
Packages		0	0	0	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
CHF per dose		0	0	0	Tarifpool: © SASIS AG, 2018-2022, © COGE GmbH, Zürich
Cost per year, CHF		0	0	0	Sum volume and prices
Number of patients		0	0	0	3 doses per year
Total patients	**25**	**2,017**	**2,823**	**3,999**	Sum 4 CGRP antagonists
CGRP antagonist uptake	**0.0%**	**1.4%**	**2.0%**	**2.8%**	Sum 4 CGRP antagonists
Total medicines costs, CHF	**139,803**	**11,186,378**	**15,352,312**	**19,335,203**	Sum 4 CGRP antagonists
Health services					
Monitoring and treatment CHF	13,083	1,047,071	1,464,928	2,075,380	Unit cost of CHF173 per neurologist x 3 visits per year x patients
Treatment initiation CHF	4,361	344,662	139,286	203,484	Unit cost of CHF173 at start of treatment x new patients
Health services, CHF	**17,445**	**1,391,733**	**1,604,214**	**2,278,864**	**Sum services costs**
Total costs, CHF	**157,248**	**12,578,111**	**16,956,525**	**21,614,066**	**Medicines and services costs**

Abbreviations
CaMEO study = Chronic Migraine Epidemiology and Outcomes study, **CGRP** = calcitonin gene-related peptide, **CHF** = Swiss Frances, **FOPH** = Federal Office of Public Health, **s.c.** = subcutaneous.

The annual cost to the insurer of CGRP antagonist products was CHF19.3 million in 2021. By product type, erenumab (Aimovig®) accounted for CHF13.8 million, followed by galcanezumab (Emgality®) and fremanezumab (Ajovy®) at CHF3.5 million and CHF2.0 million. The annual number of patients was estimated by dividing the number of packs by the dosing regimens. It was estimated that around 3,999 patients are using CGRP antagonists, equivalent to 2.8% of the eligible population. Health services costs (neurologist costs) associated with monitoring and treatment commencement accounted for 8% of the overall cost of medicines and delivery costs. The total overall medicines and services cost was estimated to be CHF21.6 million in 2021. CGRP antagonist medicines costs increased to CHF25.5 million in 2022 and overall costs were estimated to be CHF28.5 million.

8.3.3.3 Financial Implications

Uptake of CGRP antagonists is relatively low, at 2.8% of the eligible population in 2021 (3.7% in 2022), as these medicines have been only recently introduced. Three scenarios of linear uptake are estimated: 10%, 25% and 50% uptake among eligible patients. The 10% uptake scenario is outlined in ***Table 188***. The insurer cost for CGRP antagonist products is estimated to be CHF71.5 million in 2026 and the overall cost with services is estimated to be CHF79.9 million. Based on the assumptions that 25% of migraine patients would use preventive migraine treatment and 50% would fail ≥2 lines of treatment, a maximum uptake of 10% is equivalent to 1% of all adult migraine patients in Switzerland (i.e. 14,967 divided by 149,037 in 2026).

Table 188 Projected CGRP antagonists costs for 10% uptake scenario (CHF), 2022–2026

Description	2022	2023	2024	2025	2026
Swiss population					
Total population	8,808,710	8,879,180	8,950,214	9,021,815	9,093,990
Adult population	7,135,055	7,192,136	7,249,673	7,307,670	7,366,132
Female adults	3,596,068	3,624,836	3,653,835	3,683,066	3,712,530
Male adults	3,538,987	3,567,299	3,595,838	3,624,604	3,653,601
Migraine prevalence					
Female adults with migraine	767,868	774,011	780,203	786,445	792,737
Male adults with migraine	387,024	390,120	393,241	396,387	399,558
Total migraine patients	1,154,892	1,164,131	1,173,444	1,182,832	1,192,294
Total eligible population	144,362	145,516	146,681	147,854	149,037
Erenumab (Aimovig®)					
140 ml units	17,261	22,337	28,906	37,406	48,407
70 ml units	14,456	18,708	24,209	31,328	40,542
CHF per 140ml	518	518	518	518	518
CHF per 70ml	518	518	518	518	518
Cost per year, CHF	16,416,693	21,244,525	27,492,130	35,577,033	46,039,551
Number of patients	3,524	4,560	5,902	7,637	9,883
Fremanezumab (Ajovy®)					
225 mg/1.5 ml 3 pens 1.5 ml units	318	411	532	689	892
225 mg/1.5 ml pen 1.5 ml units	614	795	1,029	1,331	1,723
225 mg/1.5 ml s.c. 1.5 ml units	6,055	7,836	10,140	13,122	16,981
CHF 225 mg/1.5 ml 3 pens	1,523	1,523	1,523	1,523	1,523
CHF 225 mg/1.5 ml pen	527	527	527	527	527
CHF 225 mg/1.5 ml s.c.	527	527	527	527	527
Cost per year, CHF	4,001,233	5,177,918	6,700,644	8,671,174	11,221,198
Number of patients	847	1,096	1,418	1,836	2,375
Galcanezumab (Emgality®)					
120 mg/ml pen 1 ml units	8,852	11,455	14,823	19,183	24,824
CHF per 120 mg/ml pen 1 ml	532	532	532	532	532
Cost per year, CHF	4,711,307	6,096,811	7,889,765	10,209,992	13,212,554
Number of patients	885	1,145	1,482	1,918	2,482
Eptinezumab (Vyepti®)					
Packages	242	313	405	525	679
CHF per package	1,521	1,521	1,521	1,521	1,521
Cost per year, CHF	368,322	476,638	616,808	798,200	1,032,935
Number of patients	81	104	135	175	226
Total patients	**5,337**	**6,906**	**8,938**	**11,566**	**14,967**
CGRP antagonist uptake	**3.7%**	**4.7%**	**6.1%**	**7.8%**	**10.0%**
Total medicines costs, CHF	**25,497,555**	**32,995,893**	**42,699,347**	**55,256,400**	**71,506,238**
Health services					
Monitoring CHF	2,769,891	3,584,462	4,638,583	6,002,701	7,767,980
Treatment initiation CHF	231,504	271,524	351,374	454,706	588,426
Health services, CHF	**3,001,395**	**3,855,986**	**4,989,957**	**6,457,407**	**8,356,406**
Total costs, CHF	**28,498,950**	**36,851,879**	**47,689,304**	**61,713,807**	**79,862,644**

