PROPOSAL FOR THE ADDITION OF FREMANEZUMAB FOR THE PREVENTIVE TREATMENT OF HIGH FREQUENCY AND CHRONIC MIGRAINE IN ADULTS TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR ADULTS

Proposed listing on the EML

7. ANTIMIGRAINE TREATMENTS

7.3 Preventive treatments

CGRP-TARGETING MONOCLONAL ANTIBODIES for migraine prevention

Applicant:

The applicants are, jointly, two international scientific societies (the International Headache Society [https://ihs-headache.org/en/] and the European Headache Federation [https://www.ehf-headache.com/]), and two charities (*Lifting The Burden* [https://www.l-t-b.org/], which is in Official Relations with WHO), and Disease Relief by Excellent and Advanced Means (DREAM [https://www.dream-health.org/a-new-public-health-model/?lang=en]).

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Section 1: Summary statement of the proposal

The global migraine prevalence is 14–15%, with minor variations across regions *(1)*. Reliable estimates show that migraine accounts for 4.9% of global population ill health quantified in years lived with disability (YLDs) *(2, 3)*. Migraine manifests with recurrent and unpredictable attacks of head pain, often severe, accompanied by other disabling symptoms such as nausea, vomiting, intolerance to sensory stimuli (photophobia and phonophobia), impairing function *(4)*. Inadequately treated, it may increase in frequency and evolve into chronic migraine, with headache on more days than not, with commensurate increases in ill-health and disability burdens, and direct and indirect costs *(5, 6)*.

This submission advocates the inclusion of additional options to the Model List for the preventive treatment of migraine in adult patients.

Until recently the prophylaxis of migraine relied on non-specific drugs developed for other indications and adopted later for migraine. Adherence to these therapies is often poor due to their limited efficacy and tolerability *(7)*. In the last years, based on a broad foundation of preclinical and clinical evidence showing that calcitonin gene-related peptide (CGRP) plays a key role in the pathogenesis of migraine, new target-driven therapies have proven in complete clinical developments that controlling CGRP is efficacious, well tolerated and safe, all of which facilitate patient adherence *(8)*. Comparisons with the traditional therapies like topiramate, propranolol, amitriptyline and flunarizine have shown that these new era of therapies are better for people who suffer from migraine *(9, 10)*, with improved efficacy, optimal tolerability, long-term patient preference and increased quality of life, measured using multiple patient reported outcomes (PROs) *(11)*.

These CGRP-targeting therapies have had a transformational impact on the management of migraine, to the point that the European Headache Federation *(12)* and the American Headache Society *(13)* have recently updated their published Guidelines/ Consensus statements to propose their use their use as first-line treatment for migraine prevention.

There are several anti-CGRP treatments, among them fremanezumab, an anti-CGRP monoclonal antibody that targets the ligand, has demonstrated its efficacy, tolerability and safety in phase IIb and III trials for episodic and chronic migraine *(14-16)* and has been later approved by the FDA (2018) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761089s002lbl.pdf) and EMA (2019) (https://www.ema.europa.eu/en/medicines/human/EPAR/ajovy) for the prophylaxis of migraine in subjects with 4 or more migraine days per month.

Section 2: Consultation with WHO technical departments

During the preparation of this application there have been multiple meetings with the WHO technical department, and, in particular, with Dr Tarun Dua, Brain Health Unit, WHO Department of Mental Health & Substance Use, Dr Nicoline Schiess, World Health Organization (WHO) - Brain Health Unit and Rodrigo Cataldi World Health Organization (WHO) - Brain Health Unit.

They have provided precious guidance and suggestions and have critically assessed the drafts of the application.

Section 3: Other organization(s) consulted and/or supporting the submission

In addition to the four joint applicants (IHS, EHF, LTB and DREAM), we have also consulted the European Migraine and Headache Association (Mrs Elena Ruiz de la Torre), https://www.emhalliance.org/, who is in full support of this applicaton (see page 41).

Section 4: Key information summary for the proposed medicine(s)

□ Monoclonal antibodies targeting CGRP

INN	**fremanezumab** □
ATC code	N02CD03
Indication	Migraine - prophylaxis
ICD-11 code	8A80 1-3 Migraine, migraine with aura, chronic migraine

Dosage form	Strength	EML	EMLc
Monoclonal antibody targeting CGRP ligand	225mg	No	No
Injectable, subcutaneous Pre-filled syringe	1.5 mL (150 mg/mL)	No	No

Two dosing options are available:

- 225 mg once monthly (monthly dosing)
- 675 mg every three months (quarterly dosing)

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

The submission relates to the inclusion of fremanezumab as a preventive treatment for migraine as a new EML treatment for the prevention of migraine to be added under section 7 Antimigraine medicines – 7.2 for prophylaxis.

Justification of choices of the representative medicines

In the last years, a new group of therapies targeting calcitonin gene-related peptide (CGRP) has been developed and approved by FDA and EMA for the treatment of adults with migraine who have more than 4 days of migraine per month.

Four monoclonal antibodies against the CGRP pathway (anti-CGRP mAbs) are currently available on several markets *(8)*. One (erenumab) is directed against the CGRP receptor (R) (anti-CGRP/R mAb) and three (eptinezumab, galcanezumab and fremanezumab) against the ligand (L) (anti-CGRP/L mAbs). RCTs and real-world studies demonstrated definite efficacy and good tolerability of all these new drugs in chronic and episodic migraine, regardless of the presence of acute medication overuse and various previous treatment failures *(8, 17)*. Furthermore, anti-CGRP mAbs proved safe, with a rate of adverse events only slightly superior to placebo *(18)*. The introduction of the anti-CGRP mAbs, which are disease-specific and mechanism-based treatments for the prevention of migraine, substantially improved patients' management even if raising costs.

The high strength of evidence regarding the efficacy, safety and tolerability of the class of mAbs targeting CGRP demonstrated in large and methodologically thorough investigational programs (see Section 8 for details) strongly support the addition of at least one representative of this class of drugs in the EML for the prophylaxis of episodic and chronic migraine.

When compared and meta-analysed the four mAbs targeting CGRP have similar efficacy *(17)* (Figures 1 and 2), but we selected fremanezumab for inclusion in the EML due to the following reasons:

a) unlike eptinezumab, which is infused i.v., fremanezumab is administered subcutaneously, being therefore suitable for the self-administration at home;

b) unlike galcanezumab and erenumab, which are marketed with an auto-injector device, it is administered with a pre-filled syringe, which is more cost-effective;

c) unlike the other 3 mAbs, which are administered according to a single dosing scheme, fremanezumab has two dosing can be administered with two dosing schemes, monthly and quarterly, with this latter being more manageable in difficult environments to favour adherence and minimize the costs of refrigerated conservation;

d) there is evidence that fremanezumab treatment causes less side effects than the other anti-CGRP therapies, specifically as regards the mAb directed against the receptor, erenumab, which has been associated to a higher occurrence of constipation and some concerns about the possible induction of hypertension.

Figure 1. Comparison of different medications in available doses with placebo for primary outcomes.

Results from three separate network meta-analysis based on the route of administration. Subgroup analysis based on migraine type (episodic vs. chronic) is reported on the right side of the figures. Only studies with 100% episodic or 100% chronic migraine participants were included in the subgroup analysis. n = number, MD = mean difference, OR = odds ratio, 95% CI = 95% confidence interval (figure taken from Haghdoost et al., 2023 (17)).

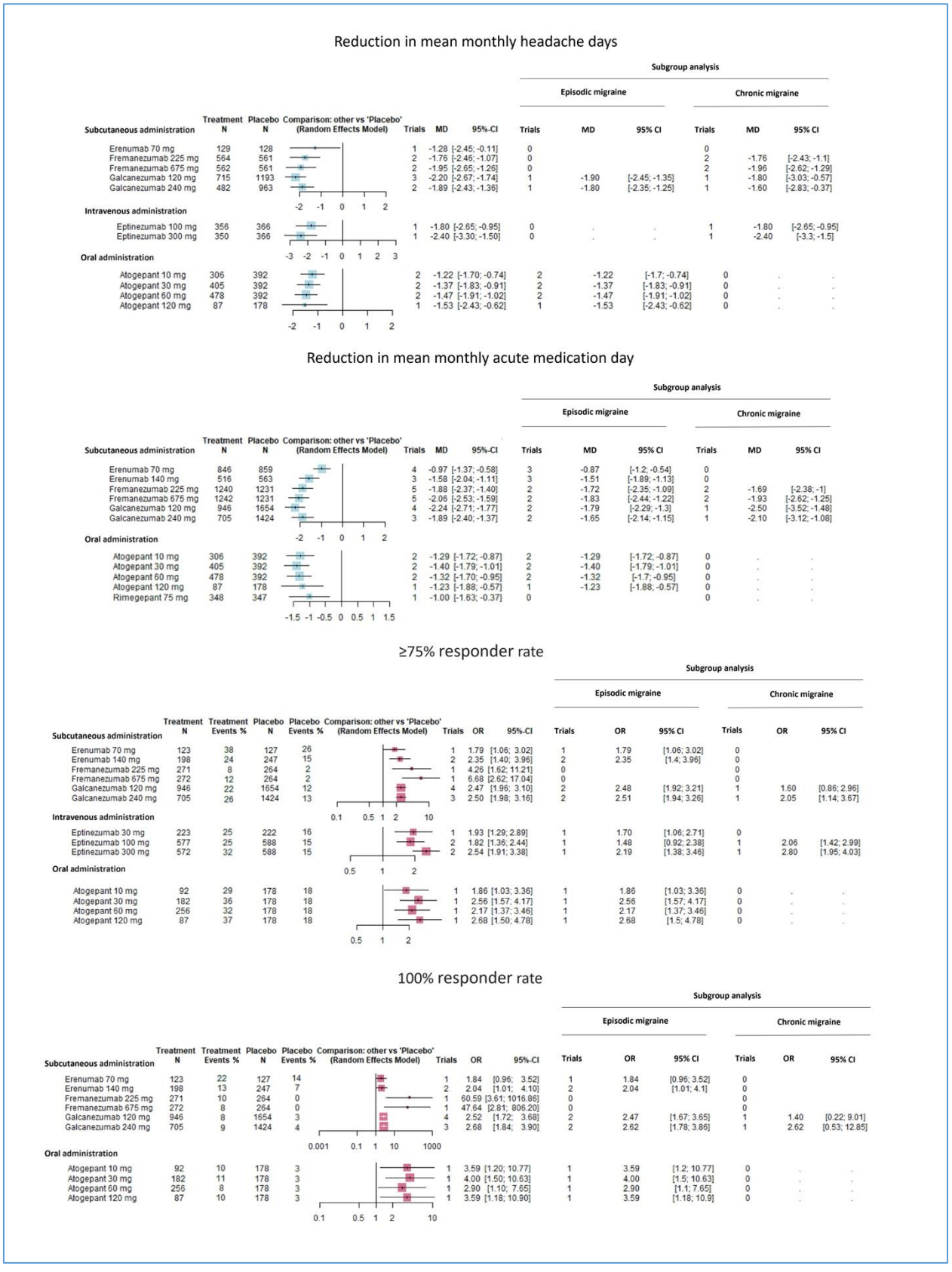


Figure 2. Comparison of different medications in available doses with placebo for secondary outcomes.

