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Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: A systematic review and network meta-analysis of phase 3 randomised controlled trials

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Abstract

Background: Several novel treatments targeting the calcitonin gene-related peptide pathway have been developed for migraine. We evaluated the efficacy of these medications, including atogepant, rimegepant, erenumab, eptinezumab, fremanezumab, and galcanezumab, for the prevention of migraine via network meta-analysis.

Methods: Databases, including MEDLINE via PubMed, EMBASE, and Cochrane central, were systematically reviewed, and all eligible phase 3 randomised controlled trials were included.

Results: Nineteen studies (n = 14,584 participants) were included. Studies included episodic (n = 11) and chronic (n = 4) migraine or both (n = 4). All interventions, except for eptinzumab 30 mg, significantly reduced mean monthly migraine days compared to placebo. All medications had a higher ≥50% responder rate than placebo and results were statistically significant in those with the subcutaneous or intravenous route of administrations, but not with the oral one. All medications significantly reduced mean monthly headache days, although no data for this outcome was available for rimegepant, and mean monthly acute medication days, with no data for eptinezumab.

Conclusion: The results show that medications targeting calcitonin gene-related peptide were effective in preventing migraine compared to placebo. Considering limitations of single studies, different populations such as episodic and chronic migraine, and the absence of head-to-head trials, all novel treatments decreased mean monthly migraine and headache days, and showed higher 50%, 75% and 100% responder rates than placebo.

Trial registration: PROSPERO registration: CRD42022310579

Keywords

CGRP, meta-analysis, migraine, prevention, randomised controlled trial, gepants

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Introduction

Migraine is one of the leading causes of disability (1,2), with over one billion people worldwide affected. This highlights the importance of seeking proper management and therapeutic options for this neurological disease (2). Migraine treatment includes non-pharmacological and pharmacological acute drugs and preventive approaches (3,4). Preventive medications should be suggested for people with migraine with severe disabilities or more than four days of headache per month regardless of the disability degree (3,4).

In recent years, a new target-driven class of migraine preventive treatments that act by blocking calcitonin gene related peptide (CGRP) has been developed. CGRP is a neurotransmitter with an essential role in migraine pathophysiology. Currently, there are two types of medications targeting CGRP for migraine prevention: a) CGRP monoclonal antibodies, or CGRP-mAbs, including erenumab which blocks CGRP receptor, and eptinezumab, fremanezumab, and galcanezumab that are CGRP blockers, and b) small molecule CGRP receptor antagonists, or gepants, including atogepant and rimegepant. Rimegepant is also used for acute management of migraine. Gepants are administered orally, erenumab, fremanezumab and galcanezumab subcutaneously and eptinezumab via intravenous injection (5–7). Dose regimens also greatly differ among these drugs, as some are administered daily (i.e. atogepant), some every other day (i.e. rimegepant), some monthly (i.e. erenumab, galcanezumab and fremanezumab) and others every trimester (i.e. eptinezumab). Overall, anti-CGRP medications have shown promising results in managing and preventing migraine (8,9).

A meta-analysis allows the comparison of available data with a high level of evidence, even though the differences described above can only fully be accounted for with direct head-to-head trials. The current study is a systematic review of the available phase 3 randomised controlled trials for atogepant, rimegepant, erenumab, eptinezumab, fremanezumab and galcanezumab in the prevention of episodic and chronic migraine and network meta-analysis to evaluate their efficacy compared to placebo. Safety evaluation was also performed and is reported separately in another manuscript as part of this Special Collection.

Methods

The current systematic review and network meta-analysis was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42022310579 and can be accessed via the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42022310579.

Search strategy

The following online databases were searched from inception until 11 February 2022 (with an updated search performed in May 2022): MEDLINE via PubMed, EMBASE and Cochrane central register of controlled trials. The search strategy was prepared to obtain all published randomised controlled trials (RCT) on the effect of atogepant, rimegepant, erenumab, eptinezumab, fremanezumab, or galcanezumab on the preventive treatment of migraine. The detailed search strategy for all databases is reported in online Supplementary Table 1.

Selection criteria

In the current systematic review and meta-analysis, we included phase 3 double-blind RCTs that fulfil the following PICOS criteria:

- Population (P): Participants over the age of 18 that were diagnosed with migraine (episodic or chronic) based on the International Classification of Headache Disorders criteria, third edition (ICHD-III) (10) or ICHD-III beta edition (11).
- Intervention (I): Studies with at least one arm evaluating the effect of atogepant, rimegepant, erenumab, eptinezumab, fremanezumab or galcanezumab. All available doses of the drugs were included in this review. Atogepant 30 mg twice daily was considered 60 mg and 60 mg twice daily as 120 mg.
- Each medication in each available dose was considered as a separate arm. Atogepant (10, 30, 60 and 120 mg), eptinezumab (30, 100 and 300 mg), erenumab (70 and 140 mg), fremazenumab (225 monthly and 675 mg quarterly), galcanezumab (120 and 240 mg) and rimegepant (75 mg every other day) were compared with each other and with placebo.
- Comparison I: Studies comparing one of the mentioned interventions with placebo.
- Outcome (O): Outcomes were selected based on the guidelines of the International Headache Society for controlled trials of preventive treatment of episodic (12) and chronic (13) migraine in adults. The following outcomes were collected if available as primary outcomes: change from baseline in monthly migraine days (MMD – where a migraine day is defined as a day with a migraine that lasts at least 30 minutes without intake of analgesics or a day with a headache that successfully responds to migraine-specific acute treatment), and $\geq$50% responder rate (defined as the percent change from baseline in the number of

migraine days or moderate/severe headache days). In addition, changes from baseline in monthly headache days (MHD), acute medication days (AMD), ≥75% and 100% responder rate were collected as secondary outcomes.
- Study design (S): Phase 3 double-blind RCTs. Phase IIIb trials with difficult-to-treat populations who failed previous preventive treatments were not included.

Only studies in English language, RCTs, and studies on participants ≥18 years old were included. Open-label studies, post-hoc and secondary analysis reports, conference abstracts, letters or editorials were excluded.