Abbreviations

CGRP = calcitonin gene-related peptide, **CHF** = Swiss francs, **HTA** = health technology assessment, **s.c.** = subcutaneous

Notes

Blue font highlights data that were not available at the time of initial report preparation, but which were made available to the research team during the latter stages of the HTA process. These data were incorporated into the budget impact model; however other assumptions underpinning the model (notably, 10%, 20% and 50% uptake by 2026 scenarios) were not altered. As such, total patient and CGRP antagonist uptake estimates for 2022 are based on actual, not projected, utilisation (packs sold) figures.

8.3.3.3.1 Scenario analysis

The proportions of patients seeking care, being diagnosed and receiving preventive therapy are uncertain. Different rates of uptake and different pricing scenarios are included in ***Table 189***. Costs in 2026 range from CHF400.9 million in 2026 under current prices and 50% uptake assumptions, to CHF43.9 million under 10% uptake and 50% price reductions across all CGRP antagonists. As noted above, an estimated uptake of 10% in the eligible population (i.e. failure of ≥2 lines of treatment) is equivalent to 1% of all adult migraine patients in Switzerland, 25% is equivalent to 3%, and 50% is equivalent to 6%. There is a high degree of uncertainty about uptake assumptions and projected costs. The episodic migraine patient group consists of high and low frequency episodic patients, costs are projected based on current market share and new products may be introduced in the Swiss market. Correspondingly, CGRP antagonist uptake may not grow linearly, and potential maximum uptake is unclear.

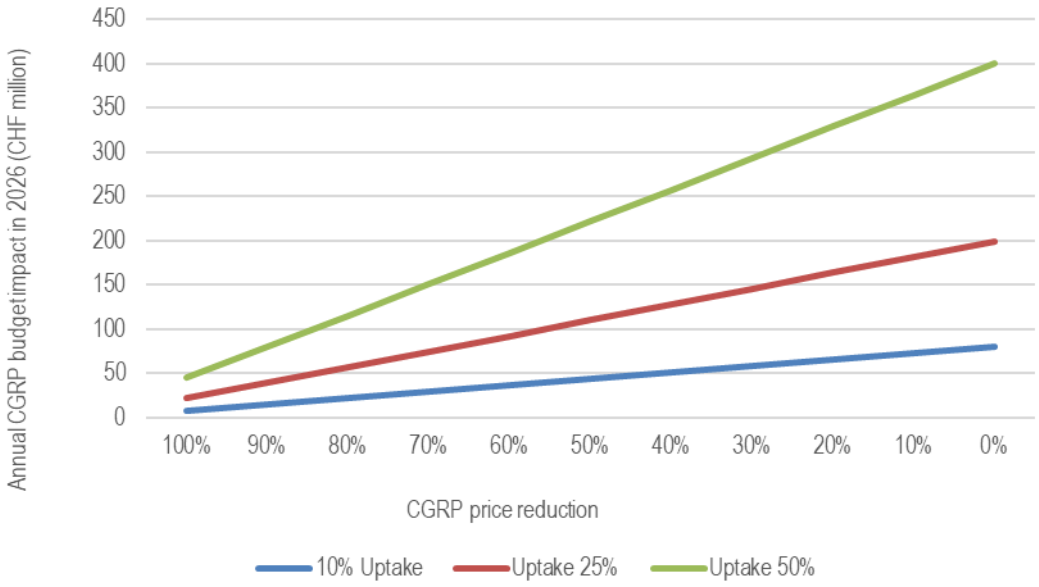
Table 189 Net health insurance provider cost sensitivity analysis (CHF)

	2022	2023	2024	2025	2026
Current price					
10% uptake	28,498,950	36,851,879	47,689,304	61,713,807	79,862,644
25% uptake	28,498,950	46,522,532	75,616,441	122,904,878	199,766,202
50% uptake	28,498,950	55,502,471	107,286,394	207,384,827	400,875,311
75% current price					
10% uptake	28,498,950	28,602,906	36,898,816	47,750,044	61,792,409
25% uptake	28,498,950	36,161,776	58,593,908	95,236,923	154,795,469
50% uptake	28,498,950	43,180,764	83,210,465	160,846,005	310,915,668
50% current price					
10% uptake	28,498,950	20,353,933	26,185,429	33,886,057	43,851,291
25% uptake	28,498,950	25,801,020	41,693,006	67,766,662	110,146,065
50% uptake	28,498,950	30,859,057	59,306,564	114,639,715	221,598,812

Abbreviations
CHF = Swiss francs.