Results from three separate network meta-analysis based on the route of administration. Subgroup analysis based on migraine type (episodic vs. chronic) is reported on the right side of the figures. Only studies with 100% episodic or 100% chronic migraine participants

were included in the subgroup analysis. n = number, MD = mean difference, OR = odds ratio, 95% CI = 95% confidence interval. Studies on eptinezumab did not report monthly acute medication day and 100% responder rate (figure taken fromHaghdoost et al., 2023(17))

Section 6: Information supporting the public health relevance

Epidemiology and burden of migraine

Migraine is a prevalent neurovascular disorder characterized by moderate to severe, frequently unilateral headache attacks, accompanied by nausea, vomiting, and photophobia/phonophobia *(1)* . The global prevalence of migraine is approximately 14-15%, with a higher incidence in women *(2)*. The prevalence of migraine varies across different regions: approximately 3% in the WHO African Region, 15% in Europe, 11% in America, 9%-13% in Southeast Asia, and 10% in the Western Pacific *(3)*. Migraine contributes significantly to the global disease burden, affecting more than one billion people worldwide each year *(4)*. The WHO lists migraine among the top 20 causes of years lived with disability (YLDs). Moreover, migraine accounted for 45.1 million disability-adjusted life years (DALYs) globally in 2016, highlighting its impact on public health *(3)*, with decreased productivity, increased healthcare costs, and overall decreased quality of life.

Migraine is characterized by recurrent, unprovoked and unpredictable episodes (migraine attacks) of cranial pain associated to nausea, vomiting and sensitivity to external stimuli (light, noise, odours). In one fourth of subjects episodes may be preceded by transient focal neurological symptoms like visual disturbances, paresthesias, motor deficit and more *(4)*. When migraine manifest in less than 15 days per month, the diagnosis is that of episodic migraine, when the number of headache days is at least equal to15 for at least 3 months the diagnosis of chronic migraine applies *(19)*. Approximately 3% of the general population suffer from chronic migraine *(5)* and every year 2-3% of subjects with migraine on less than 15/days per month transition to a chronic migraine state *(5, 6)*.

Migraine-related disability and burden can be improved with appropriate treatments to i) abort ongoing episodes (acute treatment) or ii) prevent new ones.

Preventive treatments act by reducing monthly migraine days by a percentage that varies from 30 to 75%. Hence the importance of adequate treatments to abort residual attacks in the shortest possible amount of time.

Indication

We propose fremanezumab for the preventive treatment of migraine with and without aura in adults with 8 or more days of migraine per month. This means that we are proposing it for high frequency episodic migraine and for chronic migraine. High frequency episodic migraine is defined by the presence of 8 or more migraine days per month *(20)*. This group of patients have a high disease-related burden and disability.

Alternative medicines currently included on the Model Lists for the proposed indication

The EML only lists propranolol, an old, non-specific migraine drug that has limited efficacy in migraine prevention and has no evidence of efficacy in chronic migraine. Furthermore, at the recommended doses, propranolol has limited tolerability.

Section 7: Treatment details

Fremanezumab

Fremanezumab is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

Posology and method of administration

Two subcutaneous dosing schemes are available:
• 225 mg once monthly (monthly dosing) or
• 675 mg every three months (quarterly dosing)

Fremanezumab is for subcutaneous injection only, and is available as pre-filled syringes. Fremanezumab can be injected into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. For multiple injections, injection sites should be alternated (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761089s002lbl.pdf). Patients may self-inject if instructed in subcutaneous self-injection technique by a healthcare professional. When switching dosing regimens, the first dose of the new regimen should be administered on the next scheduled dosing date of the prior regimen.
When initiating treatment with fremanezumab in a subject already taking a preventive medication for migraine, the concomitant treatment may be continued, if considered necessary by the prescriber.
The treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter.

Missed dose
If a fremanezumab injection is missed on the planned date, dosing should resume as soon as possible on the indicated dose and regimen. A double dose must not be administered to make up for a missed dose.

Special populations
Elderly
There is limited data available on the use of fremanezumab in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required.

Renal or hepatic impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment.

Paediatric population
The safety and efficacy of AJOVY in children and adolescents below the age of 18 years have not yet been established. Trials are presently ongoing, but no data is available yet.

Method of administration
AJOVY is for subcutaneous injection only. AJOVY can be injected into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. For multiple injections, injection sites should be alternated. Patients may self-inject if instructed in subcutaneous self-injection technique by a healthcare professional. For further instructions on administration.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use

Serious hypersensitivity reactions
Anaphylactic reactions have been reported rarely with fremanezumab. Most reactions have occurred within 24 hours of administration although some reactions have been delayed. Patients should be warned about the symptoms associated with hypersensitivity reactions. If a serious hypersensitivity reaction occurs, initiate appropriate therapy and do not continue treatment with fremanezumab.

Major cardiovascular diseases
Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients.

No formal clinical drug interaction studies have been performed with AJOVY, however no pharmacokinetic drug interactions are expected based on the characteristics of fremanezumab. Furthermore, concomitant use of acute migraine treatments (specifically analgesics, ergots, and triptans) and migraine preventive medicinal products during the clinical studies did not affect the pharmacokinetics of fremanezumab.

Interaction with other medicinal products and other forms of interaction

Fremanezumab contains less than 1 mmol sodium (23 mg) per dose, i.e., is essentially “sodium-free”.

Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of fremanezumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of AJOVY during pregnancy.

Breastfeeding
It is unknown whether fremanezumab is excreted in human milk. Human IgG is known to be excreted in breast milk during the initial days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. For this reason, use of fremanezumab could be considered during breast-feeding only if clinically needed. According to the practice recommendations of the International Headache Society (2024) mAbs antibodies targeting CGRP can be used with caution after at least two weeks postpartum *(21)*.

Fertility
There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility.

Driving
Fremanezumab has no or negligible influence on the ability to drive

Section 8: Review of evidence for benefits and harms

All of the available evidence from clinical trials and real-world evidence favours the inclusion of this drug to the armamentarium of options for the preventive treatment of episodic and chronic migraine.

We conducted a systematic analysis of the literature together with a large group of headache experts from several countries, including some contributors to this application, and strictly based on the use of the GRADE methodology.

Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions and overviews of reviews (Appendices 1 and 2). Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.
Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic.
A literature search for systematic reviews and meta-analyses and the RCTs published after the reviews and the meta-analyses was performed in 2022. As the process of literature search and analysis took more than 12 months, search strings were re-launched in May 2023 and November 2023 to update the search to the RCTs published from February 2022.
Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions *(22)* and overviews of reviews *(23)*. Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement *(24)*.
The literature search was performed for each pharmacological class of migraine prophylactic treatments. Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic. The same search strings were launched in two separate searches. In search 1, we looked for systematic reviews and meta-analyses, while in search 2 we looked for RCTs published after the reviews and the meta-analyses retrieved in search 1. If Search 1 did not allow to retrieve any systematic review or meta-analysis, Search 2 was considered for RCT inclusion since the beginning of indexing of each database. Search 1 was performed at the beginning of search, while Search 2 was performed at the beginning and repeated in May 2023 and November 2023. Only published literature was considered for searches. Reference management and duplicate removal were performed with EndNote X6®.

Study selection
The selection process was performed in two stages. In stage 1, systematic reviews and meta-analysis covering the topic of interest were screened to identify eligible studies. In stage 2, additional RCTs, published after the selected systematic review and meta-analyses were considered for inclusion. In case no systematic reviews and meta-analyses were available, only RCTs were selected.
Stage 1. Each module working subgroup initially received from the coordination supporting group an .xlsx file containing authors, publication year, title, abstract, and DOI of references retrieved during Search 1 (systematic reviews and meta-analyses) after duplicates were removed. Any further duplicates identified during the study

selection process were accounted for in the study selection flow-chart. Module subgroups performed the study selection process in two phases, first evaluating titles and abstracts for eligibility, and then evaluating the full text of eligible references for inclusion. Inclusion and exclusion criteria for both phases are reported in Appendix 1. The evaluation process was performed by one rater, with a second rater consulted in case of uncertainty.
Stage 2. Module working subgroups received from the coordination supporting group an .xlsx file that contained the authors, publication year, title, abstract, and DOI of references retrieved during Search 2 (RCTs) after removing duplicates. To review all the literature that was not included in the selected systematic reviews and meta-analyses, the module working subgroups identified the most recent and comprehensive systematic review or meta-analysis on each pharmacological class and extracted the temporal limit (i.e., the 'until date') of the search. They then evaluated only the studies published after the identified 'until date' following the same evaluation procedure described in stage 1. The inclusion and exclusion criteria for eligibility and inclusion in phase 2 are presented in Appendix 2.
If duplicates were identified during study selection, they were considered and accounted for in the study selection flow-chart. Full texts of all RCTs identified in all systematic reviews and meta-analyses included in stage 1 were evaluated according to the same criteria. Therefore, module subgroups selected the final number of RCTs included in the review. This final number was revised if needed after the literature search updates performed in May 2023 and November 2023.