Screening and data extraction

After removing duplications, all identified citations were imported into Rayyan, an online free web and mobile app, for screening (14). All citations were screened on different levels, including title and abstract screening and full-text screening according to the protocol by two independent reviewers, experienced in research on headache disorders (FH, DGA, FP, and RM) for each record. Conflicts were resolved by discussing with a third reviewer or senior author (PP-R).

Data extraction from included studies was performed using a predesigned excel spreadsheet. Independent reviewers (FH, DGA, FP, and RM) performed the data extraction in pairs, and conflicts were solved by discussing or involving a third reviewer or with a senior author. There were no missing data for primary outcomes. Authors were not contacted for further data and only published data reported in papers were used in the study.

In addition to mentioned primary and secondary outcomes, the following data were extracted: study title, year of publication, first author's name, demographics of participants including age, sex and ethnicity, BMI, trial registration number, total number of included participants, migraine type (episodic or chronic), presence of aura, history of prior preventive treatments, study duration, intervention type, route of administration, intervention dose, and sample size in each group. In addition, data for assessing the risk of bias was also collected.

Risk of bias assessment

Risk of bias assessment was performed using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) (15). The evaluation was done in five main domains, including 'bias arising from the randomisation process', 'bias due to deviations from intended interventions', 'bias due to missing outcome data', 'bias in measurement of the outcome' and 'bias in selection of the reported result'. Judgment for each section could be 'low risk of bias', 'some concerns' and 'high risk of bias'; finally, an 'overall bias' was reported for each study. The monthly migraine days outcome was used to assess the risk of bias in the current study. The assessment was done by two independent reviewers (FH and FP).

Data analysis

Demographic and clinical characteristics of patients randomised in the included studies were reported as mean and standard deviations or as frequencies. Frequentist random effects network meta-analyses were applied to the primary and secondary outcomes following Rücker (16) and Rücker and Schwarzer (17). Since one has to be cautious in comparing the results of the different routes of administration, as there may be an administration effect (18), separate network meta-analyses were performed for each route of administration, i.e. subcutaneous, intravenous and oral. In addition, pairwise meta-analyses were performed using the inverse variance method with restricted maximum likelihood (REML) estimation (19). Mean differences with 95% confidence intervals were estimated for continuous variables, and odds ratios with 95% confidence intervals for binary outcomes. Subgroup analyses were performed by repeating each analysis among studies only on participants with a) episodic migraine (EM) and b) chronic migraine (CM). In addition, analysis on the effect of medications on MMD was repeated after removing the studies in which MMD was not evaluated as a primary outcome. In studies with zero events arms, the treatment arm continuity correction with weights summing up to one by Sweeting et al. (20) was applied. This method considers different sample sizes and shall outperform fixed continuity corrections. Even if it is difficult to detect and to explore heterogeneity with such few studies for the single drugs, heterogeneity is here analysed in a graphical way for the pairwise comparisons. Additionally, the I^2 index, the between study variance τ^2 as well as the p-value for Cochrane's Q test are reported. In addition, network meta-regression was conducted for the primary outcome of the subcutaneous studies adjusting for the different treatments as well as some demographic and clinical characteristics including study duration, age of participants, female percentage, BMI, episodic percentage, Caucasian percentage and years of disease. For each possible confounder, a separate meta-regression was employed to use the most possible of the available data, using REML estimation with random effects for the different studies. Meta-regression was not performed for the oral and intravenous studies, as too few studies

were available. To test for local inconsistencies in the network, the SIDE (Separate Indirect from Direct Evidence) with a back-calculation was conducted to each of the networks (21). All analyses were performed in R version 4.1.2 (22) using the packages netmeta for the network meta-analyses, meta for the pairwise analyses and metafor for the network meta-regression.

Results

Included studies

The search yielded a total of 2314 citations from PubMed (n = 256), Embase (n = 1091) and Cochrane central (n = 967). After removing duplicates (n = 1181), 1133 citations were screened in two stages based on 1) title and abstract and 2) full text. Finally, 19 studies were eligible and included in the study. Figure 1 shows the flowchart of the study selection process in detail.

Out of 19 studies, five (23–27) evaluated erenumab (n = 2939), five (28–32) fremanezumab (n = 3771), four (33–36) galcanezumab (n = 3364), two (37,38) eptinezumab (n = 2019), two (39,40) atogepant (n = 1744) and one (41) rimegepant (n = 747). All studies were published after 2017. A summary of baseline characteristics of all included studies is reported in Table 1, while online Supplementary Table 2 reports overall features for each medication.

