

# Different Doses of Erenumab for Preventive Treatment of Episodic Migraine: A Systematic Review and Network Meta-Analysis

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## Research article

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# Abstract

**Background** Erenumab is a novel monoclonal calcitonin gene-related peptide receptor antibody that is used for the preventive treatment of migraine.

**Objectives** To evaluate overall safety and efficacy and dose-response relationship of erenumab in patients with episodic migraine and patients with prior migraine treatment failures.

**Methods** We searched randomized clinical trials on PUBMED, EMBASE database, and Cochrane Library database. A pair-wise meta-analysis and Bayesian network analysis were performed.

**Results** For efficacy outcomes, the network meta-analysis suggests that compared with erenumab 70 mg, participants received erenumab 140 mg reported significantly decreased MSMD and increased 50% response rate, and erenumab was most likely to be ranked first for MMD, MSMD and 50% response rate. For safety outcomes, the network meta-analysis has found no significant difference between the 70 mg group and the 140 mg group measured by AE and SAE. For patients with  $\geq 2$  treatment failures, 140mg erenumab group, patients with  $\geq 2$  treatment failures reported significantly reduced MMD and MSMD, increased 50%, and 75% response rate, compared with placebo. For safety outcomes, no significant difference was found between 140 mg erenumab group and the placebo group.

**Conclusion** Erenumab was effective in patients with episodic migraine. 140 mg erenumab was associated with better efficacy outcomes without increased risk for developing adverse events compared with 70 mg erenumab, and 140 mg erenumab was effective in patients with prior migraine treatment failures.

**Registration number:** CRD42020198985

## Introduction

Migraine is one of the most common neurological disorders, with an estimated global prevalence of 15%[1]. It is manifested by recurrent attacks of unilateral, pulsatile headache that could be triggered by daily activities. A migraine attack usually lasts for 4 to 72 hours and is frequently accompanied by nausea, vomiting, photophobia, phonophobia. Thus, patients may suffer from significant disabling pain and impaired quality of life.

As an expanding understanding of the migraine pathogenesis in the past decades, multiple targets have been identified for migraine therapy. Among them, calcitonin gene-related peptide (CGRP) is considered one of the most promising targets[2]. Small molecule CGRP antagonists have been mainly used for acute treatment of migraine, while monoclonal antibodies (mAb) against CGRP or its receptor are used for preventive migraine treatment[3]. Erenumab, an IgG2 human mAb selectively binds to the CGRP receptor, was approved by the Food and Drug Administration for the prevention of migraine[4]. Previous trials showed that erenumab given as a 70 mg or 140 mg subcutaneous injection once per month was associated with a significant reduction of monthly migraine days (MMD) and monthly acute migraine-specific medication days (MSMD) from baseline compared with the placebo, and is not related to an increased risk of developing adverse events[1]. Besides, the unique pharmacological mechanism suggests the potential advantages of erenumab in migraineurs with prior preventive treatment failures.

So far, prior studies have demonstrated that erenumab use was associated with reduced migraine frequency and improved functional outcome compared with placebo; however, no study has been performed to evaluate the dose-response relationship of erenumab for the preventive treatment of migraine. Furthermore, although the effectiveness of erenumab in patients with prior treatment failure has been demonstrated in multiple trials, no systematic approach has been used. The purpose of this study is to conduct a meta-analysis to evaluate the effectiveness and safety of different doses of erenumab in preventive treatment in migraine patients and in patients with prior preventive treatment failures.

## Methods

A meta-analysis was performed following the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[5]. The study was registered at PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>; registry number: CRD42020198985).

## Search strategy

Two researchers independently conducted the online search procedure. The related articles published before April 1, 2020, were searched through PUBMED, EMBASE database, and Cochrane Library database. The search terms include migraine, erenumab, AMG334, and randomized clinical trials. The full electronic search strategy was listed in Supplement S1. The references listed in the relevant articles were screened to avoid omissions. Disagreements were resolved through discussion.

## Study Selection

The study included in the meta-analysis all met the following criteria: 1) randomized clinical trials; 2) patients with a history of episode migraine for  $\geq 12$  months according to the International Classification of Headache Disorders; 3) using erenumab as an experimental group intervention.

## Data extraction

The extraction of data was carried out by two investigators independently. The extracted data include (1) literature information: title, author, publication time, sample size; (2) characteristic of the object of the study including region, age, sex ratio, BMI, age at migraine onset, MMD, MSMD, number of patients who have failed previous preventive migraine medication due to insufficient efficacy or (and) unacceptable tolerability; (3) interventions: the dose of erenumab included in any phase III trials; (4) outcome data: the change in MMD, MSMD at month 3, 50% response rate (the proportion of patients achieved a 50% or greater reduction in MMD from baseline) and 75% response rate (the proportion of patients achieved a 75% or greater reduction in MMD from baseline) at month 3, the change in Headache Impact Test (Hit-6) at month 3, Migraine Physical Function Impact Diary-Everyday Activities and Physical Impairment (MPFID-EA and MPFID-PI) at month 3, number of patients with adverse events (AE) and serious adverse events (SAE) throughout the study.

## Pair-wise meta-analysis

We conducted a pair-wise meta-analysis to evaluate the overall safety and efficacy of erenumab compared with the placebo and the safety and efficacy of different doses of erenumab in patients with prior treatment failures. Dosages were included if they were accessed in any phase III trials. The random-effects model with the Hartung-Knapp-Sidik-Jonkman method was used. Mean difference (MD) and risk ratio (RR) with their 95% confidence intervals (CI) were used to evaluate continuous and categorical variables, respectively. The heterogeneity between the included studies was evaluated with  $I^2$ . R Software version 3.6.2 (R Foundation for Statistical Computing) was used to conduct the analysis.

## Network meta-analysis

As studies with direct and indirect comparison exist across different dosage subgroups, we conducted a Bayesian network meta-analysis to compare safety and efficacy outcomes between different dosages using the gemtc package in R software (version 3.6.2). Both fixed-effects and random-effects models were generated with Markov Chain Monte-Carlo simulation for each outcome using default priors with 5000 adaptation iterations with 100,000 iterations of 4 chains. The model with the lowest deviance information criterion was used for further analysis. The potential scale reduction factor was used to assess the model convergence, using a cut-off value of 1.005. The node-split method was used for assessing inconsistency. Log odds ratio (LOR) and mean difference with their 95% CI were calculated for binary variables and continuous variables, respectively.

## Risk of Bias

For assessing the risk of bias of RCTs, we used the standard approach developed by the Cochrane collaboration, which included: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. The risk of bias plot in individual studies was created using the Review Manager 5.3 software.