For the analysis of the efficacy of drugs for the prophylaxis of migraine, the outcomes considered were:

- change in monthly headache/migraine days, defined as the variation in days reported by patients from baseline to the end of follow-up (as reported in headache diaries);
- ≥50% responder rate, defined as the proportions of patients reporting a ≥50% reduction in monthly headache/migraine days compared with baseline. The ≥50% reduction of monthly attacks was also considered for ≥50% responder rate whenever the reduction in monthly headache/migraine days was not available.

These outcomes are in agreement with the guidelines of the International Headache Society for clinical trials for the preventive treatment of migraine *(25, 26)*.

Methodological notes

Main evidence: Our review includes results from RCTs with measurable outcomes of interest and reporting a sample size calculation and a study hypothesis for superiority or non-inferiority in the case of comparison between two active principles or an active principle and placebo. For each comparison, data included in this section were meta-analyzed separately for each outcome, introducing, when needed, subgroup analyses to describe the effect of different dosages. Analyses referring to outcomes of interest were considered among main evidence also if those outcomes were secondary outcomes in the included studies, provided that they were pre-specified. To describe all data retrieved in a homogenous way, meta-analyses were conducted also when only one study was available for a comparison and outcome.

Additional evidence: We also assessed data from RCTs lacking a clear study hypothesis for superiority or non-inferiority or a sample size calculation related to the comparison that is being considered (or, if performed, minimum sample size was not achieved). Data were meta-analyzed with the same procedure adopted for the previous section. This section also includes summaries of data from studies reporting considered outcomes and expressed through indexes not allowing to perform meta-analyses (e.g., medians or mean without SD).

Meta-analyses were performed using RevMan®, version 5.3. Computed effect sizes were Standardized Mean Difference (SMD) for continuous outcomes and Relative Risk (RR) for categorical outcomes. Pooled effect sizes were computed using the random effect model and expressed with a 95% Confidence Interval (95% CI).

The search strings for monoclonal antibodies targeting the CGRP pathway for systematic review/meta-analysis and for additional RCTs are reported in Appendix 3.
Overall, we retrieved 1308 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included 11 systematic reviews and meta-analyses *(27-37)* that were considered as sources of randomized controlled trials (RCTs). From the 11 systematic reviews and meta-analyses 19 RCTs were included in the quantitative synthesis *(15, 38-55)* (Figure 3).

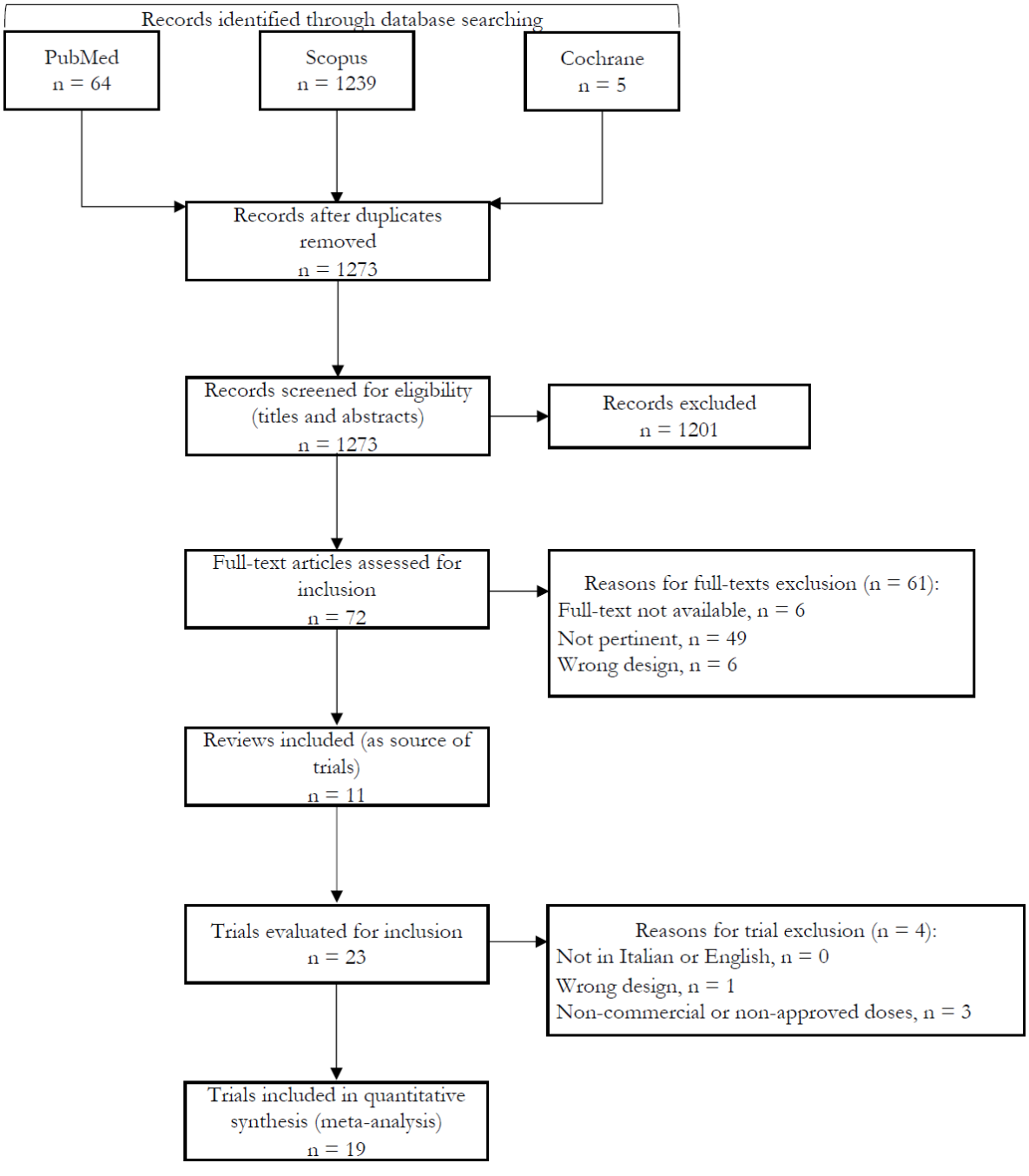


Figure 3 – Meta-analysis flowchart

More recent papers, published since October 2020 and not reported in the reviews and meta-analyses, were searched. We retrieved 2762 references from which, after removing duplicates, 5 RCTs were selected and analyzed *(9, 56-59)*. From literature search update performed in May and November 2023, three further RCTs were included *(60-62)* (Figure 4).

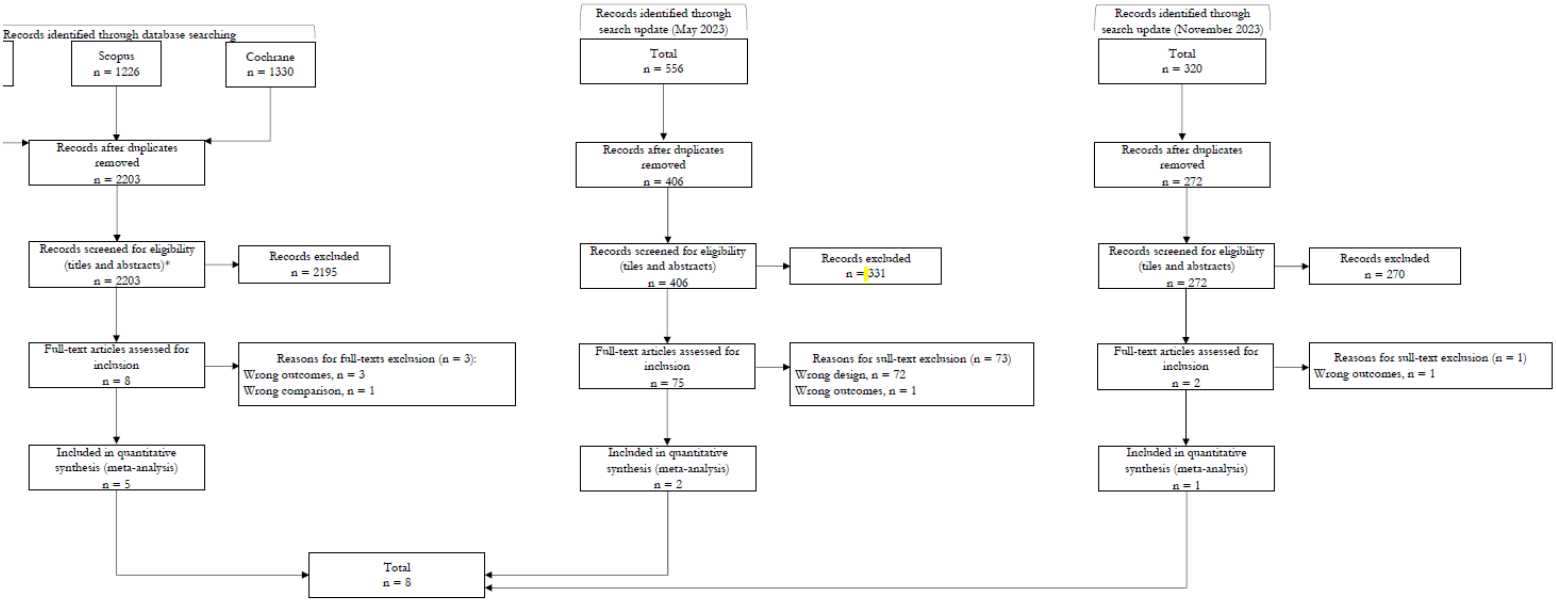


Figure 4. RCTs selection flowchart

Overall, 27 studies were included in the quantitative synthesis to develop the evidence-based guideline (meta-analyses), 8 of which assessed fremanezumab.

Episodic migraine

We found four RCTs comparing fremanezumab to placebo in patients with episodic migraine *(14, 43, 44, 56)*.