A sensitivity analysis that presents CGRP antagonist price reduction scenarios in the year 2026, across a 0–100% range, is outlined in ***Figure 47***.

Figure 47 Budget impact for CGRP antagonists, 0–100% price reduction scenario



Abbreviations

CHF= Swiss francs, **CGRP** = Calcitonin gene-related peptide antagonists.

8.4 Postface: Update to original economic evaluation

8.4.1 Introduction

The updated search for clinical evidence reported in ***Section 7.3*** identified 3 additional trials that met the PICO criteria. These provide additional clinical evidence on CGRP antagonists. One of the newly identified RCTs (DELIVER trial) was able to fill a gap in the literature by investigating the use of eptinezumab in episodic and chronic migraine patients with prior preventive treatment failure (a patient population that aligns with Swiss reimbursement).[1,2] An updated economic analysis was undertaken for eptinezumab using data from this study.

Furthermore, newly identified clinical evidence for erenumab (DRAGON trial) was used to inform an additional sensitivity analysis.[3] Throughout this HTA, sensitivity analyses were undertaken for erenumab but no other CGRP inhibitors, given the widespread use of erenumab (accounting for 66% of the total Swiss CGRP antagonist market in 2022). Therefore, additional clinical data for galcanezumab were not used in sensitivity analyses.

No updates to the budget impact analysis were made.

As this postface is a standalone body of work that updates the original HTA results, the reported tables, figures and citations are reported separately from those presented in the original document to prevent overlap.

8.4.2 Summary of findings

8.4.2.1 Trial characteristics

The newly identified clinical studies included the DRAGON trial, which examined erenumab (70mg dosing) versus standard care among chronic migraine patients in Asia (China, India, Republic of Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Vietnam);[3] the DELIVER trial, which evaluated eptinezumab (100 mg or 300 mg dosing) for migraine prevention in chronic and episodic patients across the US and Europe;[1,2] and the PERSIST trial, which evaluated galcanezumab (120 mg dosing) for episodic migraine patients across China, India and Russia.[4]

The DELIVER trial included patients with prior preventive treatment failure (a patient population that aligns with Swiss reimbursement), so an additional economic analysis was undertaken for eptinezumab using data from this study.[1,2]

The PERSIST[4] and DRAGON[3] trials excluded patients with prior migraine preventive treatment failure in more than 3 medication categories. Moreover, both trials were conducted solely in Asia and may be less representative of the Swiss population. A sensitivity analysis using the newly identified clinical

evidence was conducted for erenumab, but not for galcanezumab. Throughout this HTA, sensitivity analyses were undertaken for erenumab but no other CGRP inhibitors, given its widespread use in Switzerland.

8.4.2.2 Updated eptinezumab analysis

The DELIVER trial included a 24-week double-blind and extension period.[1,2] Results for 24 weeks were reported. Patients were assigned to eptinezumab 100 mg, eptinezumab 300 mg or placebo that allowed use of acute medication. This arm is reported as standard care. Health outcomes were reported together for episodic and chronic patients, so could not be individually assessed for these groups (***Table PS8 1*** and ***Table PS8 2***).

Table PS8 1 Eptinezumab reduced MMDs from baseline

	Eptinezumab (100 mg)			Eptinezumab (300 mg)			Best supportive care		
	Value	SE/SD	N	Value	SE/SD	N	Value	SE/SD	N
Chronic and episodic migraine									
DELIVER [1 2]									
1–12-week average	-4.80	0.40	299	-5.30	0.40	293	-2.10	0.40	291
13–24-week average	-5.40	0.40	287	-6.10	0.40	286	-2.40	0.40	295

Abbreviations
MMD = monthly migraine days, **N** = number; **SD** = standard deviation, **SE** = standard error.

Table PS8 2 Eptinezumab >50% MMD reduction response at 6 months

	Eptinezumab (100 mg)		Eptinezumab (300 mg)		Best supportive care	
	Value	N	Value	N	Value	N
Chronic and episodic migraine						
DELIVER [1 2]						
1–12-week average	42.0	299	49.0	293	13.0	298
13–24-week average (included in model)	52.0	287	59.0	286	24.0	295

Abbreviations
MMD = monthly migraine days, **N** = number.

The incremental costs and effectiveness of eptinezumab 100 mg versus BSC at 1 year among episodic and chronic migraine patients are presented in ***Table PS8 3***.The ICUR was CHF157,990, which is within the range of ICUR results for episodic and chronic migraine patients using results of the PROMISE-1 and PROMISE-2 studies (CHF825,236 and CHF108,104 for episodic and chronic migraine patients, respectively; ***Section 8.3.2.4***).[5,6]

Table PS8 3 Eptinezumab vs best supportive care (BSC) cost-effectiveness, 1 year, 100 mg

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
Episodic and chronic migraine					
Eptinezumab	8,322		0.81		
Best supportive care	3,285	5,037	0.78	0.03	157,990

Abbreviations
CHF = Swiss francs, **ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

8.4.2.3 Additional erenumab sensitivity analysis

The reductions in MMDs at 3 months and >50% MMD reduction response at 3 months from the DRAGON[3] trial are presented in ***Table PS8 4*** and ***Table PS8 5***.

Table PS8 4 Erenumab reduced MMDs from baseline

	Erenumab (70 mg)			Best supportive care		
	Value	SE/SD	N	Value	SE/SD	N
Chronic migraine						
DRAGON [3]						
3 months	-8.2		270	-6.6		274

Abbreviations
MMD = monthly migraine days, **N** = number, **SD** = standard deviation, **SE** = standard error.