## Results

### Baseline Characteristics

We pooled a total of 2453 patients from five randomized controlled trials to analyze the role of erenumab in episodic migraine[6–10]. Figure 1 showed the PRISMA flow diagram of the study inclusion process. Characteristics of included trials are listed in Table 1. Among these included trials, we found two studies reported the effect of erenumab in episodic migraineurs who had preventive treatment failures[8, 11]. The baseline characteristics of each study are shown in Table 2. Overall, 84.2% of patients were female. The baseline MMD of five episodic migraine studies were  $8.34 \pm 2.56$ . Our study included the data from erenumab 70 and 140 mg groups, as these dosages were examined in any phase III trial. The risk of bias in each included trial was plotted in Fig. 2.

Table 1  
Characteristics of included studies

Trials (NCT number)	Phase	Inclusion Criteria	Exclusion Criteria	Group*	Frequency
Sakai 2019(NCT02630459)	Phase 2	1. Aged 20–65 years 2. A diagnosis of migraine as defined by ICHD-III beta for at least 1 year prior 3. A history of 4–15 headache days per month on average across the three months prior to screening	1. Over 50 years old at migraine onset 2. History of cluster headache or hemiplegic migraine 3. Failure to respond to three or more classes of migraine preventive treatments 4. Receiving botulinum toxin within four months before screening 5. The use of interventions or devices for migraine during the two months prior to screening 6. Receiving more than 1 migraine-preventive medication	Erenumab 28 mg Erenumab 70 mg Erenumab 140 mg Placebo	Once a month for 6 months
Headache					
Multicenter					
Dodick 2018(NCT02483585)	Phase 3	1. Aged 18–65 years 2. A history of 4–15 migraine days per month and < 15 headache days per month for at least one year prior	1. Over 50 years old at migraine onset 2. History of cluster headache or hemiplegic migraine Receiving botulinum toxin within four months before screening	Erenumab 70 mg Placebo	Once a month for 3 months
Cephalalgia					
Multicenter					
Reuter 2018(NCT03096834)	Phase 3	1. Aged 18–65 years 2. A diagnosis of migraine as defined by ICHD-III beta for at least one year prior 3. A history of 4–14 headache days per month on average across the three months prior to screening 4. Have previously been treated unsuccessfully	1. Over 50 years old at migraine onset 2. History of cluster headache or hemiplegic migraine 3. Use a preventive migraine medication within five times the drug's half-life before baseline 4. Receiving botulinum toxin within four months before screening 5. The use of interventions or devices for migraine within the month prior to screening	Erenumab 140 mg Placebo	Once a month for 3 months
Lancet					
Multicenter					
Goadsby 2017(NCT02456740)	Phase 3	1. Aged 18–65 years 2. A diagnosis of migraine as defined by ICHD-III beta for at least one year prior 3. A history of 4–15 migraine days per month and < 15 headache days per month for at least three months prior	1. Over 50 years old at migraine onset 2. History of cluster headache or hemiplegic migraine 3. Receiving botulinum toxin within four months before screening 4. The use of interventions or devices for migraine within two months prior to screening	Erenumab 70 mg Erenumab 140 mg Placebo	Once a month for 6 months
New England Journal of Medicine					
Multicenter					
Sun 2016(NCT01952574)	Phase 2	1. Aged 18–60 years 2. A diagnosis of migraine as defined by ICHD-II for at least one year prior 3. A history of 4–14 migraine days per month and < 15 headache days per month for at least three months prior	1. Over 50 years old at migraine onset 2. History of cluster headache or hemiplegic migraine 3. Overuse of acute treatment for headache 4. Receiving more than 1 migraine-preventive medication during the	Erenumab 7 mg Erenumab 21 mg Erenumab 70 mg Placebo	Once a month for 3 months
Lancet Neurology					

\* We only collected data from patients who received >= 70 mg erenumab.

	two months prior to screening
Multicenter	5. Receiving botulinum toxin within six months before screening
* We only collected data from patients who received >= 70 mg erenumab.	

Table 2  
Baseline characteristics of included patients

Trials	Region	Treatment	Populations	Age (SD)	Female Sex (%)	BMI (SD)	Age at onset (SD)	MMD (SD)	MSMD (SD)	Failed previous migraine-preventive medications
Sakai 2019	Japan	Erenumab 70 mg	135	44(NA)	115(85.2%)	21.6(3.5)	NA	7.8(2.3)	5.4(2.9)	43
		Erenumab 140 mg	137	45(NA)	112(81.8%)	22(3.5)	NA	8.1(2.4)	5.9(2.9)	54
		Placebo	136	45(NA)	118(86.8%)	22.1(3.5)	NA	7.7(2.3)	5.6(2.5)	44
Dodick 2018	North America and Europe	Erenumab 70 mg	286	42(11)	245(85.7%)	27.4(6.3)	21(10)	8.1(2.7)	3.7(3.6)	117
		Placebo	291	42(12)	247(84.9%)	27.4(6.1)	22(11)	8.4(2.6)	3.4(3.6)	115
Goadsby 2017	North America, Europe and Turkey	Erenumab 70 mg	317	41.1(11.3)	268(84.5%)	27.3(5.9)	21.4(11)	8.3(2.5)	3.2(3.4)	127
		Erenumab 140 mg	319	40.4(11.1)	272(85.3%)	27(6.2)	20.7(9.9)	8.3(2.5)	3.4(3.5)	116
		Placebo	319	41.3(11.2)	274(85.9%)	27.1(6.3)	21.2(10.2)	8.2(2.5)	3.4(3.4)	127
SUN 2016	North America and Europe	Erenumab 70 mg	107	42.6(9.9)	82(76.6%)	25.8(4.9)	21.7(11.7)	8.6(2.5)	4.3(3.5)	34
		Placebo	160	41.4(10)	132(82.5%)	25.9(4.9)	20.7(11.5)	8.8(2.7)	4.5(3.9)	60
Reuter 2018	Europe and Australia	Erenumab 140 mg	121	44.6(10.5)	97(80.2)	25(4.2)	NA	9.2(2.6)	4.8(2.9)	121
		Placebo	125	44.2(10.6)	103(82.4%)	24.9(5.1)	NA	9.3(2.7)	4.4(2.8)	125

NA = not applicable; BMI = Body Mass Index; MMD = Monthly Migraine Days; MSMD = Monthly Acute Migraine-Specific Medication Treatment Days.