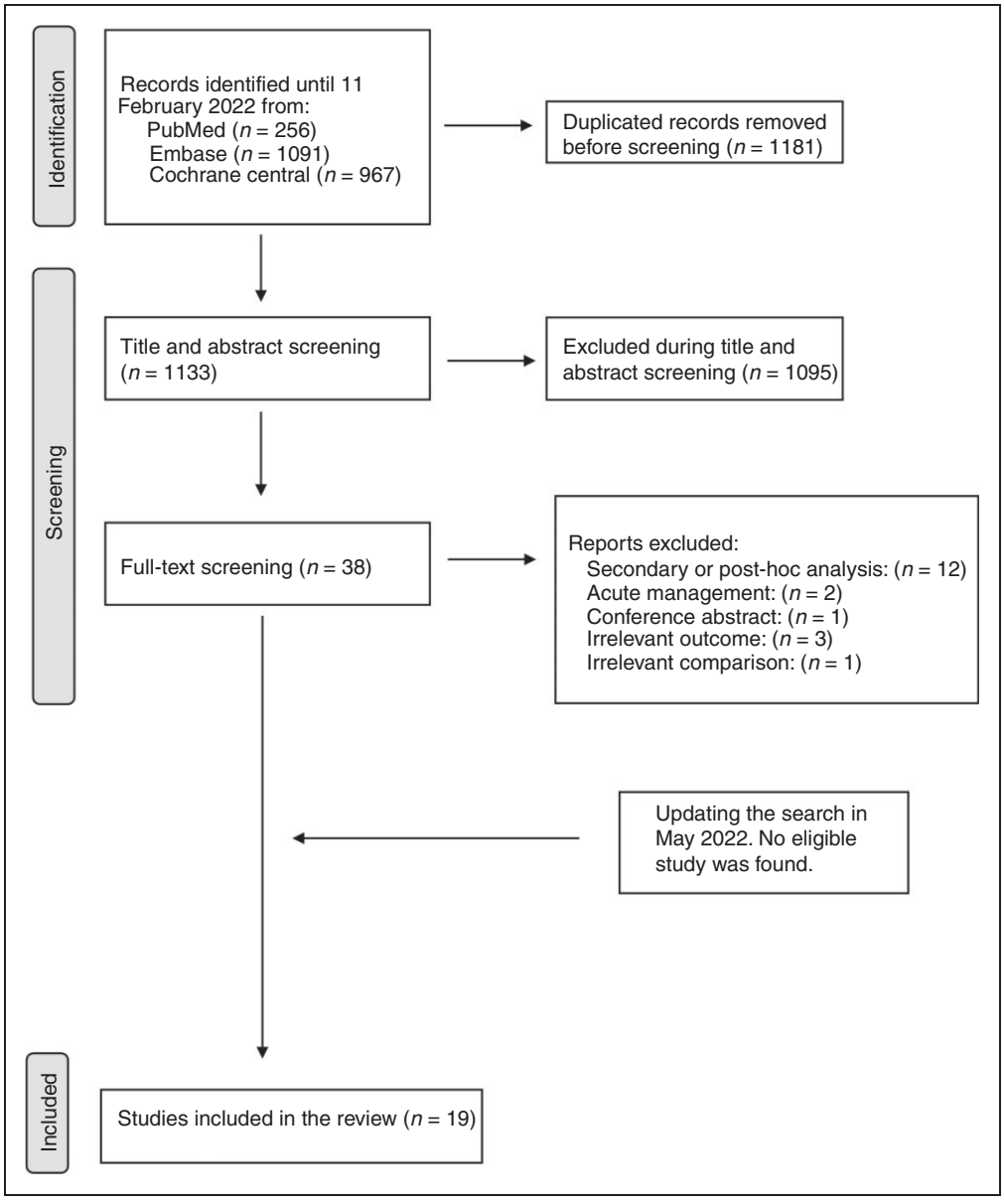

Figure 1. Flowchart of study identification, screening and inclusion.

Participants were on average 41 ± 12 years old and 85% of them were female. Most participants were Caucasian (68%), with a mean BMI between 25.4 ± 4.9 and 30.4 ± 7.6 kg/m^2. Eleven studies (23–25,27,29, 31,35–37,39,40) enrolled only participants with episodic migraine and four studies (30,32,34,38) only those with chronic migraine, one for galcanezumab, one for eptinezumab and two for fremanezumab. The remaining studies (26,28,33,41) enrolled both episodic and chronic migraine participants. Of all the erenumab studies, only one included a subgroup of CM patients (26). Of note, in the fremanezumab studies with both EM and CM participants, the monthly fremanezumab treatment was given with a higher 'loading' dose of 675 mg to chronic migraine patients in the first month, followed by 225 mg in the second and third months. Quarterly fremanezumab, on the other hand, was given as a single 675 mg dose at month one in all studies.

As shown in Table 1, the double-blind treatment period was of three months in most studies, although for some (26,27,33,35,36) this lasted a total of six months. Further, not every trial evaluated the primary efficacy outcome of change in MMD in the same way. Most studies considered the mean MMD during the double-blind treatment period with respect to baseline, whereas three studies evaluated the mean MMD of the third month of the double-blind treatment period only (weeks 9–12) and one measured months 4, 5, 6. Moreover, two of the fremanezumab (30,32) studies and one erenumab (23) study did not have MMD as primary outcome, however, as this measure was still reported as a secondary outcome, we included it in our analysis.

Figure 2 reports the network of all included arms in the study separated based on the route of administration. Online Supplementary Table 3 reports the detail of baseline characteristics of each included arm. All included studies had a low risk of bias (with 100% agreement between the reviewers), as reported in online Supplementary Figure 1.

Primary outcomes

Monthly migraine days (MMD). Based on the network meta-analysis, all medications in all different doses reduced MMD compared to placebo (Figure 3). Out of medications with subcutaneous administration, fremanezumab 675 mg quarterly (mean difference in MMD: −2.36 [95% CI: −2.87, −1.84]) galcanezumab 120 mg (mean difference in MMD: −2.28 [95% CI: −2.82, −1.74]), fremanezumab 225 mg monthly (mean difference in MMD: −2.06 [95% CI: −2.57, −1.54]) and galcanezumab 240 mg (mean difference in MMD: −2.02 [95% CI: −2.63, −1.41]), all showed comparable results with an estimated reduction of more than two days. Erenumab 70 mg (mean difference in MMD: −1.27 [95% CI: −1.81, −0.74]) and 140 mg (mean difference in MMD: −1.78 [95% CI: −2.41, −1.14]) also showed significant reduction in MMD compared to placebo. Analysis on eptinezumab (intravenous administration) showed that all doses reduced MMD compared to placebo. However, the reduction for eptinezumab 30 mg was not statistically significant (mean difference in MMD: −1.25 [95% CI: −2.71, 0.21]).

All oral medications in different doses reduced MMD compared to placebo, with atogepant 120 mg (mean difference in MMD: −1.40 [95% CI: −2.22, −0.58]) and 60 mg (mean difference in MMD: −1.35 [95% CI: −1.85, −0.85]) showing the highest effect, and rimegepant 75 mg the lowest (mean difference in MMD: −0.80 [95% CI: −1.56, −0.04]).

When considering studies only involving episodic migraine participants (middle columns in Figure 3) fremanezumab and galcanezumab still showed the highest efficacy in both available formulations followed by erenumab 140 mg and erenumab 70 mg. In addition, all doses of eptinezumab (intravenous medication) and atogepant (oral medication) showed a significant reduction with respect to placebo (no available study for rimegepant). Out of studies on participants with only chronic migraine (eptinezumab 100 and 300 mg, fremanezumab 225 and 675 mg and galcanezumab 120 and 240 mg; right columns Figure 3) all interventions reduced MMD significantly. Eptinezumab 300 mg showed higher reduction compared to placebo (mean difference in MMD = −2.60 [95% CI: −3.45; −1.75]) than eptinezumab 100 mg (mean difference in MMD = −2.10 [95% CI: −2.95; −1.25]). Galcanezumab 120 mg showed the highest (mean difference in MMD = −2.10 [95% CI: −2.90; −1.30]) and fremanezumab 225 mg the lowest (−1.54 [95% CI: −2.16; −0.93]) among medications with subcutaneous administration. Due to lack of data, atogepant was not included in the CM secondary analysis, whereas rimegepant was not included in either EM and CM secondary analyses. In most of the studies, effect estimates were comparable between episodic and chronic trials. However, the mean differences were estimated much larger in the chronic eptinezumab trial than in the episodic eptinezumab trial (mean difference of −2.10 vs. −0.7 for eptinezumab 100 mg and −2.60 vs. −1.10 for 300 mg).