Table PS8 5 Erenumab >50% MMD reduction response at 3 months

	Erenumab (70 mg)		Best supportive care	
	Proportion % >50% MMD reduction	N	Proportion % >50% MMD reduction	N
Chronic migraine				
DRAGON [3]				
3 months	47%	270	36.7%	274

Abbreviations
MMD = monthly migraine days, **N** = number.

The incremental costs and effectiveness of erenumab (70 mg) versus BSC at 1 year among chronic migraine patients using the DRAGON trial data are presented in ***Table PS8 6***. The ICUR was CHF181,469.[3] The ICUR was less cost-effective when compared to that in the base analysis (CHF84,033; ***Section 8.3.2.1***), as the response rate for the standard care arm is higher than reported by Tepper et al 2017.[7] The DRAGON trial authors suggest that the placebo effect may be higher in the Asian trials, which were conducted following large pivotal clinical trials in western countries.[3] The timing was thought to inflate the expectations of patients and physicians.

Table PS8 6 Erenumab (70 mg) vs best supportive care (BSC) cost-effectiveness, 1 year, using DRAGON trial

	Cost (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICUR (CHF per QALY)
Chronic migraine					
Erenumab	11,029		0.68		
Best supportive care	5,813	5,215	0.65	0.03	181,469

Abbreviations
CHF = Swiss francs, **ICUR** = incremental cost-utility ratio, **QALY** = quality-adjusted life years.

8.4.3 Postface references

1. Ashina M, Lanteri-Minet M, Pozo-Rosich P, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet Neurology* 2022;21(7):597-607.
2. Goadsby PJ, Barbanti P, Lambru G, et al. Eptinezumab improved patient-reported outcomes and quality of life in patients with migraine and prior preventive treatment failures. *European journal of neurology* 2022
3. Yu S, Kim BK, Wang H, et al. A phase 3, randomised, placebo-controlled study of erenumab for the prevention of chronic migraine in patients from Asia: the DRAGON study. *Journal of Headache and Pain* 2022;23(1):146.
4. Hu B, Li G, Wu S, et al. Galcanezumab in episodic migraine: the phase 3, randomized, double-blind, placebo-controlled PERSIST study. *Journal of Headache and Pain* 2022;23(1):90.
5. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia* 2020;40(3):241-54.
6. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology* 2020;94(13):e1365-e77.
7. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *The lancet Neurology* 2017;16(6):425-34.

9 Additional issues

9.1 Clinical practice position statements and guidelines

In total, 18 clinical practice position statements, guidelines, consensus statements and technology appraisal guidance documents were identified through the systematic search and targeted searches (***Appendix N***). Overall, 10 of these were clinical practice guidelines,[15,18,128,191-197] 2 were clinical practice position statements,[198,199] 3 were consensus statements[35,200,201] and 3 were technology appraisal guidance documents.[143-145] The issuing organisations were from Europe, UK, France, Germany, Poland, Portugal, Switzerland, Argentina, Mexico, Denmark and USA (multiple publications were identified for some countries).

There was some disagreement in the guidelines regarding the use of CGRP antagonists for the treatment of chronic and episodic migraine. For example, recommendations for use varied amongst guidelines to include those who experience ≥2 to ≥8 MMDs. In addition, the Mexican Association of Headache and Migraine[196] listed CGRP antagonists as first-line prophylactic treatments, whereas most other countries list them as second- or third-line treatments for chronic and episodic migraine after the failure of ≥2–5 previous prophylactic treatments. The length of treatment with a CGRP antagonist prior to assessing its effectiveness also varied from 6 weeks to 6 months across these guidelines. Where reported, the doses of each drug were fixed, citing the same dosages/intervals as outlined in the PICO criteria (***Table 3***). Both the French Headache Society[192] and the British Association for the Study of Headache,[199] recommend that clinicians consider trialling a second or subsequent CGRP antagonist[199] if a patient does not respond to the first choice.

Further details on each clinical practice position statement and guideline are provided in ***Appendix N***.

9.2 Ongoing clinical trials

The search of clinical trial registries uncovered a multitude of relevant ongoing clinical trials. Overall, 27 ongoing clinical trial records were identified, 22 via ClinicalTrials.gov and a further 5 via the EU Clinical Trials Registry (summarised in ***Appendix M***). Of the 27 ongoing clinical trial records identified, 14 are being conducted in a mixed population of both episodic and chronic migraine patients, or migraine type was not reported; 7 are being conducted in episodic migraine patients and 6 are being conducted in chronic migraine patients.

Of the ongoing trials, 13 are evaluating erenumab, 5 are evaluating eptinezumab, 4 are evaluating fremanezumab, 3 are evaluating galcanezumab and 2 are evaluating more than one CGRP antagonist. The most common comparator across these ongoing trials is placebo (n = 12); 12 trials have no

comparator. Two ongoing trials seek to compare erenumab to oral prophylactics (e.g. beta blockers, calcium antagonists, anticonvulsants, antidepressants) and one seeks to compare galcanezumab to rimegepant. All ongoing clinical trials are expected to be complete by July 2025.

Based on the total number, estimated sample sizes and designs of the identified ongoing clinical trials, they are likely to contribute significant new information that would warrant reconsideration of the evidence base, particularly trials with active drug comparators.

10 Discussion

The objective of this HTA is to evaluate the clinical effectiveness and safety, costs, cost-effectiveness and budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who experience episodic and chronic migraine.