## Overall safety and efficacy

First, we evaluated the overall efficacy of erenumab. The pooled results showed that patients in the erenumab group achieved a greater 50% reduction in MMD from baseline, compared with the placebo group (RR: 1.63, 95% CI: 1.28 to 2.08,  $I^2 = 30.88\%$ ) (Fig. 3). Subsequently, our results found that the erenumab group had a significant reduction of MMD from baseline compared with the placebo group (MD: -1.41, 95% CI: -1.80 to -1.03,  $I^2 = 0\%$ ) (Fig. 3). Furthermore, in comparison to the placebo group, the use of erenumab was associated with a significant reduction of MSMD (MD: -1.18, 95% CI: -1.83 to -0.54) (Fig. 3); considerable heterogeneity was found ( $I^2 = 78.12\%$ ) (Fig. 3). For functional improvement, no significant difference between the placebo group and the erenumab group was found measured change of MPFID-EA and MPFID-PI score from baseline (MD: -2.26, 95% CI: -5.50 to 0.99,  $I^2 = 67.37\%$ ; MD: -2.00, 95% CI: -4.32 to 0.32,  $I^2 = 40.45\%$ , respectively) (Fig. 3). However, for the HIT-6 score, patients received erenumab reported significantly improved HIT-6 score from baseline compared with the placebo group (MD: -2.30, 95% CI: -3.41 to -1.19) (Fig. 3). For the safety outcomes, no significant differences were found in adverse events (RR: 0.94, 95% CI: 0.86 to 1.03,  $I^2 = 0\%$ ) and serious adverse events (RR: 0.79, 95% CI: 0.33 to 1.91,  $I^2 = 0\%$ ) between the placebo and erenumab groups with low heterogeneity (Fig. 4).

## Network meta-analysis comparing different doses of erenumab

Then, we conducted a Bayesian network meta-analysis accessing the safety and efficacy of different doses of erenumab for the preventive treatment of episodic migraine. In adult patients diagnosed with episodic migraine, the use of 70 mg and 140 mg erenumab was associated with significantly decreased MMD, MSMD, and increased 50% response rate compared with placebo (MMD, 70 mg, MD: -1.28, 95% CI: -1.62 to -0.95, MMD, 140 mg, MD: -1.67, 95% CI: -2.08 to -1.25; MSMD, 70 mg, MD: -0.81, 95% CI: -1 to -0.6; MSMD, 140 mg, MD: -1.32, 95% CI: -1.58 to -1.04; 50% response rate, 70 mg, LOR: 0.64, 95% CI: 0.43 to 0.85; 50% response rate, 140 mg, LOR: 0.91, 95% CI: 0.67 to 1.17) (Fig. 5). Subsequently, compared with erenumab 70 mg, participants received erenumab 140 mg reported significantly decreased MSMD and increased 50% response rate, and

erenumab was most likely to be ranked first for MMD, MSMD and 50% response rate. (MSMD, MD: -0.51, 95% CI: -0.79 to -0.23; 50% response rate, LOR: 0.28, 95% CI: 0.03 to 0.53) (Fig. 5). For functional improvement, patients received 70 mg and 140 mg erenumab reported improved MPFID-EA and MPFID-PI at month 3 (MPFID-EA, 70 mg, MD: -1.75, 95% CI: -2.52 to -0.98, MPFID-EA, 140 mg, MD: -2.63, 95% CI: -3.56 to -1.69; MPFID-PI, 70 mg, MD: -1.55, 95% CI: -2.36 to -0.74; MSMD, 140 mg, MD: -2.58, 95% CI: -3.59 to -1.58) (Fig. 6). When comparing 140 mg and 70 mg, although 140 mg erenumab has a high probability to outperform 70 mg, the analysis fails to demonstrate a significant difference in MPFID-EA and MPFID-PI (MPFID-EA, MD: -0.88, 95% CI: -1.87 to 0.11; MPFID-PI, MD: -1.03, 95% CI: -2.1 to 0.03) (Fig. 6). For safety outcomes, the network meta-analysis has found no significantly increased risk for patients received erenumab 70 mg and 140 mg developing adverse events and serious adverse events compared with patients who received placebo (AE, 70 mg, LOR: -0.15, 95% CI: -0.34 to 0.04; AE, 140 mg, LOR: -0.18, 95% CI: -0.4 to 0.05; SAE, 70 mg, LOR: -0.13, 95% CI: -0.9 to 0.61; SAE, 140 mg, LOR: -0.31, 95% CI: -1.2 to 0.53) (Fig. 7). However, the placebo group has the highest probability to be ranked first. Furthermore, no significant difference was found between the 70 mg group and the 140 mg group measured by AE and SAE (AE, LOR: -0.03, 95% CI: -0.27 to 0.21; SAE, LOR: -0.17, 95% CI: -1.13 to 0.73) (Fig. 7). Detailed rank probability chart was listed in Supplement S2, Inconsistency analysis, DIC for random and fixed model, and diagnosis for convergence of each model was listed in Supplement S3-S5.

## Safety and efficacy of erenumab in patients with prior treatment failures

We then assessed the safety and efficacy of different doses of erenumab in patients with  $\geq 2$  treatment failures. For efficacy endpoints, compared with the placebo group, patients treated with 70 mg erenumab showed no significant difference in all the pooled efficacy endpoints compared with the placebo group (MMD, MD: -0.9, 95% CI: -2.41 to 0.6; MSMD, MD: -0.1, 95% CI: 1.23 to 1.03; 50% response rate, RR: 1.79, 95% CI: 0.65 to 4.95; 75% response rate, RR: 3.86, 95% CI: 0.5 to 29.72) (Table 3). Subsequently, for safety outcomes, compared with placebo, the use of 70 mg erenumab is not associated with increased risk for developing adverse events or serious adverse events (adverse events, RR: 0.96, 95% CI: 0.7 to 1.31; serious adverse events, RR: 11.59, 95% CI: 0.02 to 6481.06) (Table 3, Supplement S6-11). As one study was included in the analysis, the heterogeneity was not accessed. Then, for 140 mg erenumab, patients in the 140 mg erenumab group reported significantly reduced MMD and MSMD (MMD, MD: -1.98, 95% CI: -2.93 to -1.03; MSMD, MD: -1.68, 95% CI: -2.27 to -1.09) (Table 4). As for the 50% and 75% response rate, the use of 140 mg erenumab was related to significantly increased 50% and 75% reduction in MMD from the baseline compared with placebo (50% response rate, RR: 2.39, 95% CI: 1.52 to 3.77; 75% response rate, RR: 3.32, 95% CI: 1.37 to 8.05) (Table 4). For safety outcomes, compared with placebo, we found no significant difference in 140 mg erenumab compared with placebo (AE, RR: 0.96, 95% CI: 0.79 to 1.15; SAE, RR: 2.66, 95% CI: 0.29 to 24.79) (Table 4, Supplement S12-17). Heterogeneity was low in all the included outcomes.