When repeating this analysis by including only studies that reported MMD as a primary outcome (and thus excluding three studies) results were found to be nearly identical (see online Supplementary Figure 2).

≥50% responder rate. Data for this outcome was available for all studies and interventions. The network meta-analysis on medications with subcutaneous and intravenous route of administration showed significantly higher ≥50% responder rate for all medications compared to placebo (Figure 3) with fremanezumab

Table 1. Summary of baseline characteristics of all included studies.

Author, year	Acronym	Studied medication	Route of administration	Dose (mg)	Registration code	Study duration (months)	Total randomized (n)	Female (%)	Countries	Caucasian (%)
Goadsby, 2020	–	Atogepant	Oral	10, 30, 60, 120	NCT02848326	3	834	86%	USA	79%
Ailani, 2021	ADVANCE	Atogepant	Oral	10, 30, 60	NCT03777059	3	910	88%	USA	86%
Croop, 2021	–	Rimegepant	Oral	75	NCT03732638	3	747	82%	USA	87%
Ashina, 2020	PROMISE-1	Eptinezumab	Intravenous	30, 100, 300	NCT02559895	3	898	83%	USA, Republic of Georgia	84%
Lipton, 2020	PROMISE-2	Eptinezumab	Intravenous	100, 300	NCT02974153	3	1121	84%	USA, Europe, Ukraine, Russia, UK, Republic of Georgia	91%
Goadsby, 2017	STRIVE	Erenumab	Subcutaneous	70,140	NCT02456740	6	955	85%	USA, Europe, Turkey	90%
Dodick, Ashina, 2018	ARISE	Erenumab	Subcutaneous	70	NCT02483585	3	577	85%	USA, Europe	90%
Reuter, 2018	LIBERTY	Erenumab	Subcutaneous	140	NCT03096834	3	246	81%	Australia, Europe, Switzerland, UK	95%
Takeshima, 2021	–	Erenumab	Subcutaneous	70	NCT03812224	6	261	87%	Japan	0%
Wang, 2021	EMPOwER	Erenumab	Subcutaneous	70, 140	NCT03333109	3	900	82%	Asia, Middle East, Latin America	17%
Silberstein, 2017	–	Fremanezumab	Subcutaneous	225 monthly*, 675 quarterly	NCT02621931	3	1130	88%	USA, Japan, Europe, Russia, Canada, Israel	–
Ferrari, 2019	FOCUS	Fremanezumab	Subcutaneous	225 monthly*, 675 quarterly	NCT03308968	3	838	84%	USA, Europe, UK, Switzerland	94%
Dodick, Silberstein, 2018	HALO EM	Fremanezumab	Subcutaneous	225 monthly, 675 quarterly	NCT02629861	3	875	85%	Ca-da, Europe, Israel, Japan, Russia, USA	–
Sakai, 2021, CM	–	Fremanezumab	Subcutaneous	225 monthly*, 675 quarterly	NCT03303079	3	571	86%	Japan, South Korea	0%
Sakai, 2021, EM	–	Fremanezumab	Subcutaneous	225 monthly, 675 quarterly	NCT03303092	3	357	85%	Japan, South Korea	0%
Mulleners, 2020	CONQUER	Galcanezumab	Subcutaneous	120 §	NCT03559257	6	463	86%	USA, Japan, South Korea, Europe, UK	79%
Detke, 2018	REGAIN	Galcanezumab	Subcutaneous	120 §, 240	NCT02614261	3	1117	85%	USA, UK, Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan	79%
Skljarevski, 2018	EVOLVE-2	Galcanezumab	Subcutaneous	120, 240	NCT02614196.	6	922	85%	USA, UK, Europe, Argentina, Israel, Korea, Taiwan, Mexico	70%
Stauffer, 2018	EVOLVE-1	Galcanezumab	Subcutaneous	120, 240	NCT02614183	6	862	83%	USA, Puerto Rico, Ca-da	80%

(continued)

Table 1. Continued.