10.1 Comparison to previous HTA reports

10.1.1 Comparison to existing clinical evaluations

10.1.1.1 Comparison to Canadian Agency for Drugs and Technologies in Health (CADTH) HTA reports

CADTH has published Common Drug Review Clinical Review Reports on erenumab[146] and fremanezumab,[147] with a further Reimbursement Review on galcanezumab.[148] Each publication evaluates the findings from the large-scale clinical trials included in this HTA report.

The results from this HTA report are generally in accordance with the findings of the published CADTH reports. For example, CADTH reported that erenumab, galcanezumab and fremanezumab are clinically effective at reducing MMDs in both episodic and chronic migraine patients, irrespective of dose.[146-148] The current HTA produced similar statistically significant findings (where meta-analyses were possible), with individual trial results also typically in favour of CGRP antagonists compared to placebo when meta-analysis was not possible.[146-148]

A 50% reduction in the number of MMDs was found to be statistically significant when assessing both fremanezumab and erenumab in the CADTH reports (this outcome was not assessed within the CADTH report on galcanezumab).[146,147] Within the current HTA, a 50% reduction in MMDs was also found to be significantly greater among patients receiving erenumab, galcanezumab, fremanezumab and eptinezumab compared to placebo at all timepoints.

In the current HTA, where data on MSQ was reported across the populations and interventions of interest, significant improvements were more commonly reported among patients who received an active intervention than among those who received placebo at the majority of timepoints. This result reflects that of the CADTH reports, which also found improvements across the total MSQ score or within individual MSQ domains (RFR, RFP and EF).[146-148]

No serious safety concerns regarding AEs, SAEs or AEs leading to discontinuation were uncovered in the current HTA or the CADTH reports in relation to erenumab, galcanezumab or fremanezumab.[146-148]

10.1.1.2 Comparison to National Institute for Health and Care Excellence (NICE) technology guidance documents

Technology appraisal guidance documents have been published by NICE on erenumab, galcanezumab and fremanezumab.[143-145] The NICE recommendations are similar to those made in the current HTA report, recommending the use of erenumab, fremanezumab and galcanezumab. The population of the current HTA report differs from the NICE report in that NICE included patients who had failed ≥3 preventative treatments: the NICE recommendations encompass this population only. The current HTA report considers a broader population of chronic and episodic migraine patients.[143-145]

In this HTA, no evidence was identified to answer the research questions relating to whether switching from one CGRP antagonist to another is effective/efficacious in patients who previously experienced inadequate treatment using a different CGRP antagonist. Similarly, as the NICE reports on erenumab[143] and galcanezumab[145] found, this question could not be assessed due to the lack of clinical evidence. This question was not addressed in the NICE report on fremanezumab.[144]

In contrast to the NICE reports,[143-145] onabotulinumtoxinA was not considered as a comparator in this HTA report because this intervention is not reimbursed in Switzerland. In further contrast to the reports published by NICE,[143-145] no indirect treatment comparisons were conducted in the current HTA as this was outside the scope of this review

To the authors' knowledge, no published HTAs have evaluated the effectiveness and safety of eptinezumab against any relevant comparator. However, a full HTA is currently being conducted by National Centre for Pharmacoeconomics, Ireland,[202] and by CADTH,[203] which may address this question.

10.1.2 Comparison to existing economic evaluations

10.1.2.1 Erenumab

The results of the current report are similar to those of the reanalyses of the chronic migraine model submitted for CADTH review,[146] which had a 5-year time horizon. Erenumab 140 mg was calculated to have an ICUR of CAD66,359 (CHF45,245) per QALY gained, although erenumab 70 mg was extendedly dominated in the sequential analysis. CGRP antagonists are reimbursed for a maximum of one year in Switzerland, after which a patient is assessed and can then recommence treatment following clinical guidance. Correspondingly, base modelling assumed a 1-year time frame in our report. Extending the modelling time frame to 5-years had a positive impact on cost-effectiveness. Over 5-years, erenumab

140 mg was calculated to have an ICUR of CHF39,970 per QALY gained among chronic migraine patients.

In the reanalysis, the CADTH review group developed scenarios that included the removal of hospitalisation and nurse visits. The all-cause long-term negative discontinuation rate was adjusted from 2.38% to 3% for consistency with the latest follow-up from Study 178,[175] and MMD distributions were not stratified by response when calculating health-state utilities.

The Mahon et al 2021[137] model-calculated erenumab treatment resulted in ICERs of EUR3,310 (CHF3,152) and EUR28,769 (CHF27,401) per QALY gained in the total migraine and episodic migraine populations, respectively, which was dominant among chronic migraine patients. This model had a 10-year horizon and included a positive discontinuation state. Positive discontinuation assumed 20% of patients did not return to treatment, but sustained treatment benefits. The model submitted to NICE[204] was revised by the review group (outlined in the committee papers) resulting in the erenumab 140 mg ICUR being GBP15,641 (CHF16,665) per QALY gained versus BSC among chronic migraine patients, and erenumab 70 mg was dominated. For the episodic migraine group, erenumab 70 mg had an ICUR of GBP10,207 (CHF10,875) compared to BSC and erenumab 140 mg was dominated. The UK model did not focus on patients with ≥3 prior failed treatments and included a life-time projection.

10.1.2.2 Fremanezumab

A model was submitted to CADTH[147] that assumed episodic and chronic migraine patients have 17.3 MMDs and 9.3 MMDs, respectively. The model had a projection of 10 years and assumed patients had failed ≥2 prior preventive therapies.