Table 3  
Efficacy and safety of 70 mg erenumab in patients with  $\geq 2$  prior treatment failures

Outcomes	Erenumab 70 mg group (n = 49)	Placebo group (n = 27)	Number of trials included (total patients)	Combined risk ratio or mean difference (95% CI)	$I^2$
MMD	-1.8 (3.09), n = 49	-0.9 (3.29), n = 27	1 (n = 76)	-0.9 (-2.41 to 0.61) #	NA
MSMD	-1.1 (2.46), n = 49	-1 (2.38), n = 27	1 (n = 76)	-0.1 (-1.23 to 1.03) #	NA
50% response rate	13/49 (26.53%)	4/27 (14.81%)	1 (n = 76)	1.79 (0.65 to 4.95) *	NA
75% response rate	7/49 (14.29%)	1/27 (3.7%)	1 (n = 76)	3.86 (0.5 to 29.72) *	NA
AE	33/49 (67.35%)	19/27 (70.37%)	1 (n = 76)	0.96 (0.7 to 1.31) *	NA
SAE	2/49 (4.08%)	0/27 (0%)	1 (n = 76)	11.59 (0.02 to 6481.06) *	NA
Outcome data are mean (SD) or n/N (%). <b>NA</b> = not applicable; <b>MMD</b> = Monthly Migraine Days; <b>MSMD</b> = Monthly Acute Migraine-Specific Medication Treatment Days; <b>AE</b> = Adverse Events; <b>SAE</b> = Serious Adverse Events; <b>CI</b> = Confidence Interval. *Risk ratio (binary outcomes). #Mean difference (quantitative outcomes).					

Table 4  
Efficacy and safety of 140 mg erenumab in patients with  $\geq 2$  prior treatment failures

Outcomes	Erenumab 140 mg group (n = 177)	Placebo group (n = 151)	Number of trials included (total patients)	Combined risk ratio or mean difference (95% CI)	$I^2$
MMD	-2.36 (4.05), n = 176	-0.33 (4.2), n = 147	2 (n = 323)	-1.98 (-2.93 to -1.03) #	11.43
MSMD	-1.66 (2.3), n = 176	0.22 (3.19), n = 147	2 (n = 323)	-1.68 (-2.27 to -1.09) #	0
50% response rate	63/177 (35.59%)	21/151 (13.91%)	2 (n = 328)	2.39 (1.52 to 3.77) *	0
75% response rate	26/177 (14.69%)	6/151 (3.97%)	2 (n = 328)	3.32 (1.37 to 8.05) *	0
AE	100/177 (56.5%)	86/151 (56.95%)	2 (n = 328)	0.96 (0.79 to 1.15) *	0
SAE	5/177 (2.82%)	1/151 (0.66%)	2 (n = 328)	2.66 (0.29 to 24.79) *	0

Outcome data are mean (SD) or n/N (%). **NA** = not applicable; **MMD** = Monthly Migraine Days; **MSMD** = Monthly Acute Migraine-Specific Medication Treatment Days; **AE** = Adverse Events; **SAE** = Serious Adverse Events; **CI** = Confidence Interval. \*Risk ratio (binary outcomes). #Mean difference (quantitative outcomes).

## Discussion

Our study pooled five randomized clinical trials evaluating the safety and efficacy of erenumab for the treatment of episodic migraine. Our analysis showed that erenumab was efficacious and safe for the treatment of migraine. Furthermore, our study pooled both direct and indirect evidence with the Bayesian network meta-analysis method and demonstrated 140 mg erenumab outperforms 70 mg erenumab in multiple efficacy endpoints while related to the same risk for developing adverse events. In addition, our study demonstrated that 70 mg and 140 mg erenumab were associated with significantly reduced migraine frequency and improved functional outcome in patients with prior migraine treatment failures. The heterogeneity was low across all the primary outcomes, indicating a high level of clinical evidence. It is the first meta-analysis comparing the safety and efficacy of different doses of erenumab and the first meta-analysis to demonstrate the safety and efficacy of erenumab in patients with  $\geq 2$  prior migraine treatment failures.

Targeting CGRP is considered a breakthrough in migraine therapy in the past decades. Serum CGRP levels are elevated during migraine attacks[12]. Meanwhile, the infusion of human CGRP could induce headaches and migraine in migraineurs[13]. These evidences showed that CGRP might play an essential role in migraine attacks. CGRP receptors are widely distributed in both the central and peripheral nervous systems[14]. Since CGRP antagonists have a limited ability to cross the blood-brain barrier (BBB) and there is no increase in BBB permeability during a migraine attack[15], the brainstem, which has a high level of CGRP receptor expression and defective BBB, was considered the target of action of CGRP receptor antibodies[16]. Drugs targeting CGRP were developed based on the role of CGRP in the pathogenesis of migraine, which is highly selective for migraine treatment. CGRP antagonists and CGRP receptor monoclonal antibodies are mainly used as migraine prevention, and small-molecule CGRP antagonists are mainly used for acute management of migraine.

Although current evidence suggests the effectiveness of CGRP monoclonal antibodies in migraine treatment is not dramatically increased compared with traditional therapy, the monoclonal antibodies targeting CGRP and its receptors have their unique advantages in migraine treatment. Low compliance in patients with migraine with chronic prophylactic medication use is frequently reported[17]. Erenumab has been designed and modified to extend its circulating half-lives[18]. In clinical practice, it could be given once per month, which could potentially increase compliance among migraineurs. A cost-analysis based on US societal perspective Markov health state transition model has demonstrated the use of erenumab was associated with reduced migraine-related direct and indirect costs compared with supportive care[19].

As CGRP ligand could dilate blood vessels, the potential risk on the cardiovascular system caused by CGRP targeted therapies attracts much attention. A study conducted on human isolated cranial arteries has found that the use of erenumab was not associated with direct vasoconstriction and did not influence the effect of endogenous or exogenous vasoactive compounds[20]. A 12-week trial conducted by Tepper et al. confirmed that erenumab did not affect the blood pressure and 24-hour blood pressure changes in healthy volunteers[21]. No significant difference was found in the emergence of vascular adverse events between the erenumab group and the placebo group in the short-term migraine treatment phase[22]. In addition, a study conducted in patients with stable angina has found that the use of erenumab had no effect on exercise time[23]. Although these studies have demonstrated CGRP targeted therapies are not likely to induce severe adverse events caused by vasoconstriction, CGRP may play a more critical role in the change of vascular tension in hypertensive rats than in normotensive rats[24]. Hence, future researches are still needed to evaluate the long-term use of erenumab in patients with cardiovascular risk or hypertension.