Author, year	Acronym	EM, CM, mixed (% for EM)	Disease duration, years (mean ± SD)	Baseline days of acute migraine treatment per month (mean ± SD)	History of prior preventive treatment, (%)	Baseline migraine days per month (mean ± SD)	Baseline headache days per month (mean ± SD)	Evaluation of primary outcome of change in MMD from baseline
Goadsby, 2020	–	EM	19.4 ± 12.2	6.5 ±3.2	28%	7.7 ± 2.5	8.9 ± 2.7	MMD of months 1, 2, 3
Ailani, 2021	ADVANCE	EM	–	6.7 ±3.1	–	7.4 ± 2.5	9.3 ± 2.7	MMD of months 1, 2, 3
Croop, 2021	–	mixed (EM 77%)	–	–	–	7.8 ± 2.7	–	MMD of month 3
Ashina, 2020	PROMISE-1	EM	17.4 ± 11.27	–	–	8.6 ± 2.9	10 ± 3.1	MMD of months 1, 2, 3
Lipton, 2020	PROMISE-2	CM	18.1 ± 11.8	–	43 %	16.1 ± 4.6	20.5±3.1	MMD of months 1, 2, 3
Goadsby, 2017	STRIVE	EM	–	3.3 ± 3.4	41%	5.2 ± 1.5	9.2 ± 2.6	MMD of months 1, 2, 3
Dodick, Ashina, 2018	ARISE	EM	21 ± 12	–	46%	8.3 ± 2.6	–	MMD of month 3
Reuter, 2018	LIBERTY	EM	–	4.8 ±2.9	–	9.3	10.1	**MMD of month 3
Takeshima, 2021	–	mixed (EM 61%)	–	–	77%	–	–	MMD of months 4, 5, 6
Wang, 2021	EMPOwER	EM	11.7 ± 9.8	5.1 ± 2.6	53%	8.3 ± 2.8	9.3 ± 3.1	MMD of month 3
Silberstein, 2017	–	CM	19.9 ± 12.6	11 ± 6.2	–	16.2 ± 5.1	13.1 ± 5.7	**MMD of months 1, 2, 3
Ferrari, 2019	FOCUS	mixed (EM 39%)	24.2 ± 12.8	12.4	100%	14.2	–	MMD of months 1, 2, 3
Dodick, Silberstein, 2018	HALO EM	EM	20.2 ± 12.3	6.6 ± 3.1	–	9.1 ± 2.6	–	MMD of months 1, 2, 3
Sakai, 2021, CM	–	CM	18.7 ± 11.9	–	–	15.7 ± 5.1	21.3 ± 4.1	**MMD of months 1, 2, 3
Sakai, 2021, EM	–	EM	19.9 ± 12.6	–	–	8.8 ± 2.6	11.0 ± 2.4	MMD of months 1, 2, 3
Mulleners, 2020	CONQUER	mixed (EM 58.2%)	22.7 ± 13.2	12.3±6	98%	13.4 ± 6.1	15.3 ± 6.4	MMD of months 1, 2, 3
Detke, 2018	REGAIN	CM	20.8	–	78%	19.4	–	MMD of months 1, 2, 3
Skljarevski, 2018	EVOLVE-2	EM	20.6 ± 12.4	7.5 ± 3.4	65%	5.7 ± 1.8	10.7 ± 3.5	MMD of months 1, 2, 3
Stauffer, 2018	EVOLVE-1	EM	20 ± 12.4	7.4 ± 3.5	60%	5.7 ± 1.7	9.1 ± 3	MMD of months 1, 2, 3

EM, episodic migraine; CM, chronic migraine; * A dose of 675 mg was administrated during the first month of treatment in chronic migraine patients. § A loading dose of 240 mg was administrated during the first month of treatment. ** MMD is reported in the paper but as a secondary outcome.

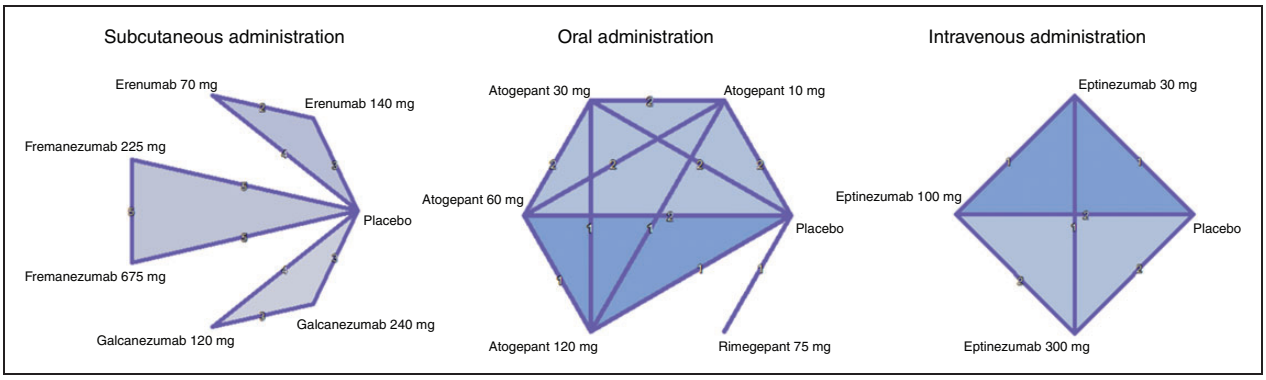

Figure 2. Network of included arms in the meta-analysis based on the monthly migraine days outcome. The lines between the interventions show the direct comparison in different studies. There are three separate nodes based on the drug route of administration.