The episodic migraine ICER was CAD138,122 (CHF99,691) per QALY (incremental cost CAD12,198; incremental QALYs 0.09) for fremanezumab compared with placebo. For chronic migraine patients with ≥2 prior preventive therapies the ICER was CAD102,184 (CHF73,752) per QALY (incremental cost CAD11,649; incremental QALYs 0.114) for fremanezumab compared with placebo. The incremental costs and effectiveness of fremanezumab versus BSC at 1 year are presented in ***Table 183*** for chronic migraine patients being treated with 225 mg and 625 mg regimens, respectively, which are similar to the sponsor-submitted model to CADTH for chronic patients.

CADTH reviewers undertook a series of reanalyses, with costs related to hospitalisation removed and the time horizon reduced to 5 years. The episodic migraine patient ICER was CAD164,243 (CHF118,544) per QALY (incremental cost CAD13,571, QALYs 0.08) compared with BSC, while the chronic migraine patient ICER was CAD128,950 (CHF93,071) per QALY (incremental cost CAD13,436, incremental QALYs 0.10) compared with BSC. The reviewers noted that price reductions of 61–90% would be required for fremanezumab to be considered optimal compared with BSC at a WTP threshold

of CAD50,000 (CHF32,876) per QALY. The CADTH review noted that fremanezumab dominated erenumab and galcanezumab in the Sponsor's economic analysis. The modelling did not use head-to-head evidence and heterogeneity among included patients introduced bias that possibly favoured fremanezumab. Based on these limitations, comparisons among CGRP antagonists were not considered to be robust.

10.1.2.3 Galcanezumab

A galcanezumab model was also submitted to CADTH.[148] The sponsor sought a price of CAD623 (CHF411) per 120 mg single dose. The model has a 20-year time horizon and a cycle length of 30 days and included patients with a history of ≥2 prior preventive treatment failures due to a lack of efficacy or tolerability. Episodic migraine patients using galcanezumab who had failed ≥2 prior preventive treatments due to a lack of efficacy or tolerability[148] were calculated to gain an additional 0.706 QALYs at an additional cost of CAD27,524 (CHF18,154) over BSC, resulting in an ICER of CAD39,010 (CHF28,185) per QALY gained. Chronic migraine patients using galcanezumab who had failed ≥2 prior preventive treatments due to a lack of efficacy or tolerability gained 1.573 additional QALYs and an additional cost of CAD26,101 (CHF17,162) over BSC, resulting in an ICER of CAD16,594 (CHF11,989) per QALY gained.[148]

CADTH undertook a re-evaluation for episodic migraine patients who had failed ≥2 prior preventive migraine therapies, which resulted in an additional cost of CAD14,563 (CHF9,605) and 0.053 additional QALYs over BSC over 5 years. This resulted in an ICER of CAD273,560 (CHF197,445) per QALY gained. The re-evaluation for chronic migraine resulted in an additional cost of CAD18,247 (CHF12,034) for galcanezumab and 0.167 additional QALYs compared to BSC, corresponding to an ICER of CAD109,325 (CHF78,906) per QALY gained. In the current HTA, the incremental costs and effectiveness of galcanezumab versus BSC at 1 year among episodic and chronic migraine patients are presented in ***Table 184*** and are more in line with the CADTH revised estimates than the original submitted model.

10.1.2.4 Eptinezumab

A NICE evidence review of eptinezumab for preventing migraine is currently under development, with an expected publication date of 5 May 2023. A reimbursement review is being conducted at CADTH, with the draft recommendation being issued to the sponsor on 7 November 2022.

10.2 Limitations in the clinical evaluation

10.2.1 Limitations of the included trials

The available data were reported over short timeframes across most of the included studies. Considering the length of time that most patients had experienced migraine (majority >20 years) it is surprising that longer-term data regarding the ability of CGRP antagonists to prevent migraine in these patients has not been reported. Only one trial reported outcomes to 12 months, with the majority reporting outcomes at 1–6 months. Future trials would benefit from following patients for several years to confirm that the preventative effects seen in this HTA remain stable over time.

Some outcomes in this review were reported by relatively few studies, or by none at all. This is not unexpected; however, data for outcomes related to the patient (pain intensity; AEs upon discontinuation, also known as a rebound effect; and some QoL measures) were reported infrequently by most trials or not at all. Because the measurement tools for migraine rely completely on patient reporting, it would be helpful if future trials focus on QoL measures, so a more comprehensive picture of patient satisfaction with and adherence to treatment can be further understood.

10.2.2 Limitations of the review methodology

Strengths of the methodology of this review lie in the systematic approach and the comprehensive search strategies employed. Following a prespecified protocol enhances the quality of a review and helps to control against bias. A protocol was in place for this review prior to its commencement. Comprehensive searches and study selection were conducted independently by 2 reviewers, providing confidence that the included studies represent the available evidence.

Systematic reviews can have weaknesses, the majority of which stem from the eligibility criteria and limits imposed on the selection of studies. For this HTA, study design limitations were applied whereby RCT data was sought first to answer the additional question(s) (***Section 6.1***), followed by nonrandomised designs. While both date and study design limits are common practice in systematic reviews, excluding older and noncomparative studies may mean that relevant data are missed, particularly in terms of safety outcomes. A cut-off of fewer than 50 patients was also applied, meaning such studies were ineligible for inclusion. Often, very small studies do not make substantial differences to the overall evidence; however, it is acknowledged that excluding these studies from the current review may mean that relevant data were not included.