Our study mainly pooled short-term placebo-controlled trials for episodic migraineurs. Erenumab also showed its effect on chronic migraine patients[25]. So far, a handful of studies have been conducted to evaluate the long-term use of erenumab. An open-label study evaluating long-term safety and efficacy of erenumab in patients with episodic migraine found that erenumab use is related to improved function and a favorable safety and tolerability profile[26]. The long-term adverse effects of erenumab include injection-site reactions, constipation, and muscle spasm[27]. In another similar long-term study, erenumab was found to be safe and well-tolerated, and the adverse events were considered consistent with shorter-term placebo treatment[28]. Furthermore, evidence suggests that the long-term use of erenumab increased the conversion from chronic migraine to episodic migraine[29], especially 140 mg dose[30]. Besides, a previous study reported that erenumab use was associated with a higher response rate in patients who had a high susceptibility to migraine induction by CGRP[31].

As a preventive therapy, erenumab is likely to be prescribed for long term use. Thus, the cross-talk of erenumab with other commonly-used drugs is another concern for physicians. From the pharmacokinetics perspective, as mAbs are eliminated via catabolic pathways, they may not compete directly with other small molecule drugs that are mainly eliminated via hepatic, renal, or biliary processes[32]. A study conducted in 2017 found that subcutaneous erenumab did not influence the effect of estrogen/progestin combination oral contraceptives among healthy females[33]. A placebo-controlled trial investigating co-administration of erenumab 140 mg and sumatriptan 12 mg have found no additional effect on averages of mean arterial pressure or on the pharmacokinetics of sumatriptan[34].

Optimal management of chronic migraine patients with concurrent overuse of acute medications poses a challenge for clinicians[35]. Results from clinical trials have demonstrated that erenumab is effective in patients with medication overuse[36–38]. In a post-hoc analysis, erenumab showed comparable efficacy between medication over-users and the non-medication overuse group[39].

Preventive treatment of migraine is an essential component of migraine management. To date, multiple drugs have been applied to the preventive treatment of migraine, including beta-blockers, topiramate, amitriptyline, and onabotulinumtoxinA[40]—however, none of these drugs highly selective to pharmacological targets on the migraine pathogenesis pathway which would lead to disturbing adverse events. Propranolol and timolol are the only beta-blockers approved by the FDA for migraine prevention[41]. Frequently reported adverse events for beta-blockers include fatigue, exercise intolerance, and orthostatic hypotension. Besides, beta-blockers are contraindicated in patients with decompensated heart failures and patients with asthma. Valproate and topiramate are frequently used as migraine preventive therapy. Previous evidence suggests about 50% of patients who received valproate and topiramate achieve a 50% reduction in headache frequency[42]. However, for the safety outcomes, the use of valproate and topiramate is related to increased adverse events. Commonly reported adverse events for valproate including nausea, fatigue, tremor, weight gain, and hair loss, and topiramate commonly causes paresthesias, fatigue, cognitive impairment, taste perversion, weight loss, and nephrolithiasis[43]. When compared with valproate and topiramate, erenumab is related to comparable efficacy outcomes and is not associated with increased risk for developing adverse effects. Amitriptyline is the only tricyclic antidepressant shown to be effective for migraine prevention in clinical trials, but it often causes sedation, dry mouth, and weight gain[44]. To sum up, although no clinical trial has been conducted to evaluate the safety and efficacy of erenumab versus other traditional methods, current evidence indirect comparison suggests erenumab outperform these traditional migraine preventive drugs[45]. Pericranial intramuscular injections of onabotulinumtoxinA (Botox) is another FDA-approved novel therapy for the prevention of headaches in adults with chronic migraine[46]. However, until now, the effectiveness of Botox in episodic migraineurs remains uncertain on account of the low quality of limited evidence[47].

Our study had a few limitations. First, although our study included five multicenter randomized trials that have a low risk for bias, the heterogeneity of overall functional improvement in the pair-wise meta-analysis was considerably high, indicating a low level of clinical evidence. Second, all the included clinical trials were limited to short-term use; further pooled analysis based on long-term, or real-world studies are needed. Third, our analysis of 70 mg erenumab in patients with previous treatment failure only includes one trial with an insufficient sample size. Further studies are still needed to provide more robust evidence.

## Conclusion

In this systematic review and meta-analysis, the use of erenumab given subcutaneously once per month as a preventive treatment for episodic migraine in adults led to a significantly decreased MMD and MSMD and increased 50% response and was not associated with increased risk for developing adverse events compared with placebo. Our results from network meta-analysis suggest that 140 mg erenumab was related to better safety outcomes compared with 70 mg. Furthermore, current evidence suggests that 140 mg erenumab was effective in patients with previous migraine treatment failure.

## Abbreviations

CGRP: calcitonin gene-related peptide; CI: confidence intervals; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCTs: randomized clinical trials; RR: relative risk; MMD: monthly migraine days; MSMD: monthly acute migraine-specific medication treatment days; MPFID-EA: migraine physical function impact diary-everyday activities; MPFID-PI: migraine physical function impact diary-physical impairment; HIT: headache impact test; SAE: serious adverse events; TEAE: treatment-emergent adverse events.

# Declarations

## Ethics Approval and consent to participate

Not Applicable

## Consent for Publication

Not Applicable

## Data Availability

All the additional data involved in the study was provided in the supplement file.

## Conflict of interest statement

The authors declare that they have no conflict of interest.

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We are thankful to all participants from the team of neurosurgical study.

## Author contributions

YY performed the statistical analysis, and drafted the first manuscript, MC and Zilan Wang contributed in the study selection, risk of bias assessment, data extraction process. Zilan Wang, YS, FJ contributed to the literature review. YY, ZC, and Zhong Wang designed the study and completed the final manuscript. All authors read and approved the final version of this manuscript.