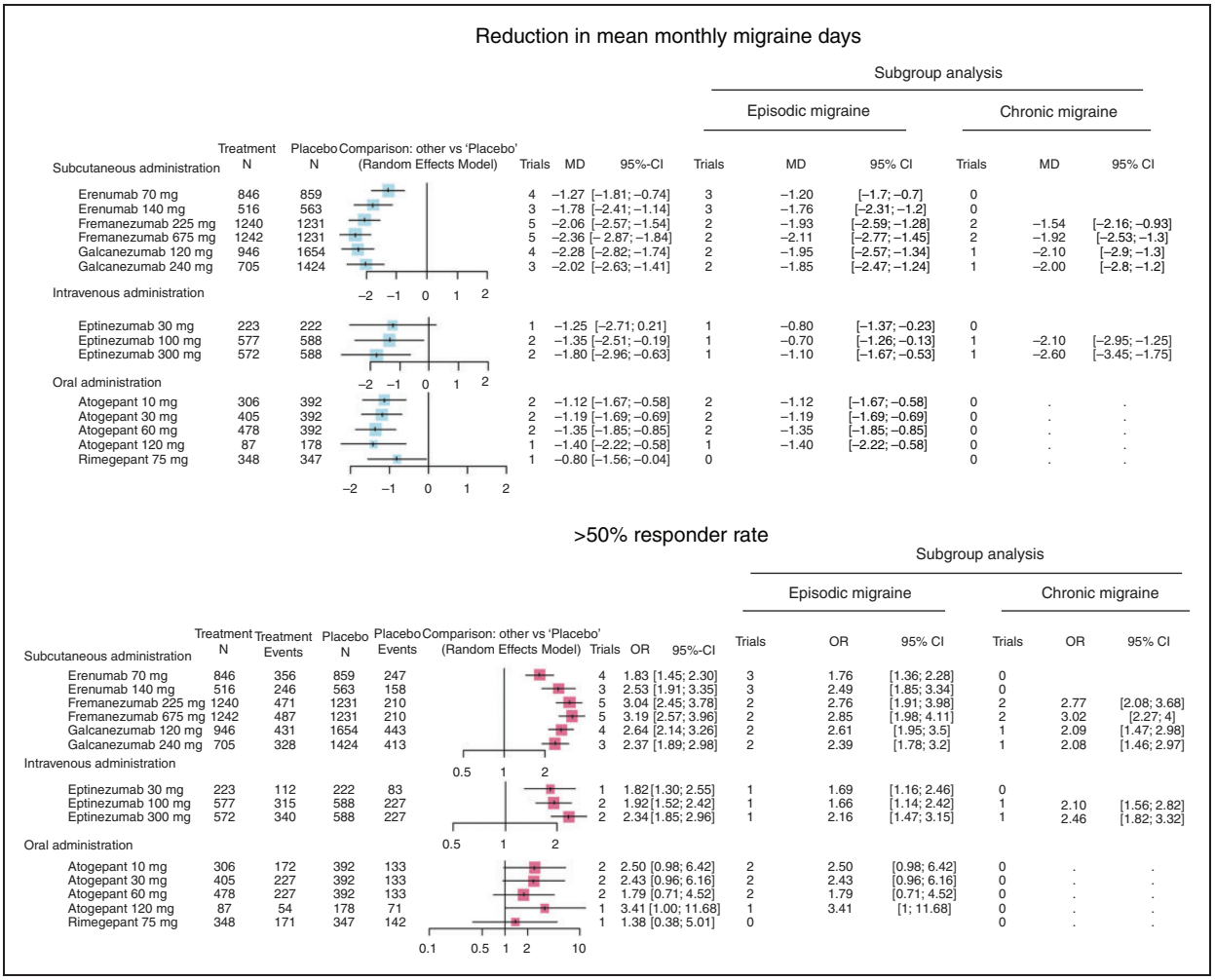

Figure 3. Comparison of different medications in available doses with placebo for primary outcomes. Results from three separate network meta-analysis based on the route of administration. Subgroup analysis based on migraine type (episodic vs. chronic) is reported on the right side of the figures. Only 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.

675 mg and 225 mg showing estimated odds ratios above three (OR = 3.19 and 3.04, respectively). Analysis of oral medications showed higher ≥50% responder rate in medications compared to placebo. Although atogepant 120 mg, with one available study, had a ≥50% responder rate odds ratio over 3 (OR: 3.41 [95% CI: 1.00; 11.68]), the results for oral medications was not statistically significant, probably due to the small number of patients.

A similar pattern was observed by repeating the analysis in studies only including participants with episodic migraine. The analysis on chronic migraine studies showed that all available medications (eptinezumab 100 and 300 mg), fremanezumab (225 and 675 mg), and galcanezumab (120 and 240 mg) had a significantly higher ≥50% responder rate compared to the placebo.

Secondary outcomes

Figure 4 reports the result of the network meta-analysis of the comparisons of all available medications with placebo for the secondary outcomes, including MHD, AMD, ≥75% responder rate and 100% responder rate.

All arms with available data (atogepant, fremanezumab and galcanezumab all doses, eptinezumab 100 and 300 mg, and erenumab 70 mg) reduced the mean MHD compared to the placebo. Eptinezumab 300 mg had higher estimated difference in means (−2.40 [95% CI: −3.30; −1.50]) compared to eptinezumab 100 mg (−1.80 [95% CI: −2.65; −0.95]). Among subcutaneous medications, galcanezumab 120 mg had the highest effect (mean difference in MHD: −2.20 [95% CI: −2.67; −1.74]) followed by fremanezumab 675 mg (mean difference in MHD: −1.95 [95% CI: −2.65; −1.26]). All doses of atogepant showed a significant reduction in MHD compared to placebo with a dose related trend i.e., atogepant 10 mg had the lowest effect (−1.22 [95% CI: −1.70; −0.74], and atogepant 120 mg had the highest effect (−1.53 [95% CI: −2.43; −0.62]. Among the studies on subcutaneous medications with available data for AMD, galcanezumab 120 had the highest reduction compared to placebo (mean difference: −2.24 [95% CI: −2.71; −1.77]) followed by fremanezumab 675 mg (mean difference: −2.06 [95% CI: −2.53; −1.59]). All available arms significantly reduced AMD compared to placebo. There were no data for the effect of intravenous medication on AMD, however data on oral medications showed that all arms significantly reduced AMD compared to placebo all with estimated differences between −1.00 (rimegepant 75 mg) and −1.40 (atogepant 30 mg).

Out of the arms with data on ≥75% responder rate, all arms of subcutaneous and intravenous medications had a significantly higher rate compared to placebo. There was no data on 100% responder rate for intravenous arms, but subcutaneous medications showed a higher rate compared to placebo which was statistically significant for all arms except for erenumab 70 mg (OR = 1.84 [95% CI: 0.96, 3.52]). Although all oral medication arms showed a higher ≥75% and 100% responder rate compared to placebo, this was not significant for atogepant 60 mg.

Pairwise analysis, network meta-regression and further analyses

Results of pairwise analyses for all outcomes are reported in online Supplementary Figures 3–8. In general, pairwise analyses supported the results found in the network meta-analysis. All arms with available data reduced MMD, MHD and AMD compared to placebo and had a higher rate of ≥50%, ≥75% and 100% responder rate. When looking at the heterogeneity within each treatment dose combination, some heterogeneity can be observed graphically. Naturally, heterogeneity can be better detected when more studies are available. Here, two fremanezumab studies in particular (28,29) seem to have larger treatment effects compared to the other three fremanezumab studies, as they showed higher reduction in MMD and higher ≥50% responder rate. To explore heterogeneity, network meta-regression was conducted. A significant effect can be detected for age (effect estimate: −0.19 [95% CI: −0.33; −0.06]). Using the SIDE approach for separating indirect from direct evidence, no significant local inconsistencies could be detected.

Discussion

The current study aimed to evaluate the efficacy of atogepant, rimegepant, erenumab, eptinezumab, fremanezumab, and galcanezumab on patients with migraine through network meta-analysis, in 19 phase 3 randomised controlled trials published from 2017 to May 2022 (23–41). It should be mentioned that all comparisons between different treatments are indirect and there are no head-to-head studies in the literature for comparison of CGRP mAbs and gepants with each other.