The language of publication was limited to the inclusion of English, French, German and Italian. Given the number of multicentre, international studies in countries in Asia, the Middle East and Latin America

and the 3 trials conducted across Japan and Korea, this limitation may mean that studies conducted in countries where English, French, German and Italian are not the principal language were missed.

Although studies that met the IHS ICHD[6] criteria of episodic or chronic migraine were eligible for inclusion, studies conducted in patients who had failed ≥2 prior treatments were of interest (PICO population: subgroup 1 and 2), particularly as they relate to the economic model. Unfortunately, there was an insufficient number of studies conducted in these two subgroups to enable meta-analysis; with the majority of reported outcome data coming from a single trial.

Evidence defining the clinical importance of each outcome was limited, despite actively seeking data regarding MCIDs (***Appendix E***). There was insufficient data available to confirm whether the MCID reported for the number of headache days (difference of one day) was accurate, as it was reported in only one study, which was conducted in 2010.[205] More recent evidence was available for differences in MSQ[206] and MIDAS[207] (QoL outcomes). Further research should focus on clarifying what constitutes a clinically important difference in the number of headache days, so results of this and other reviews of CGRP antagonists can be interpreted within this context. The results of this review were interpreted in terms of statistically significant differences; no attempt was made to address whether these differences were clinically meaningful.

10.3 Limitations in the economic evaluation

The economic model was limited by the relatively short maximum follow-up of high-quality blinded RCTs. Most of the blinded RCTs had follow-up of 3–6 months, with a limited number extending beyond this period. Given that the model includes projections of 1–10 years, there is uncertainty associated with the long-term effectiveness of CGRP antagonists. Justifications for sustained response and MMD reduction assumptions used in the current analysis are supported by data from open label trial extensions. These studies are subject to bias and, in the case of erenumab, the extension involved a switch in dose from 70 mg erenumab to 140 mg. Additional issues such as long-term adherence to prophylactic treatment also create uncertainty when projecting effectiveness.

Sensitivity analyses were undertaken where CGRP antagonist non-responders are assumed to experience BSC MMDs and associated utility and BSC responders are assumed to experience baseline MMDs and associated utility. These assumptions had a large impact on the calculated ICURs. The model does not explicitly consider the impacts of factors such as menopause, chronification which affect migraine frequency. These issues were highlighted in CADTH[146] reviews of sponsor-submitted models. Data were unavailable to model these considerations. The impact of their omission is unclear.

The economic model did not include all relevant comparators stated in the HTA protocol. Limited clinical evidence prevented the comparison of the 4 included CGRP antagonists with other preventive

treatments. Only one identified RCT included a comparison to topiramate rather than BSC. Results of this trial were presented in a sensitivity analysis; however, it is difficult to generalise results given data limitations. Base economic modelling results included the comparison to BSC, which involved use of data from the placebo arms of key trials presented in the clinical evidence. The placebo arm allowed use of acute medication. The NICE[145] galcanezumab review group noted in committee papers that 'patients in the placebo arms of these trials used acute treatments that would normally be prescribed in clinical practice for the management of migraine symptoms.' (ibid, p. 11)

The Spezialitätenliste requires patients being treated with CGRP antagonists to have reduced MMDs at 3 months and a 50% reduction in MMDs at 6 months for treatment eligibility.[2] Some blinded RCTs reported 50% response at 12 weeks, so there is uncertainty about response at longer periods of follow-up. Open label trial extensions suggest these responses were sustained; however, as already noted, there are biases in these extension phases.

Moreover, trials did not report the proportions of patients experiencing MMD reductions at 3 months and 50% MMD reduction at 6 months. Correspondingly, there is uncertainty about the proportions of patients who would continue treatment based on Swiss stopping rules. Model results are sensitive to the proportion of the CGRP antagonist arm deemed to be responsive under Swiss conditions for reimbursement. CGRP antagonists are reimbursed for a maximum of one year in Switzerland and base modelling assumed a 1-year time frame in our report. Extending the modelling time frame to 5-years had a positive impact on cost-effectiveness. Longer time frames have been used in other modelling studies reviewed in the report.

Health-state utility values were included in the model in relation to MMDs. A mapping algorithm based on EQ-5D and MSQ data presented in sponsor-submitted analyses from erenumab trials such as Tepper et al 2017[79] and STRIVE[48] was used. The CADTH[146] review of the sponsor model noted that the trials used to develop the mapping analysis were not homogenous and used differing definitions of episodic and chronic migraine patients. Notably, STRIVE[48] excluded patients who had failed 2 previous treatments, while LIBERTY[49] enrolled these patients. In addition, the current model does not account for migraine severity. Utility is calculated using MMDs. Sensitivity analysis indicates that utility has a large impact on calculated ICURs. The direction and magnitude of the omission of severity on cost-effectiveness results is unclear.

The budget impact analysis comprised hypothetical scenarios to calculate the net cost impacts of differing uptake rates and pricing scenarios. The pricing and usage of different medicines has been changing in Switzerland over the last 4 years, as CGRP antagonists have been only recently listed for reimbursement. Future projections of costs are subject to uncertainty as differing regimes and brands are likely to be used over the next 5 years. Additionally, the proportions of episodic and chronic migraine

patients using preventive migraine medicines in Switzerland is uncertain. The episodic migraine patient group consists of high and low frequency episodic patients, costs are projected based on current market share and new products may be introduced in the Swiss market. Correspondingly, CGRP antagonist uptake may not grow linearly, and potential maximum uptake is unclear.