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# References

1. Lattanzi S, Brigo F, Trinka E, Vernieri F, Corradetti T, Dobran M, Silvestrini M (2019) Erenumab for Preventive Treatment of Migraine: A Systematic Review and Meta-Analysis of Efficacy and Safety. *Drugs* 79:417–431
2. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 28:183–187
3. Burch R, Rayhill M (2018) New preventive treatments for migraine. *BMJ* 361:k2507
4. Traynor K (2018) FDA approves licensing of erenumab-aooe to prevent migraine. *Am J Health Syst Pharm* 75:929–930
5. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj* 339:b2700
6. Sakai F, Takeshima T, Tatsuoka Y et al (2019) A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults. *Headache* 59:1731–1742
7. Dodick DW, Ashina M, Brandes JL et al (2018) ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia: an international journal of headache* 38:1026–1037
8. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, Klatt J (2018) Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet* 392:2280–2287
9. Goadsby PJ, Reuter U, Hallstrom Y et al (2017) A Controlled Trial of Erenumab for Episodic Migraine. *N Engl J Med* 377:2123–2132
10. Sun H, Dodick DW, Silberstein S et al (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol* 15:382–390
11. Goadsby PJ, Paemeleire K, Broessner G, et al. Efficacy and safety of erenumab (AMG334) in episodic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia: an international journal of headache* 2019
12. Goadsby PJ, Edvinsson L, Ekman R (1988) Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. *Ann Neurol* 23:193–196
13. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J (2002) CGRP may play a causative role in migraine. *Cephalalgia: an international journal of headache* 22:54–61

14. Diener HC (2014) CGRP as a new target in prevention and treatment of migraine. *Lancet Neurol* 13:1065–1067
15. Schankin CJ, Maniyar FH, Seo Y et al (2016) Ictal lack of binding to brain parenchyma suggests integrity of the blood-brain barrier for 11C-dihydroergotamine during glyceryl trinitrate-induced migraine. *Brain* 139:1994–2001
16. Raffaelli B, Reuter U (2018) The Biology of Monoclonal Antibodies: Focus on Calcitonin Gene-Related Peptide for Prophylactic Migraine Therapy. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics* 15:324–335
17. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB (2015) Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia: an international journal of headache* 35:478–488
18. Jain S, Yuan H, Spare N, Silberstein SD (2018) Erenumab in the treatment of migraine. *Pain Manag* 8:415–426
19. Lipton RB, Brennan A, Palmer S et al (2018) Estimating the clinical effectiveness and value-based price range of erenumab for the prevention of migraine in patients with prior treatment failures: a US societal perspective. *Journal of medical economics* 21:666–675
20. Ohlsson L, Haanes KA, Kronvall E, Xu C, Snellman J, Edvinsson L (2019) Erenumab (AMG 334), a monoclonal antagonist antibody against the canonical CGRP receptor, does not impair vasodilatory or contractile responses to other vasoactive agents in human isolated cranial arteries. *Cephalalgia: an international journal of headache* 39:1745–1752
21. Tepper SJ, Pascual J, Reuter U et al Analysis of blood pressure following short-term and long-term treatment with erenumab. *Journal of Headache and Pain* 2017; 18
22. Kudrow D, Pascual J, Winner PK et al (2020) Vascular safety of erenumab for migraine prevention. *Neurology* 94:e497–e510
23. Depre C, Antalik L, Starling A, Koren M, Eisele O, Lenz RA, Mikol DD (2018) A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina. *Headache* 58:715–723
24. Balfagon G, Marquez-Rodas I, Alvarez Y, Alonso MJ, Cachofeiro V, Salasces M, Lahera V (2004) Aldosterone modulates neural vasomotor response in hypertension: role of calcitonin gene-related peptide. *Regul Pept* 120:253–260
25. Tepper S, Ashina M, Reuter U et al (2017) Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 16:425–434
26. Ashina M, Dodick D, Goadsby PJ et al (2017) Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. *Neurology* 89:1237–1243
27. Ashina M, Kudrow D, Reuter U et al (2019) Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: A pooled analysis of four placebo-controlled trials with long-term extensions. *Cephalalgia: an international journal of headache* 39:1798–1808
28. Ashina M, Goadsby PJ, Reuter U et al (2019) Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. *Cephalalgia: an international journal of headache* 39:1455–1464
29. Lipton RB, Tepper SJ, Silberstein S et al Conversion from chronic to episodic migraine with erenumab, a specific inhibitor of the calcitonin gene-related peptide receptor. *Journal of headache and pain* 2018; 19
30. Lipton R, Tepper S, Silberstein S et al Conversion from chronic migraine (CM) to episodic migraine (EM) with long-term erenumab treatment. *Neurology* 2019; 92
31. Christensen CE, Younis S, Deen M, Khan S, Ghanizada H, Ashina M. Migraine induction with calcitonin gene related peptide in patients from erenumab trials. *Journal of headache and pain* 2018; 19
32. Zhou H, Mascelli MA (2011) Mechanisms of monoclonal antibody-drug interactions. *Annu Rev Pharmacol Toxicol* 51:359–372
33. Xu Y, Gabriel K, Wang Y et al (2019) A Multi-Center, Open-Label, Pharmacokinetic Drug Interaction Study of Erenumab and a Combined Oral Contraceptive in Healthy Females. *CNS Drugs* 33:513–522
34. de Hoon J, Van Hecken A, Vandermeulen C et al (2019) Phase 1, randomized, parallel-group, double-blind, placebo-controlled trial to evaluate the effects of erenumab (AMG 334) and concomitant sumatriptan on blood pressure in healthy volunteers. *Cephalalgia: an international journal of headache* 39:100–110
35. Dodick DW. Migraine (2018) *Lancet* 391:1315–1330
36. Diener HC, Ashina M, Brandes J et al (2017) Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse. *European journal of neurology* 24:472-
37. Dodick D, Tepper S, Diener HC et al (2019) Efficacy of erenumab in chronic migraine patients with medication overuse and prior preventive treatment failure. *European journal of neurology* 26:811-
38. Tepper S, Diener HC, Ashina M et al (2017) Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse. *Schmerz (berlin germany)* 31:S66-
39. Tepper SJ, Diener HC, Ashina M et al (2019) Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. *Neurology* 92:e2309–e2320
40. Dodick DW, Turkel CC, DeGryse RE et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 50:921–936

41. Loder E, Burch R, Rizzoli P (2012) The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache* 52:930–945
42. Mulleners WM, McCrory DC, Linde M (2015) Antiepileptics in migraine prophylaxis: an updated Cochrane review. *Cephalalgia: an international journal of headache* 35:51–62
43. Prevention of Migraine (2017) *Jama* 317:2230–2231
44. Dodick DW, Freitag F, Banks J et al (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther* 31:542–559
45. Lin Y, Chen D, Xu D, Liu L (2018) Efficacy and safety of erenumab in the preventive treatment of migraine in adults: a systematic review. *Chinese Journal of Contemporary Neurology Neurosurgery* 18:647–653
46. Tassorelli C, Sances G, Avenali M et al (2018) Botulinum toxin for chronic migraine: Clinical trials and technical aspects. *Toxicon* 147:111–115
47. Herd CP, Tomlinson CL, Rick C et al (2018) Botulinum toxins for the prevention of migraine in adults. *Cochrane Database Syst Rev* 6: Cd011616