The pooled analysis showed benefits of subcutaneous fremanezumab 225 mg monthly and 675 mg quarterly over placebo considering the outcomes of change in monthly migraine days (Figure 5) and ≥50% response rate (Fig. 6). The quality of evidence for both outcomes was considered high (see Table 1).

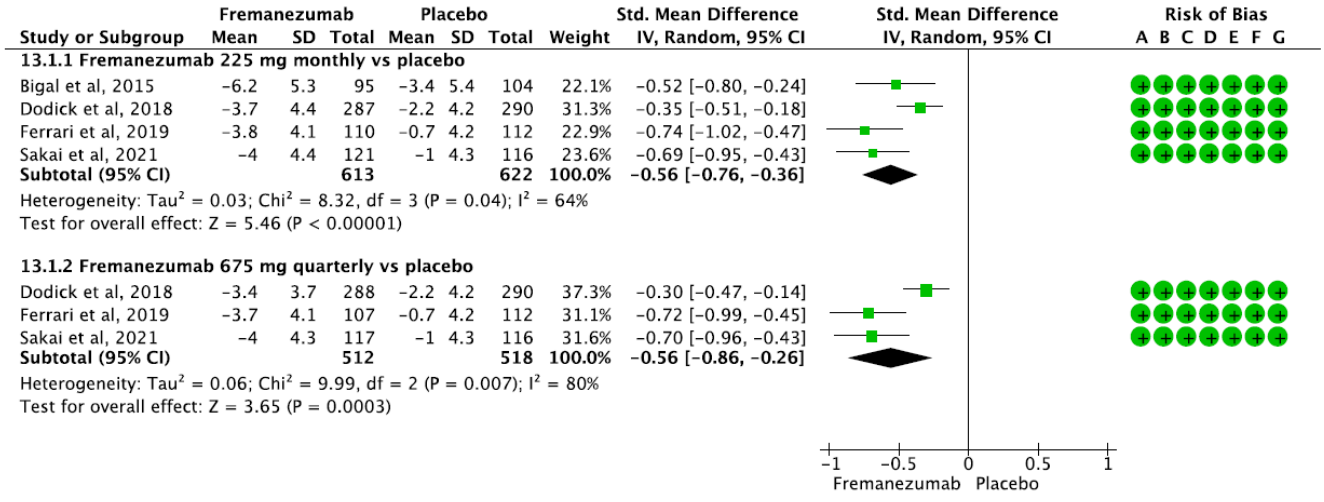


Figure 5. *Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly or 675 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with episodic migraine at 12 weeks.*

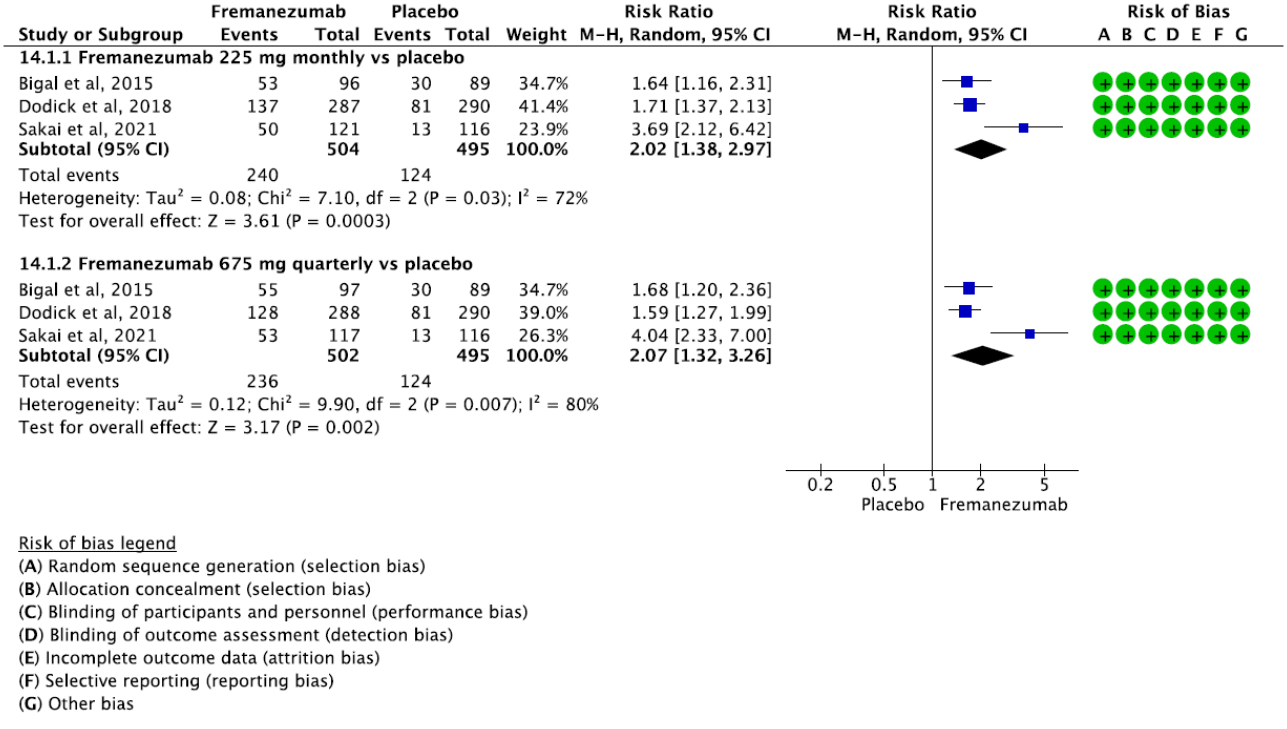


Figure 6. *Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly or 675 mg quarterly) and placebo for the outcome ≥50% response rate in patients with episodic migraine at 12 weeks*

Table 1. *Comparison of fremanezumab 225mg (monthly), fremanezumab 675 mg (quarterly) and placebo considering change in monthly migraine days in pooled analysis in episodic migraine*

Certainty assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Change in monthly migraine days - Fremanezumab 225 mg monthly subcutaneous vs Placebo												
4	RCTs	Not serious	Not serious	Not serious	Not serious	None	613	622	-	SMD **0.6 lower** (0.8 lower to 0.4 lower)	⨁⨁⨁⨁ High	Critical
Change in monthly migraine days - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	512	518	-	SMD **0.6 lower** (0.9 lower to 0.3 lower)	⨁⨁⨁⨁ High	Critical
≥50% responder rate - Fremanezumab 225 mg monthly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	240/504 (47.6%)	124/495 (25.1%)	**RR 2.02** (1.38 to 2.97)	**256 more per 1.000** (from 95 more to 493 more)	⨁⨁⨁⨁ High	Critical
≥50% responder rate - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	236/502 (47.0%)	124/495 (25.1%)	**RR 2.07** (1.32 to 3.26)	**336 more per 1.000** (from 7 less to 1000 more)	⨁⨁⨁⨁ High	Critical

Chronic migraine

We found four RCTs comparing fremanezumab to placebo in patients with chronic migraine *(15, 16, 44, 57)* that met the criteria to be included in the analysis.

The pooled analysis showed benefits of subcutaneous fremanezumab 225 mg monthly (with 675 mg loading dose) and 675 mg quarterly mg over placebo considering the outcomes change in monthly headache days (Fig. 7) and ≥50% response rate (Figure 8). The quality of evidence for both outcomes was high for fremanezumab 675 mg quarterly. For both outcomes related to fremanezumab 225 mg monthly the quality of evidence was downgraded to moderate since in RCTs the intervention also included a loading dose of 675 mg that is not approved for clinical use (see Table 2).

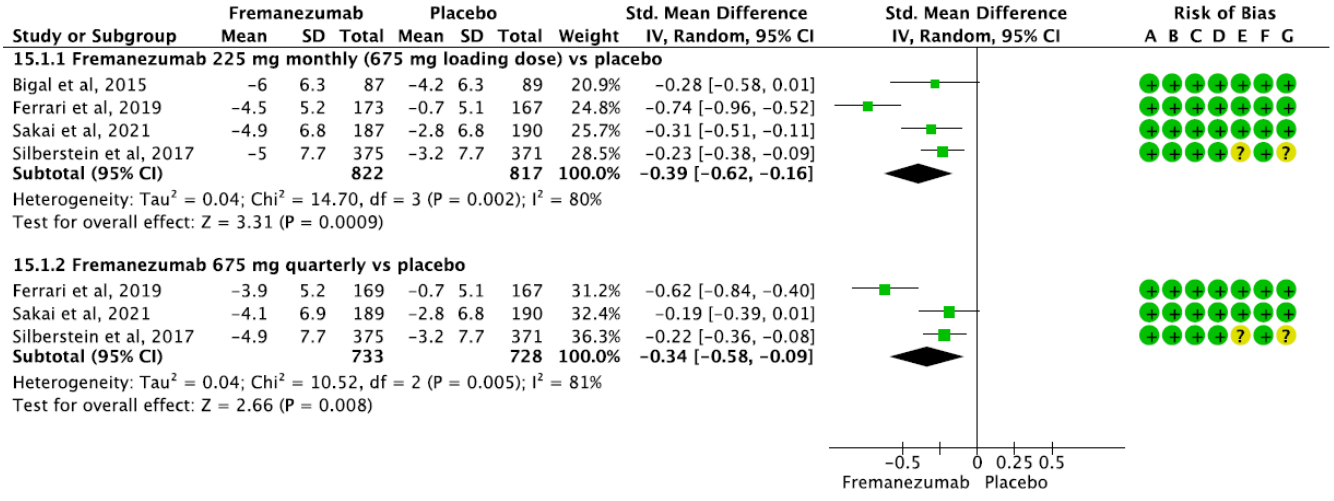


Figure 6. *Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly plus 675 mg loading dose or 675 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with chronic migraine at 12 weeks*