10.4 Evidence gaps

The most significant gap in the evidence relates to the limited available RCT evidence comparing CGRP antagonists to beta blockers (propranolol, metoprolol), calcium antagonists (flunarizine), anticonvulsants (topiramate) and antidepressants (amitriptyline) for migraine prophylaxis. This HTA was unable to draw evidence-based conclusions on the head-to-head effectiveness and safety of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate] and antidepressants [amitriptyline]), as only scarce evidence was available. Furthermore, no available evidence (as assessed against the study inclusion and exclusion criteria) was identified to answer the additional HTA question(s) (***Section 6.1***), which sought to identify whether switching from one CGRP antagonist to another is effective in those who previously experienced inadequate treatment effects using a CGRP antagonist.

10.5 Postface: Update to original discussion

The available evidence on CGRP antagonists is continuously evolving, so updated database searches were conducted to capture literature published during the production of this HTA report. In brief, 3 additional RCTs were identified. One RCT each investigated erenumab, galcanezumab and eptinezumab. Each of these RCTs also investigated the use of these interventions in a different population of interest: erenumab use was explored in chronic migraine patients, galcanezumab use was explored in episodic migraine patients and eptinezumab use was explored in episodic and chronic migraine patients with 2–4 prior treatment failures. No additional RCT evidence was uncovered for fremanezumab.

The objective of this update was to summarise these additional RCTs to ensure that the results of these trials did not change the overall findings and conclusions of this HTA report. Due to the narrative nature of this additional body of work, results were not combined via meta-analysis. Instead, a strong emphasis was placed on the direction of effect of the RCT results compared with other trials with similar PICO characteristics and reported timepoints.

In general, where similar PICO characteristics were identified between the newly identified RCTs and those included via the original database search, the directions of effect of the outcomes assessed were

typically in agreeance. Most efficacy/effectiveness outcomes showed statistical significance in favour of the intervention (compared to placebo). For example, significantly fewer MMDs, significantly more patients with a response rate of >50% and >75%, and significant improvements in reported QoL measures (e.g. HIT-6, MSQ, MIDAS, EQ-5D) for erenumab, eptinezumab and galcanezumab compared to placebo. No evident directional effect or statistical significance was commonly reported for the safety outcomes of interest.

Of particular importance to the Swiss context, one of the newly identified RCTs (DELIVER 2022) was able to fill a gap in the literature by investigating the use of eptinezumab in episodic and chronic migraine patients with 2–4 prior treatment failures. As previously discussed, in Swiss clinical practice migraine preventive treatment failures are considered to meet the criteria for reimbursement. This study is therefore of importance to the economic evaluations conducted in this HTA report and an updated economic analysis was undertaken for eptinezumab (100 mg) using data from this study. The ICUR for a combined population of episodic and chronic migraine patients is in line with the initial ICURs, falling between the initial findings for separate episodic or chronic migraine patient populations. Additional clinical evidence for erenumab for an Asian population contributed to a less cost-effective ICUR when compared to the base case analysis.

As previously advised in the section on the applicability of the evidence to Switzerland, 2 of the RCTs from the updated literature search were conducted solely in Asia. These trials may be less representative of the Swiss population, as the prevalence of migraine is reportedly lower among Asian populations.

11 Conclusions

Almost all of the included studies reported significantly fewer MMDs, significantly fewer MHDs, significantly fewer days with acute medication use, significantly more patients with a response rate of >50% and >75%, and significant improvements in QoL measures for all CGRP antagonists compared to placebo. Very few studies reported migraine pain intensity. More evidence was available for patients with episodic migraine than for chronic migraine and a greater number of trials were conducted for erenumab and galcanezumab compared to fremanezumab or eptinezumab. Subgroup analyses of patients with >2 prior treatment failures were reported for studies of erenumab, with one each conducted for fremanezumab and galcanezumab. While almost all trials of CGRP antagonists reported significantly fewer MMDs, the evidence was strongest for erenumab, followed by galcanezumab.

AEs were not well reported in the included studies for any drug type. Where reported, most trials showed no differences in the numbers of AEs, TRAEs, SAEs or AEs leading to discontinuation, compared to placebo. No studies reported AEs upon discontinuation (rebound effect) or mortality. Again, more evidence was available for patients with episodic migraine than for chronic migraine. A greater number of trials were conducted for erenumab, fremanezumab and galcanezumab compared to eptinezumab. Subgroup analyses of patients with >2 prior treatment failures were reported for studies of erenumab and fremanezumab. While almost all trials of CGRP antagonists reported no differences in any type of AE, the evidence was strongest for erenumab, followed by fremanezumab and galcanezumab.

A Markov model was developed to quantify the cost-utility of CGRP antagonists using incremental QALYs with univariate, scenario and probabilistic sensitivity analyses evaluating uncertainties in the model. The economic model was limited by the relatively short maximum follow-up of high-quality blinded RCTs and a lack of comparator evidence. Despite this uncertainty, the results correspond with a number of models reviewed by HTA agencies as part of recent reimbursement requests.

11.1 Postface: Update to original conclusion

The updated database searches and RCT findings generated no major changes to the conclusions as previously stated in this HTA report. However, it is worth highlighting that the new evidence identified investigates the use of eptinezumab in episodic and chronic migraine patients with 2–4 prior treatment failures.

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