With regards to primary outcomes, all drugs and doses reduced MMD compared to placebo, with a range from about 2.3 days for fremanezumab 675 mg and galcanezumab 120 mg to 0.8 days for rimegepant 75 mg. All medications showed a higher ≥50% responder rate compared to placebo, with significant results for subcutaneous and intravenous medications. Although eptinezumab 30 mg reduced MMD and atogepant and rimegepant had a higher ≥50% responder rate compared to placebo, the results were not statistically significant.

All arms with available data on mean monthly headache day outcome, including atogepant 10, 30, 60 and

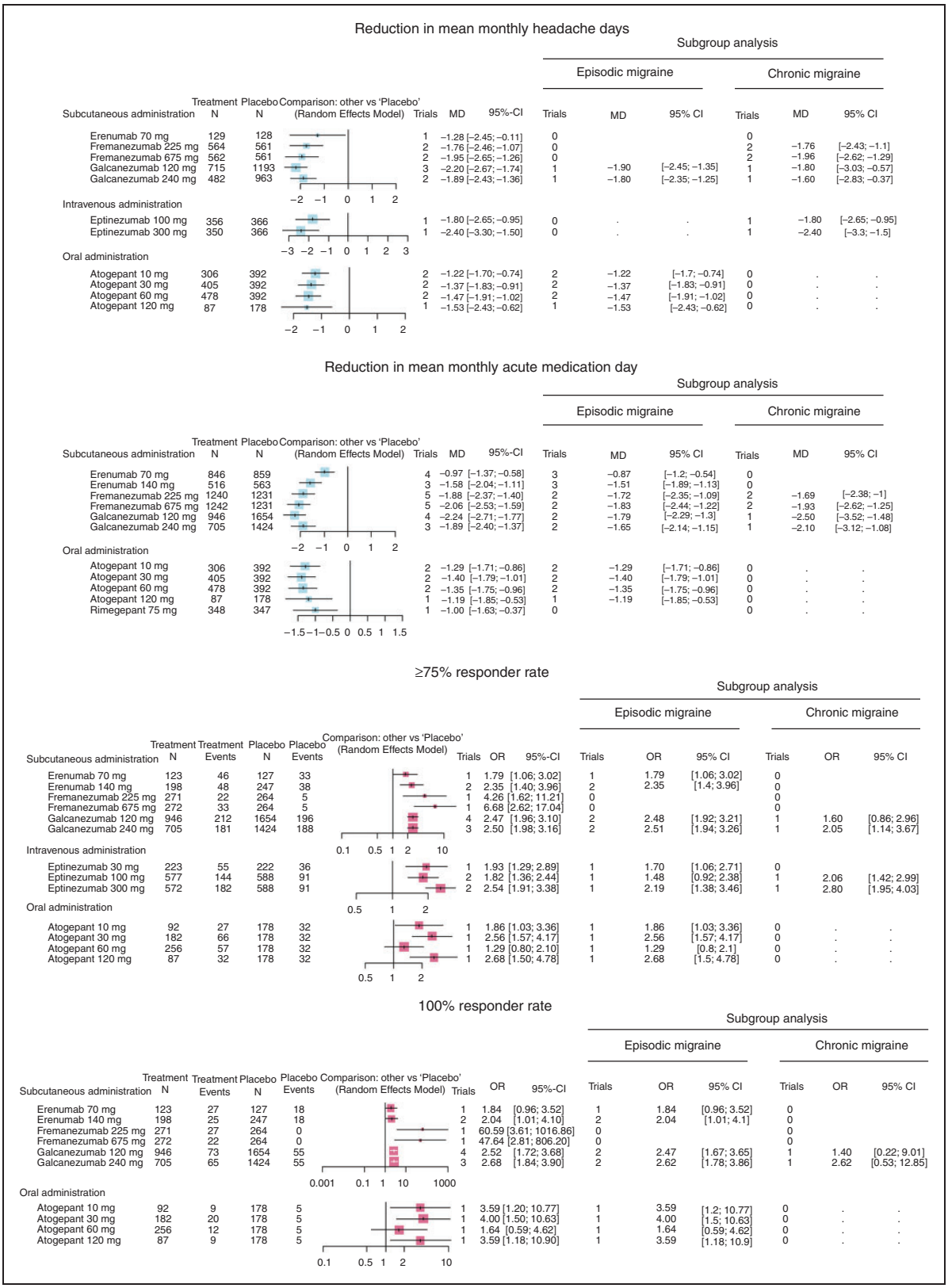

Figure 4. Comparison of different medications in available doses with placebo for secondary outcomes. Results from three separate network meta-analysis based on the route of administration. Subgroup analysis based on migraine type (episodic vs. chronic) is reported on the right side of the figures. Only 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.

120 mg, eptinezumab 100 and 300 mg, erenumab 70 mg, fremanezumab 225 and 675, and galcanezumab 120 and 240 mg, showed a significant reduction of MHD compared to placebo. Similarly, the mean monthly AMD was significantly reduced compared to placebo in all available arms, with the highest levels found for galcanezumab 120 mg and the lowest for erenumab 70 mg.

Arms including atogepant 10, 30 and 120 mg, eptinezumab 30, 100 and 300 mg, erenumab 70 and 140 mg, fremanezumab 225 and 675 mg and galcanezumab 120 and 240 mg had significantly higher odds of $\geq$75% responder compared to placebo. Out of studies with a reported 100% responder rate, fremanezumab, and galcanezumab in all doses, erenumab 140 mg, and atogepant in all doses except for 60 mg, had significantly higher odds compared to placebo.

The current meta-analysis shows the beneficial effects of anti-CGRP monoclonal antibodies in preventive migraine treatment compared to placebo. Our results support a previously published meta-analysis (42) on the impact of CGRP monoclonal antibodies on episodic migraine. Authors reported that medications improved preventive migraine outcomes such as MMD, AMD, and $\geq$50% responder rate. According to their results, eptinezumab showed the lowest amount of reduction in MMD compared to placebo among all medications (mean difference: –1 [95% CI: –2.20; 0.20]) in participants with episodic migraine. Our results presented a similar finding, as all doses of eptinezumab had lower MMD reduction compared to placebo among all arms in participants with episodic migraine. However, our subanalysis looking into drug effects of both EM and CM groups allowed us to show that eptinezumab 100 and 300 mg doses were the most effective intervention for MMD and MHD reduction in chronic migraine.