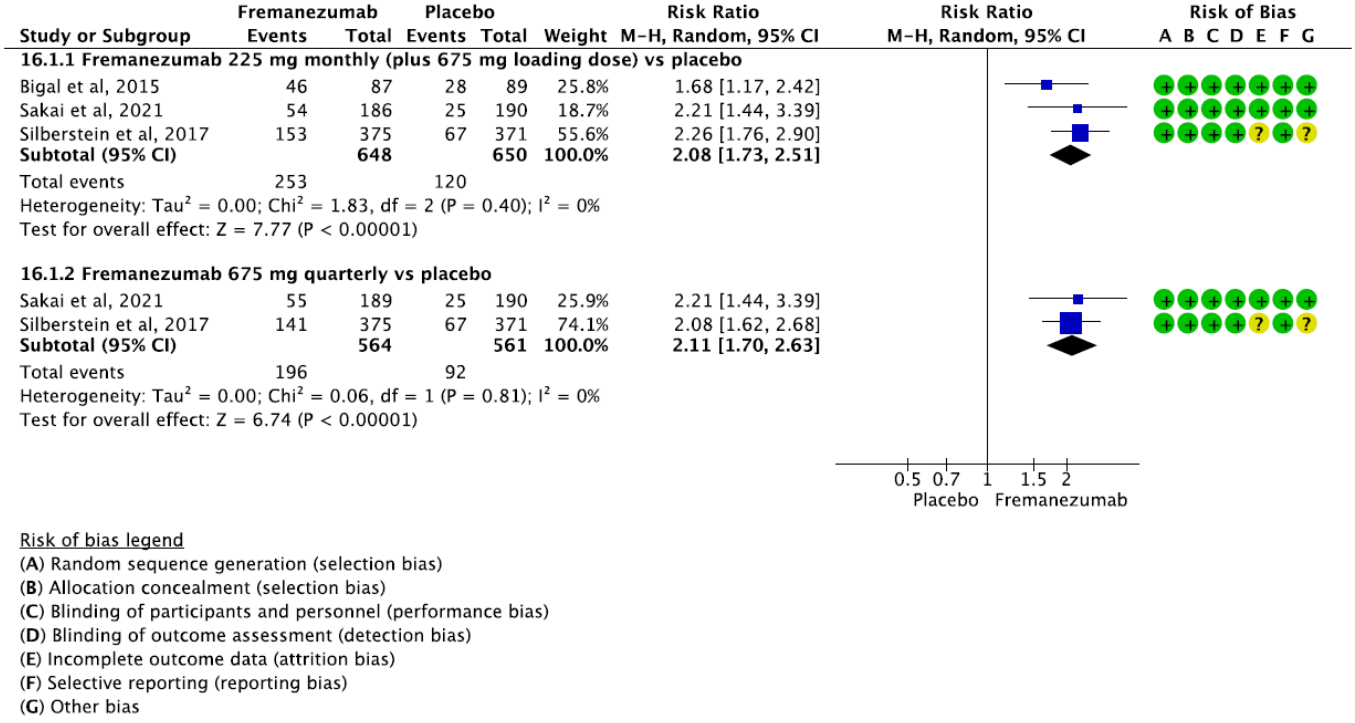


Figure 7. *Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly plus 675 mg loading dose or 675 mg quarterly) and placebo for the outcome ≥50% response rate in patients with chronic migraine at 12 weeks*

Table 2. *Comparison of fremanezumab 225mg (monthly), fremanezumab 675 mg (quarterly) and placebo considering change in monthly migraine days in pooled analysis in chronic migraine*

Certainty assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Change in monthly migraine days - Fremanezumab 225 mg monthly (675 mg loading dose) subcutaneous vs Placebo												
4	RCTs	Not serious	Not serious	Not serious	Not serious	Serious[1]	822	817	-	SMD **0.4 lower** (0.6 lower to 0.2 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	733	728	-	SMD **0.3 lower** (0.6 lower to 0.1 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Fremanezumab 225 mg monthly (plus 675 mg loading dose) subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	Serious[1]	253/648 (39.0%)	120/650 (18.5%)	**RR 2.08** (1.73 to 2.51)	**199 more per 1.000** (from 135 more to 279 more)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	196/564 (34.8%)	92/561 (16.4%)	**RR 2.11** (1.70 to 2.63)	**182 more per 1.000** (from 115 more to 267 more)	⊕⊕⊕⊕ High	Critical

Safety

For the assessment of safety we considered the meta-analysis by Messina et al. *(18)*. Anti-CGRP therapies are safe and well tolerated overall.

No significant differences in serious adverse events were found between active treatments and placebo. Eptinezumab was associated with the lowest odds of treatment-emergent adverse events and serious adverse events compared to placebo, whereas erenumab was associated with the lowest odds of any adverse events and quarterly fremanezumab with the lowest odds of treatment discontinuation due to adverse events.

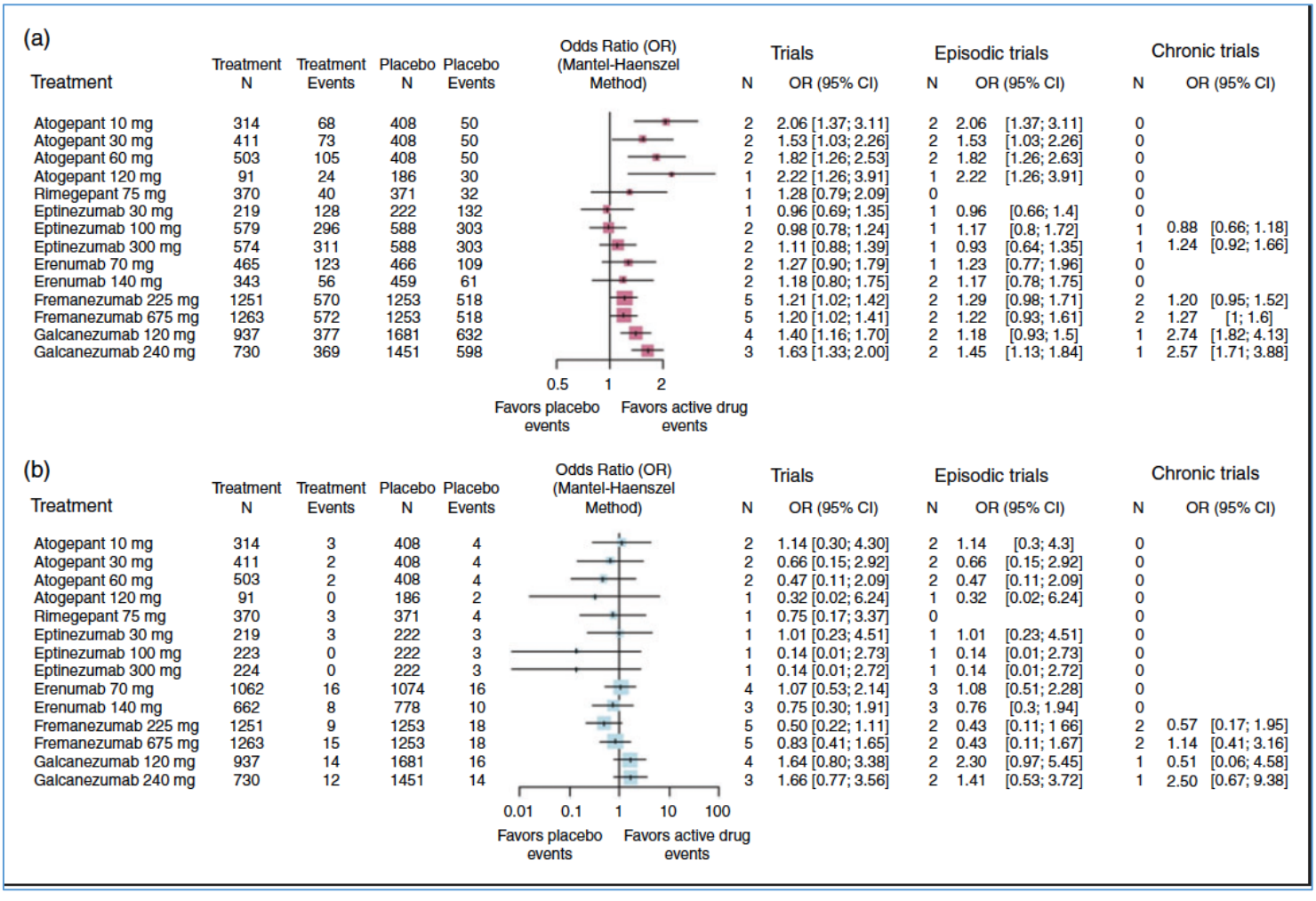


Figure 8. *Forest plots representing results from network meta-analysis comparing active treatments and placebo for treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Odds ratios higher than 1 indicate that the odds of having a treatment-emergent adverse event (a) or a serious adverse event (b) is higher in the treatment group compared to the placebo. Odds ratios were reported for all RCTs and for studies investigating only episodic or chronic migraine patients. Abbreviations: CI=confidence interval, OR=odds ratio. (from Messina et al., 2023) (18).*