## Figures

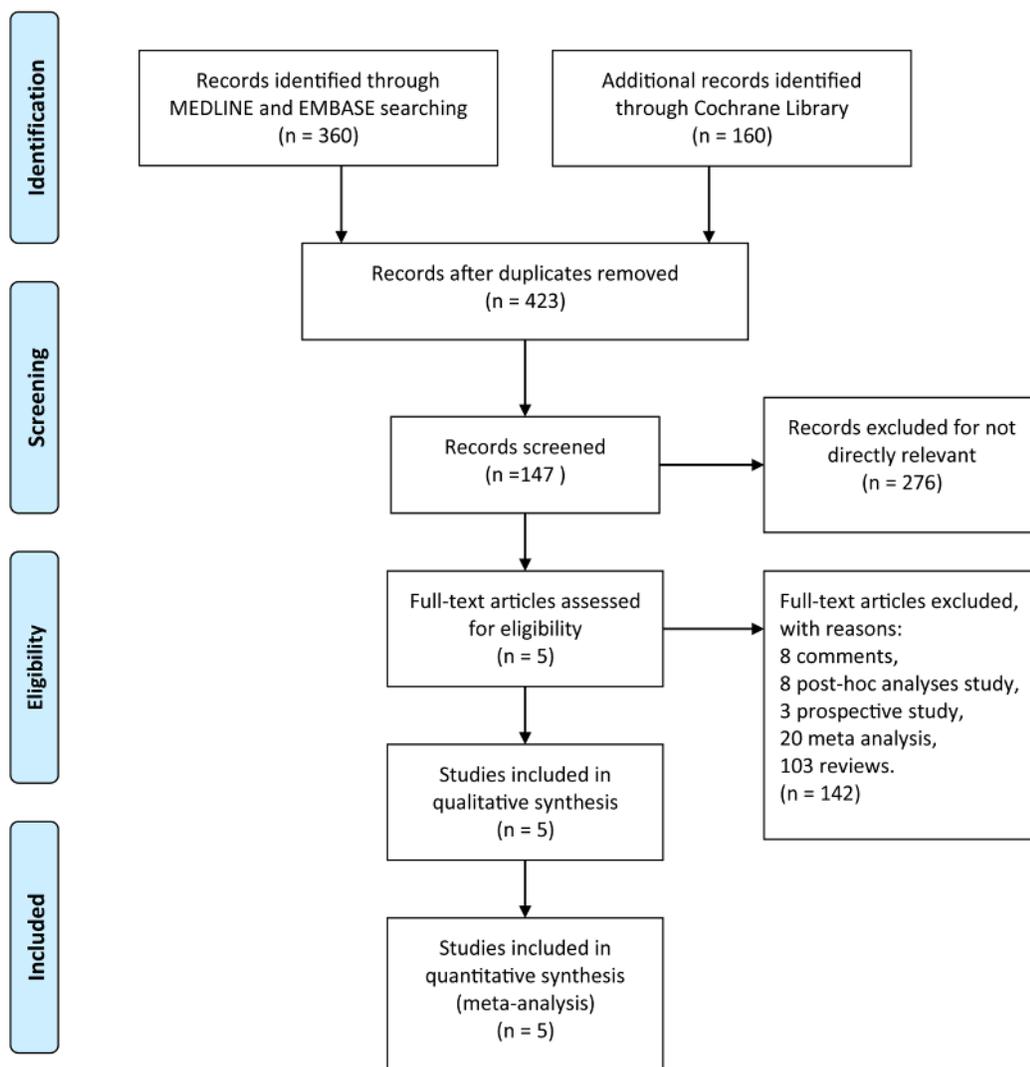


Figure 1

PRISMA Flow Diagram of study inclusion process

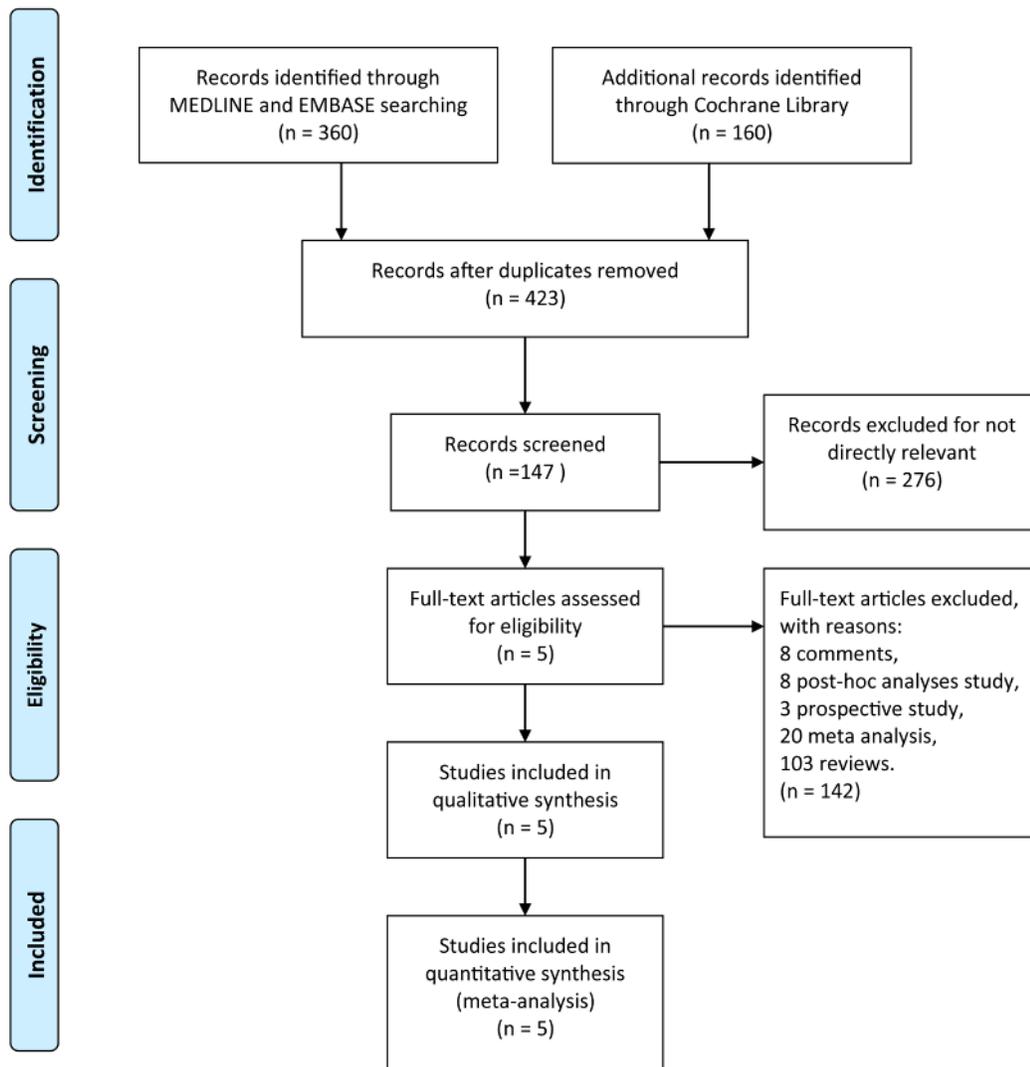


Figure 1

PRISMA Flow Diagram of study inclusion process

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dodick 2018	+	+	+	+	+	?	+
Goadsby 2017	+	+	+	+	-	+	+
Reuter 2018	+	+	+	+	+	+	+
Sakai 2019	+	+	+	+	+	+	+
SUN 2016	+	+	+	+	+	+	?

Figure 2