Masoud et al. (43) showed that fremanezumab reduced MMD to a higher degree than other monoclonal CGRP antibodies. Our results reflect this outcome, but further show that galcanezumab at all doses had very similar efficacy rates. A network meta-analysis by Wang et al. (44) showed that all anti-CGRP monoclonal antibodies were effective in the reduction of MMD compared to placebo and that all medications were statistically similar compared to each other in $\geq$50% responder rates except for fremanezumab, which was significantly superior to eptinezumab. Our results showed similar pattern but as we had three nodes and performed separate network meta-analysis based on route of administration, we could not compare fremanezumab with eptinezumab. Further, their comparisons across drugs did not include different doses and the literature search, which included phase 2 trials, was until October 2020. Soni et al. (45) reported similar results to our review by evaluating the effect of different CGRP mAbs at different doses on participants with chronic migraine; they included phase 2 and 3 trials.

Overall, when considering methodological differences in the trials such as inclusion of chronic vs episodic migraine, duration of the randomisation period (three or six months) and different use of primary efficacy outcomes, the differences in efficacy profiles of the four antibodies are quite minor and all show clear superiority to placebo. A recent review comes to a similar conclusion (46), and for this same reason, the updated European Headache Federation guidelines on using CGRP mAbs for migraine prevention state these medications should be considered as first-line treatment (47). However, this might not be an option in many countries, as reimbursement and insurance coverage often require the proven failure of other prophylactic medications, such as onabotulinumtoxinA. These guidelines also state that efficacy should be checked after at least three months of treatment and, if there is no satisfactory responder, changing from one medication to another might be adequate (47).

Our results further showed that atogepant in all available doses improved efficacy outcomes after three months, including MMD, $\geq$50% responder rate, MHD, and AMD compared to placebo. Based on available data, rimegepant also improves MMD and AMD compared to placebo. For reasons that include oral administration and a shorter half-life (particularly important for women who plan a pregnancy), these gepants, particularly atogepant at the 120 mg dose, could thus represent the drug of choice over monoclonal antibodies for some patients.

Study strength and limitations

The current study is limited to papers in English and to published data. In addition, we did not include post-hoc analyses or open-label follow up studies, however, these have been covered in other papers within this Special Collection. Further, a parallel meta-analysis investigating the tolerability and efficacy of these same treatments is included in the Collection.

This study shows some limitations which are inherent with the available evidence on the topic, such as caucasian over-representation and episodic migraine predominance, as well as with the types of included studies. A direct example is that of studies using different timings for randomisations periods (three vs six months) and different primary outcomes (MHD instead of MMD reduction), showing heterogeneity even within the same intervention.

Our results should thus be regarded with caution, as they cannot substitute direct comparative studies and have limitations which are within the nature of a meta-analysis. To ensure that treatments with different

routes of administration are comparable, direct comparison studies employing a double dummy technique are needed. The here included studies do not only differ in terms of route of administration, but also in terms of other characteristics. Overall, studies on fremanezumab and galcanezumab had older participants and with longer duration of the disease. These treatments showed also the largest effects compared to placebo regarding the primary outcome. This is another finding that highlights the importance of head-to-head studies to compare different anti-CGRP medications with each other in order to diminish the risk of confounders. It is also important to mention that our search was finalised in May 2022 and thus might have excluded important studies published after this date.

Although including just phase 3 trials resulted in missing some data, the current network meta-analysis is a report and summary of high-quality evidence. The result of RoB showed that all the studies had a low risk of bias. In addition, in the current study, all available migraine medications targeting CGRP are included at all doses as separate arms. Another strength of our study is represented by the analogous results of the pairwise comparisons that were conducted in parallel to the network meta-analysis.

Future directions

There is a lack of studies on comparing CGRP mAbs and gepants with each other and other medications. As an example, erenumab showed less adverse events and more efficacy based on $\geq$50% reduction in MMD, when compared to topiramate in a phase 4 clinical trial (48). Direct comparisons with a double dummy technique between different anti-CGRP medications in clinical trials, as well as comparisons with other available medications, are needed in the future.

Conclusion

The current systematic review and meta-analysis showed that the monoclonal antibodies against CGRP or its receptor, namely erenumab, eptinezumab, fremanezumab and galcanezumab, as well as small molecule CGRP receptor antagonists atogepant and rimegepant, are effective in the prevention of migraine compared to placebo. All medications reduced MMD and had higher $\geq$50% responder rate compared to placebo, even though MMD for eptinezumab 30 mg, as well as $\geq$50% responder rate for oral medications were not statistically significant. Overall, differences between drugs were small, with fremenezumab quarterly dose and galcanezumab 120 among subcutaneous medications, eptinezumab 300 among arms with intravenous administration, and atogepant 120 in oral medications showing particularly high reduction in monthly migraine days.

Article Highlights

- A systematic review and network meta-analysis of phase 3 clinical trials on the efficacy of the calcitonin gene-related peptide mAbs and gepants on migraine prevention was conducted.
- This study showed that novel treatments targeting the CGRP pathway including, atogepant, rimegepant, erenumab, eptinezumab, fremanezumab, and galcanezumab, are effective in the prevention of migraine compared to placebo.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FH, EMH and FP report no conflict of interest.

RM reports personal fees from Eli-Lilly, Lunbeck and Bromatech for participating in advisory boards and speaker activities over the last 36 months.

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PP-R in the last 36 months has received honoraria as a consultant and speaker for: AbbVie, Biohaven, Chiesi, Eli Lilly, Medscape, Lundbeck, Novartis, Pfizer and Teva. Her research group has received research grants from AbbVie, Novartis and Teva; has received funding for clinical trials from Alder, Amgen, Biohaven, Electrocore, Eli Lilly, Lundbeck, Novartis, Teva. She is the Honorary Secretary of the International Headache Society. She is in the editorial

board of *Revista de Neurologia*. She is an editor for *Cephalalgia*, *Headache*, *Neurologia*, *Frontiers of Neurology* and advisor for *The Journal of Headache and Pain*. She is a member of the Clinical Trials Guidelines Committee of the International Headache Society. She has edited the Guidelines for the Diagnosis and Treatment of Headache of the Spanish Neurological Society. She is the founder of www.midolordecabeza.org. PP-R does not own stocks from any pharmaceutical company.

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