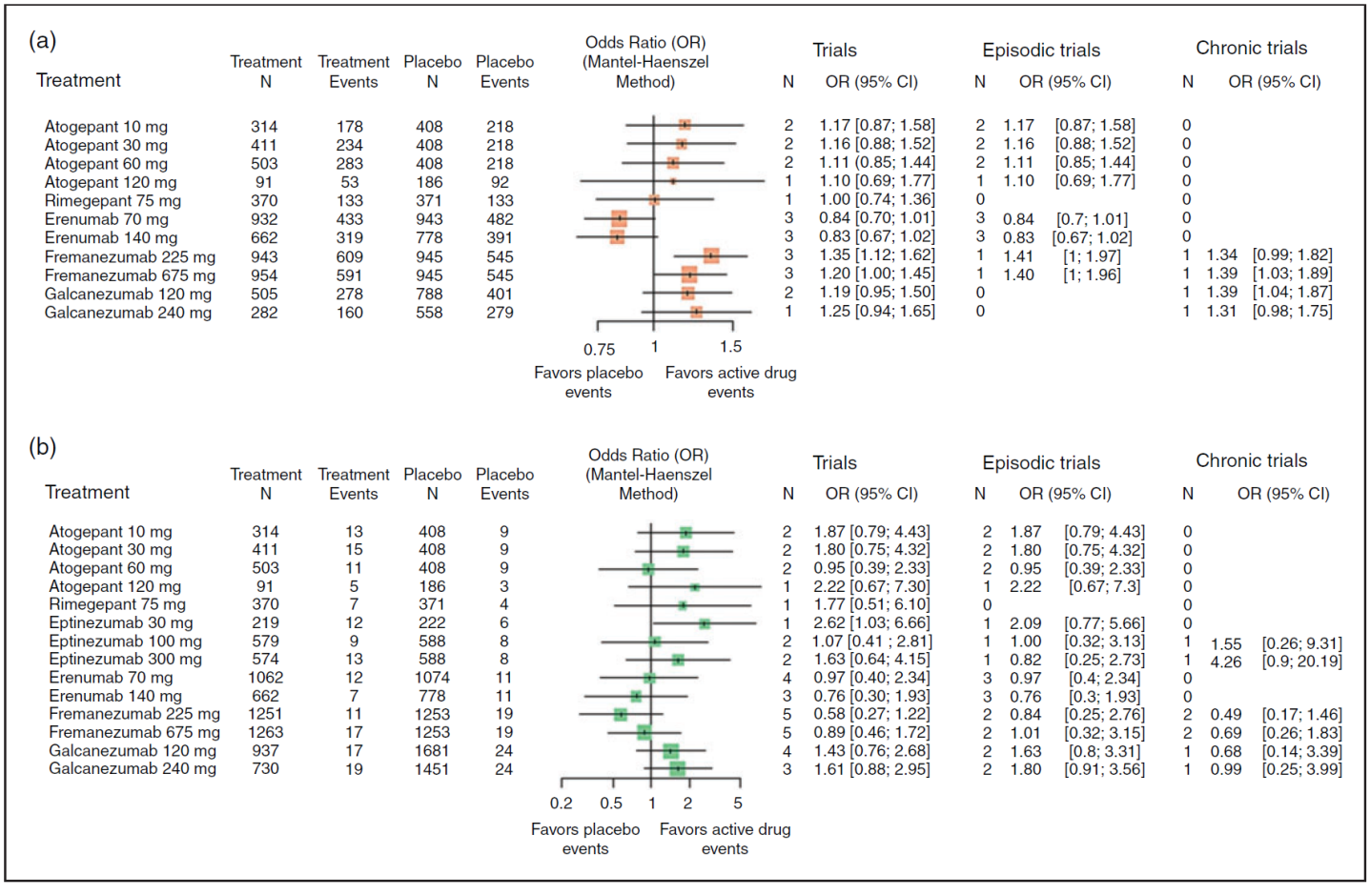


Figure 9. *Forest plots representing results from network meta-analysis comparing active treatments and placebo for secondary safety outcomes: any AEs, AEs leading to treatment discontinuation and individual AEs most frequently reported in previous RCTs. Odds ratios higher than one indicate that the odds of having any adverse event (a) or adverse event leading to treatment discontinuation (b) is higher in the treatment group compared to the placebo. Odds ratios were reported for all RCTs and for studies investigating only episodic or chronic migraine patients. Abbreviations: CI=confidence interval, OR=odds ratio (from Messina et al., 2023) (18).*

Summary of the safety profile of fremanezumab

A total of over 2,500 patients (more than 1,900 patient years) have been treated with AJOVY in registration studies. More than 1,400 patients were treated for at least 12 months.

Commonly reported adverse drug reactions (ADRs) were local reactions at the injection site (pain [24%], induration [17%], erythema [16%] and pruritus [2%]).

Adverse reactions to fremanezumab

These are presented in figure 5.

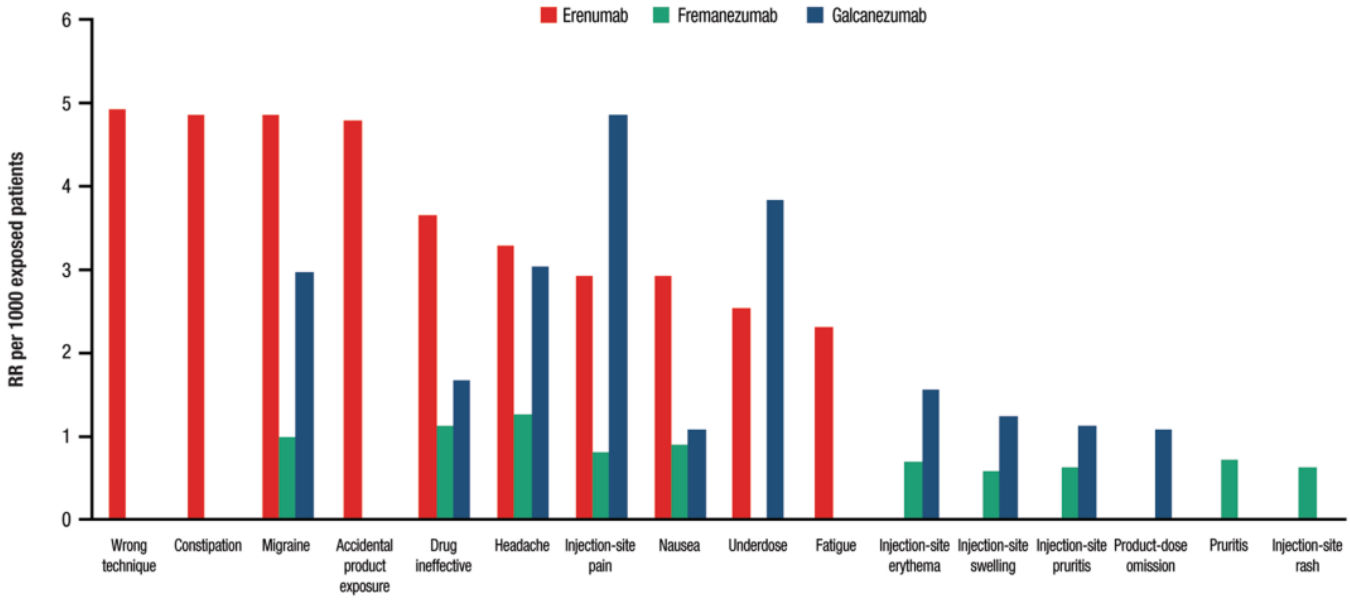


Figure 10. Reporting rate of the *top ten adverse event per 1000 exposed patients for erenumab, fremanezumab, and galcanezumab during the first 6 months after their launch (from Silberstein et al., 2023)(63).*

Description of selected adverse reactions

Injection site reactions

The most frequently observed local reactions at the injection site were pain, induration and erythema. All local injection site reactions were transient and predominantly mild to moderate in severity. Pain, induration and erythema were typically observed immediately after injection while pruritus and rash appeared within a median of 24 and 48 hours, respectively. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Serious hypersensitivity reactions

Anaphylactic reactions have been reported rarely. These reactions mostly occurred within 24 hours of administration although some reactions have been delayed.

Immunogenicity

In placebo-controlled studies, 0.4 % of patients (6 out of 1,701) treated with fremanezumab developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed neutralising antibodies. With 12 months of treatment, ADA were detected in 2.3% of the patients (43 out of 1,888) with 0.95% of the patients developing neutralising antibodies. The safety and efficacy of fremanezumab were not affected by ADA development

Section 9: Summary of recommendations in current clinical guidelines

Recommendations in existing WHO guidelines

N.A.

Recommendations in other current clinical guidelines

Summary of recent guidelines and recommendations including fremanezumab for the preventive treatment of migraine.

Guideline	Year	Recommendation
Danish Headache Society Guidelines *(64)*	2021	• In Denmark, erenumab and fremanezumab are currently recommended as possible preventive treatment for patients with chronic migraine who have experienced treatment failure in previous preventive treatments with at least one anti-hypertensive and one anti-epileptic.
American Headache Society Guidelines *(65)*	2021	• Fremanezumab has established efficacy in migraine prevention
French Headache Society Guidelines *(66)*	2021	• Strong recommendation for fremanezumab (225 mg SC monthly 675 mg SC quarterly) for episodic and chronic migraine prevention
European Headache Federation Guidelines *(12)*	2022	• Strong recommendation for the use of monoclonal antibodies in patients with episodic or chronic migraine
German Headache Society Guidelines *(67)*	2022	• The monoclonal antibodies against CGRP (eptinezumab, fremanezumab and galcanezumab) or against the CGRP receptor (erenumab) are superior to treatment with placebo in the prevention of episodic migraine.
Korean Headache Society Guidelines *(68)*	2023	• We strongly recommend using fremanezumab for the preventive treatment of episodic migraine (Level of Evidence: I, Recommendation grade: Strong for).

		• We strongly recommend using fremanezumab for the preventive treatment of chronic migraine (Level of Evidence: I, Recommendation grade: Strong for).
SISC-IHS Guidelines (preventive)- in press	2024	• Fremanezumab subcutaneous injection (225 mg monthly or 675 mg quarterly) is included as recommended preventive treatment for both episodic and chronic migraine with a high quality of evidence and a strong strength of recommendation. • If an initial migraine preventive drug is ineffective or not well tolerated, we suggest switching to a different class of medication. In individuals with multiple drug failures, a further option may be switching to a different preventive treatment in the same therapeutic class or to drugs such as […] monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) • Some drugs targeting the CGRP pathway have been tested in populations up to 80 years old without safety issues and can therefore represent an option.

Section 10: Summary of available data on comparative cost and cost-effectiveness

Khanal et al. *(69)*vperformed an early (in the context of CGRP monoclonal antibodies) systematic review of economic evaluations of pharmacological treatments for adults with chronic migraine. Searches of multiple databases, including economics/HTA specific sources, used both free text keywords and thesaurus (MeSH) terms for migraine/headache and prophylactic drug interventions (including named drugs of interest). These were combined with a search filter for economic and cost studies. No language or date limits were applied. Sixteen citations met the inclusion criteria, of which only two (one from the US, one from the UK) evaluated fremanezumab as the main treatment. In a US study (Institute for Clinical and Economic Review, 2018), the ICER for fremanezumab vs no preventative treatment was US$ 115,000/QALY ("way above the baseline willingness-to-pay limit of US$ 50,000/QALY"). The UK NICE evaluation (original guidance, 2019) reported that fremanezumab had higher costs, but also gained more QALYs, than both best supportive care and botulinum toxin type A (Botox), with ICERs respectively of £11,825 and £16,227/QALY gained. The reasons for the large disparity are not clear, other than that these two evaluations used utility values from two different trials.

The NICE final evaluation supported its original guidance*(70)*. It first concluded that the most relevant comparators were best supportive care for episodic migraine, and botulinum toxin type A (Botox) plus best supportive care for chronic migraine.
It focused on people for whom at least three previous preventative treatments had failed. It accepted a negative stopping rule as appropriate to the evaluation: those whose migraine did not respond to treatment (a reduction in monthly migraine days from baseline of >50% for episodic migraine or >30% for chronic migraine) would stop treatment after 12 weeks. It concluded: "… the most plausible ICER for fremanezumab compared with best supportive care for episodic migraine after three preventive treatments [had] failed was below £20,000 per QALY gained" (less than the lower end of the range NICE normally considered an acceptable use of NHS resources). Therefore, it further concluded, fremanezumab was a cost-effective use of NHS resources for those with episodic migraine in whom three preventative treatments had failed. With regard to chronic migraine, it was more circumspect: "… although there were still uncertainties with fremanezumab's clinical effectiveness … fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after three

preventive treatments had failed." The evaluation recommended use of fremanezumab in the NHS for both indications.

An analysis in the Dutch population *(71)*, supported by Teva Pharmaceuticals, took indirect costs (lost productivity) into account. Adhering to the Netherlands Authority guidelines, the base-case cost-effectiveness analysis compared fremanezumab with best supportive care (acute migraine treatment only) in patients with chronic migraine and an inadequate response to topiramate or valproate and onabotulinumtoxin A. A supportive analysis was conducted in the broader group of chronic migraine patients with prior inadequate response to 2–4 different classes of migraine preventative treatments. The base-case analysis concluded that "Over a lifetime horizon, fremanezumab is cost saving compared with best supportive care (saving of €2514 per patient) and led to an increase of 1.45 QALYs" (Table 1: prices in 2020 terms). In the supportive analysis, "fremanezumab was cost effective compared with best supportive care, with an incremental cost-effectiveness ratio of €2547/QALY gained." It was noted that fremanezumab remained cost effective in all sensitivity and scenario analyses.

Table 3. *Base case model results (adapted from Wolters et al, 2024) (71)*

	Best supportive care (acute migraine treatment only)	**Fremanezumab**
Base case analysis		
Total costs (€)	€161,554	€159,040
Preventive treatment costs (€)	€0	€24,868
Monitoring costs (€)	€0	€1,066
Resource use costs (€)	€8,108	€7,502
Productivity costs (€)	€153,447	€125,603
Incremental costs (€)	–	–€2,514
Total QALYs	11.35	12.80
Incremental QALYs	–	1.45
ICER vs BSC (€/QALY)	–	**Dominant**
Supportive analysis		
Total costs (€)	€127,743	€132,368
Preventive treatment costs (€)	€0	€30,500
Monitoring costs (€)	€0	€1,312
Resource use costs (€)	€7802	€6,782
Productivity costs (€)	€119,942	€93,773
Incremental costs (€)	–	€4,624
Total QALYs	12.55	14.37
Incremental QALYs	–	1.82

ICER vs BSC (€/QALY)	–	€2,547

Table 4. Total mean outcomes per patient of the deterministic base-case analysis (adapted from Takeshima et al, 2024) *(72)* (¥ 1.00 = US$ 0.00652)

Treatment	QALYs	Costs, ¥	Incremental QALYs	Incremental costs, ¥	ICER, ¥
Episodic migraine					
standard care	13.38	26,364,783			
fremanezumab	13.53	27,292,163	0.15	927,380	6,334,861
Chronic migraine					
standard care	12.21	30,316,481			
fremanezumab	12.29	30,888,446	0.08	571,965	7,393,824
EM (70%) and CM (30%) (weighted average)					
standard care	13.03	27,550,292			
fremanezumab	13.15	28,371,048	0.13	820,755	6,530,398

A Japanese study *(72)* determined the cost effectiveness of fremanezumab compared with standard care in episodic and chronic migraine within the Japanese population (Table 4). It used regression models of treatment effect of fremanezumab on monthly migraine days (MMDs) and health-related quality of life (HRQOL). The base-case analysis included productivity losses, and applied a Japanese public healthcare perspective. The ICERs of fremanezumab compared with standard care were ¥6,334,861 (US$ 41,345) for episodic migraine, ¥7,393,824 (US$ 48,257) for chronic migraine and ¥6,530,398 (US$ 42,621) for the total migraine population. Higher ICERs (¥9,442,917 to ¥9,952,007 [US$ 61,630 to US$ 64,953]) were found in scenarios excluding productivity losses. The authors noted that, if a WTP threshold of ¥5.0 million (US$ 32,633) were adopted, fremanezumab would have only about a 26% chance of being cost effective compared with standard care.

In conclusion, there are differences between the findings of these studies, which may be country-specific but also methodology dependent. And, of course, the analyses were sensitive to the price of fremanezumab, which is very widely variable across countries: from €102.05 in Argentina to €786.27 in USA per 225 mg injection (current wholesale prices for Ajovy, provided by Teva Pharmaceuticals). Other costs are

associated with this medication. The Dutch analysis assumed therapy initiation was performed during a neurologist visit and further administrations were self-injections at home following nurse training. The Japanese analysis was on the basis that treatment required a trained specialist to perform each administration, and assumed that all patients had the injections administered in the base case. The NICE final evaluation (which used a price of £450.00 per 225-mg injection, or £1,350 per 675 mg-injection [the ex-manufacturer price of Ajovy, according to Teva Pharmaceuticals]) took a nuanced view: while clinical experts suggested that most people would be capable of self-administering fremanezumab, the committee concluded that it was unlikely that everyone would be capable of doing so, and applied administration costs for 10% of people (with "little effect on the model results").

The NICE evaluation ("… the most plausible ICER for fremanezumab compared with best supportive care for episodic migraine after three preventive treatments [had] failed was below £20,000 per QALY gained" and "fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after three preventive treatments had failed") appears to be the most objective and most balanced. On this evaluation, fremanezumab is cost-effective at a price of £450 (US$ 584; €541) per 225 mg-injection, administered monthly, wherever the willingness-to-pay ceiling is at or above £20,000/QALY gained (US$ 25,970; €24,027); at the lowest available price (€102.05 in Argentina), it remains cost-effective with a willingness-to-pay ceiling as low as £5,000/QALY gained (US$ 6,492; €6,007).

Section 11: Regulatory status, market availability and pharmacopoeial standards

Fremanezumab is a prescription drug.
It has been approved by US FDA and Europe EMA approval under the trade name Ajovy® produced by TEVA Pharmaceuticals.

Pharmacopoieal standards

PHARMACEUTICAL PARTICULARS

List of excipients
L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate
Polysorbate 80 (E 433)
Water for injections

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life
Pre-filled syringe
3 years

Special precautions for storage
Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe(s) in the outer carton in order to protect from light.
Fremanezumab may be stored unrefrigerated for up to 7 days at a temperature up to 30 °C.
AJOVY must be discarded if it has been out of the refrigerator for longer than 7 days.
Once stored at room temperature, do not place back in the refrigerator.

Nature and contents of container
Pre-filled syringe

1.5 mL solution in a 2.25 mL Type I glass syringe with plunger stopper (bromobutyl rubber) and needle.
Pack sizes of 1 or 3 pre-filled syringes. Not all pack sizes may be marketed.

Pre-filled pen containing 1.5 mL solution in a 2.25 mL Type I glass syringe with plunger stopper (bromobutyl rubber) and needle.
Pack sizes of 1 or 3 pre-filled pens. Not all pack sizes may be marketed.

Special precautions for disposal and other handling
Instructions for use
The detailed instructions for use provided at the end of the package leaflet must be followed step-by-step carefully.
The pre-filled syringe and the pre-filled pen are for single use only.
AJOVY should not be used if the solution is cloudy or discoloured or contains particles.
AJOVY should not be used if the solution has been frozen.
The pre-filled syringe and the pre-filled pen should not be shaken.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Appendix 1

Inclusion and exclusion criteria for evaluation of references in eligibility and inclusion phases for stage 1.

Phase	Inclusion criteria	Exclusion criteria
Eligibility (evaluation of titles and abstracts)	1) Studies meeting all of the following criteria: - Systematic review and meta-analysis - Including randomized controlled trials - Trials performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs 2) Abstract not available 3) Abstract not allowing to fully assess eligibility	1) Study design was not a systematic review and meta-analysis 2) The systematic review/meta-analysis did not include studies on migraine 3) The systematic review/meta-analysis did not include studies assessing the outcome of a pharmacological therapy versus placebo or other drugs
Inclusion (evaluation of full texts)	1) Studies meeting all of the following criteria: - Systematic review and meta-analysis - Including randomized controlled trials	1) Full text not available (e.g., conference abstracts, conference proceedings) 2) Wrong design (not a systematic review or meta-analysis) 3) Wrong comparison (the systematic review/meta-analysis did not include studies

- Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs	assessing the outcome of a pharmacological therapy versus placebo or other drugs) 4) Wrong population (the systematic review/meta-analysis included studies on other types of headache apart from migraine and did not report separate findings for patients with migraine) 5) Pediatric population (0–18-year-old subjects) 6) Overcome by a more recent systematic review and meta-analysis (i.e., all RCTs included in the systematic review/meta-analysis were also included in another included systematic review/meta-analysis) 7) Wrong outcomes (i.e. the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

Appendix 2

Inclusion and exclusion criteria for evaluation of references in eligibility and inclusion phases for stage 2.

Phase	Inclusion criteria	Exclusion criteria
Eligibility (evaluatlion of titles and abstracts)	1) Studies meeting all of the following criteria: - RCT - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs 1) Abstract not available 2) Abstract not allowing to fully assess eligibility	1) Study design was not RCT 2) The RCT was not performed in patients with migraine 3) The RCT did not assess the outcome of a pharmacological therapy versus placebo or other drugs
Inclusion (evaluation of full)	1) Studies meeting all the following criteria: - RCT - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs	1) Full text not available (e.g., conference abstracts, conference proceedings) 2) Wrong design (not a RCT) 3) Wrong comparison (the RCT did not assess the outcome of a pharmacological therapy versus placebo or other drugs) 4) Wrong population (the RCT included patients with headache other than migraine, or included mixed samples and no separate findings were reported for patients with migraine) 5) Pediatric population (0–18-year-old subjects) 6) The RCT included only patients with menstrual migraine 7) The RCT only assessed non-commercial and non-approved doses of the selected drugs

8) The RCT tested an intravenous drug for acute treatment

10) Wrong outcomes (i.e. the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

Appendix 3

Search strings for all databases to retrieve systematic review/meta-analysis and additional RCTs - monoclonal antibodies targeting the CGRP pathway.

Database	Search 1	Search 2
PubMed	("migrain*"[All Fields] AND ("erenumab"[Supplementary Concept] OR "erenumab"[All Fields] OR ("galcanezumab"[Supplementary Concept] OR "galcanezumab"[All Fields]) OR ("fremanezumab"[Supplementary Concept] OR "fremanezumab"[All Fields]) OR ("eptinezumab"[Supplementary Concept] OR "eptinezumab"[All Fields]) OR "Calcitonin Gene-Related Peptide"[All Fields] OR "GCRP"[All Fields] OR "CGRP monoclonal antibody"[All Fields] OR "CGRP receptor"[All Fields] OR (("moab s"[All Fields] OR "moabs"[All Fields]) AND "anti"[All Fields] AND "cgrp"[All Fields]) OR (("moab s"[All Fields] OR "moabs"[All Fields]) AND "anti"[All Fields] AND "cgrp"[All Fields]))) AND (meta-analysis[Filter] OR systematicreview[Filter])	("migrain*"[All Fields] AND ("erenumab"[Supplementary Concept] OR "erenumab"[All Fields] OR ("galcanezumab"[Supplementary Concept] OR "galcanezumab"[All Fields]) OR ("fremanezumab"[Supplementary Concept] OR "fremanezumab"[All Fields]) OR ("eptinezumab"[Supplementary Concept] OR "eptinezumab"[All Fields]) OR "Calcitonin Gene-Related Peptide"[All Fields] OR "GCRP"[All Fields] OR "CGRP monoclonal antibody"[All Fields] OR "CGRP receptor"[All Fields] OR (("moab s"[All Fields] OR "moabs"[All Fields]) AND "anti"[All Fields] AND "cgrp"[All Fields]) OR (("moab s"[All Fields] OR "moabs"[All Fields]) AND "anti"[All Fields] AND "cgrp"[All Fields]))) AND (randomizedcontrolledtrial[Filter])
Scopus	ALL(migrain* AND (erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR "Calcitonin Gene-Related Peptide" OR gcrp OR "CGRP monoclonal antibody" OR "CGRP receptor" OR (moabs AND anti AND cgrp)) AND ("systematic review" OR "meta-analysis")) AND (LIMIT-TO (DOCTYPE,"re"))	ALL (migrain* AND (erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR "Calcitonin Gene-Related Peptide" OR gcrp OR "CGRP monoclonal antibody" OR "CGRP receptor" OR (moabs AND anti AND cgrp)) AND ("randomized controlled trial" OR rct)) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "ch"

		) OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "bk") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "er"))
Cochrane	(migrain* AND (erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR "Calcitonin Gene-Related Peptide" OR gcrp OR "CGRP monoclonal antibody" OR "CGRP receptor" OR (moabs AND anti AND cgrp))) Limit to review	(migrain* AND (erenumab OR galcanezumab OR fremanezumab OR eptinezumab OR "Calcitonin Gene-Related Peptide" OR gcrp OR "CGRP monoclonal antibody" OR "CGRP receptor" OR (moabs AND anti AND cgrp))) Limit to trial

Appendix 4

Availability of fremanezumab the World (International Headache Society internal survey coordinated by Dr Francesca Puledda, 2024)

Fremanezumab				
Country	Available	Prescription	Reimbursement	Within country differences
Algeria	No			Unknown
Argentina	Yes			Yes
Armenia	No			No
Australia	Yes	Prescription – specialist only	Partial reimbursement	No
Austria	Yes	Prescription – specialist only	Full reimbursement	No
Azerbaijan	No			No
Belgium	Yes	Prescription – GP	Partial reimbursement	No
Bolivia (Plurinational State of)	No			No
Bosnia and Herzegovina	No			No
Brazil	Yes	Pharmacy	No reimbursement	No
Brunei Darussalam	Expected within 5 years			Unknown
Bulgaria	No			No
Burkina Faso	No			Unknown
Burundi	No			No
Cabo Verde	No			No
Cameroon	No			No
Canada	Yes	Prescription – GP	Partial reimbursement	No
Chad				No
Chile	Yes	Prescription – specialist only	No reimbursement	Unknown
China	Expected within 5 years			Unknown
Colombia	No			Unknown
Côte D'Ivoire	No			Unknown
Czech Republic	Yes	Prescription – specialist only	Full reimbursement	No
Denmark	Yes	Prescription – specialist only	Full reimbursement	No
Djibouti	No			No

Dominican Republic				No
Ecuador	No			Unknown
Egypt	No			No
El Salvador	No			No
Ethiopia				Unknown
Finland	Yes	Prescription – specialist only	Partial reimbursement	No
France	Yes	Prescription – specialist only	No reimbursement	Yes
Gabon	Don't know			Unknown
Georgia	No			Unknown
Germany	Yes	Prescription – specialist only	Full reimbursement	No
Ghana	No			Unknown
Greece	Yes	Prescription – specialist only	Full reimbursement	No
Guinea				Unknown
India	No			No
Iran (Islamic Republic of)	No			No
Italy	Yes	Prescription – specialist only	Full reimbursement	No
Latvia	Yes	Prescription – GP	No reimbursement	No
Libya	No			No
Lithuania	Yes	Prescription – specialist only	Full reimbursement	No
Madagascar	No			No
Mali	No			Unknown
Mexico	No			Yes
Mongolia	No			Unknown
Nepal	No			No
Netherlands	Yes	Prescription – specialist only	Full reimbursement	No
New Zealand	No	Other	No reimbursement	No
Niger	No			Unknown
Nigeria	Expected within 5 years			Yes
Norway	Yes	Prescription – specialist only	Full reimbursement	No
Pakistan	No			Yes
Panama	No			No
Peru	No			Unknown
Poland	Yes	Other	Full reimbursement	No
Portugal	Yes	Prescription – specialist only	Full reimbursement	Yes
Republic of Korea	Yes	Prescription – GP	Full reimbursement	No

Republic of Moldova	No			No
Romania	No			No
Russian Federation	Yes	Prescription – specialist only	No reimbursement	Yes
Rwanda	No			Unknown
Senegal	No			Unknown
Singapore				Unknown
Slovenia	Yes	Prescription – specialist only	Full reimbursement	No
South Africa	Don't know			Unknown
Spain	Yes	Prescription – specialist only	Full reimbursement	Yes
Sudan				Unknown
Switzerland	Yes	Prescription – specialist only	Full reimbursement	No
Thailand	Yes	Prescription – specialist only	No reimbursement	Yes
Togo	No			No
Tunisia	No			No
Turkey	No			No
Uganda	No			No
Ukraine	Yes	Prescription – specialist only	No reimbursement	No
United Kingdom of Great Britain and Northern Ireland	Yes	Prescription – specialist only	Full reimbursement	No
United Republic of Tanzania	No			Yes
United States of America	Yes	Prescription – GP	Partial reimbursement	No
Uruguay	No			Unknown
Vietnam	No	Other	No reimbursement	No
Zambia	No			No
Zimbabwe	No			Unknown

To whom it may concern

Re: Support and Endorsement for the application for the inclusion of additional drugs for the treatment of migraine in the WHO Essential Medicines List

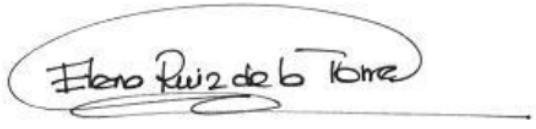
On behalf of EHMA, the leading non-profit umbrella organization of 34 patient associations for Migraine, Cluster Headache, Trigeminal Neuralgia and other headache diseases, dedicated to supporting individuals with migraine and other headache, I am writing to express our wholehearted support and endorsement for the joint application made by the International Headache Society, Lifting the Burden and European Headache Federation to include addition drugs for the acute and preventive treatment of migraine in the World Health Organization Essential Medicines List.

Migraine, characterized by their severe and debilitating nature, pose a significant challenge to those affected, impacting their quality of life and daily functioning. As a patient organization, we witness firsthand the profound suffering experienced by individuals with this condition. Despite the availability of effective treatments, many patients still face barriers to accessing these critical therapies, particularly in regions with limited healthcare resources.

The inclusion of additional treatment options, such as naproxen, eletriptan, amitriptyline, bisoprolol and fremanezumab in the WHO Essential Medicines List is a crucial step towards improving global access to these essential medications. It would ensure that effective and life-changing treatments are available to individuals regardless of their geographic or economic circumstances. This inclusion not only aligns with the WHO's mission to improve global health equity but also represents a significant advancement in the fight against a condition that affects millions worldwide.

Our organisation is committed to supporting this initiative and are available to provide any further information or assistance. We look forward to the positive impact this development will have on the global health landscape.

Sincerely,
EMHA – European Migraine and headache Alliance



Section 12: Reference list

1. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):954-76 (https://doi.org/10.1016/s1474-4422(18)30322-3).
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