Summary of risk of bias. Green low risk of bias, yellow unclear risk of bias, red high risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dodick 2018	+	+	+	+	+	?	+
Goadsby 2017	+	+	+	+	-	+	+
Reuter 2018	+	+	+	+	+	+	+
Sakai 2019	+	+	+	+	+	+	+
SUN 2016	+	+	+	+	+	+	?

Figure 2

Summary of risk of bias. Green low risk of bias, yellow unclear risk of bias, red high risk of bias

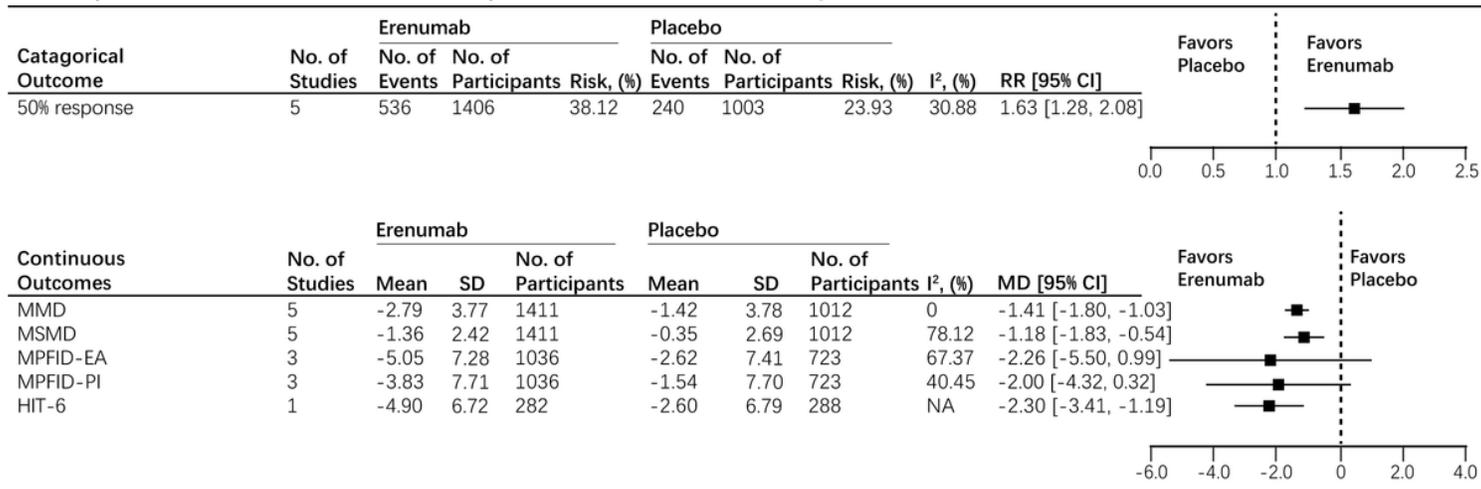
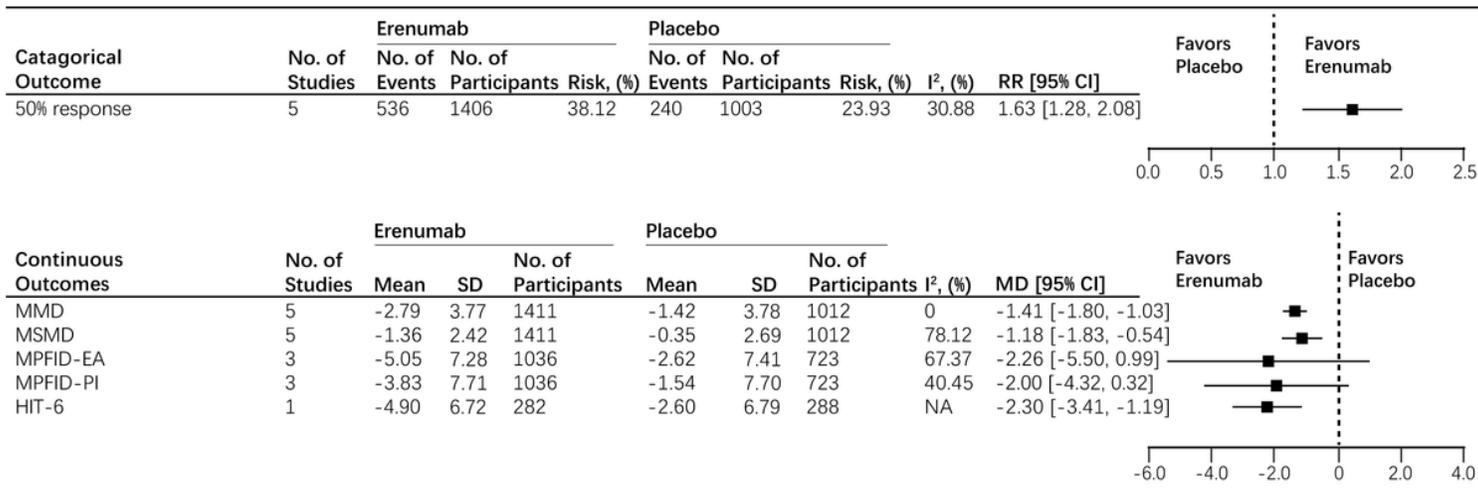
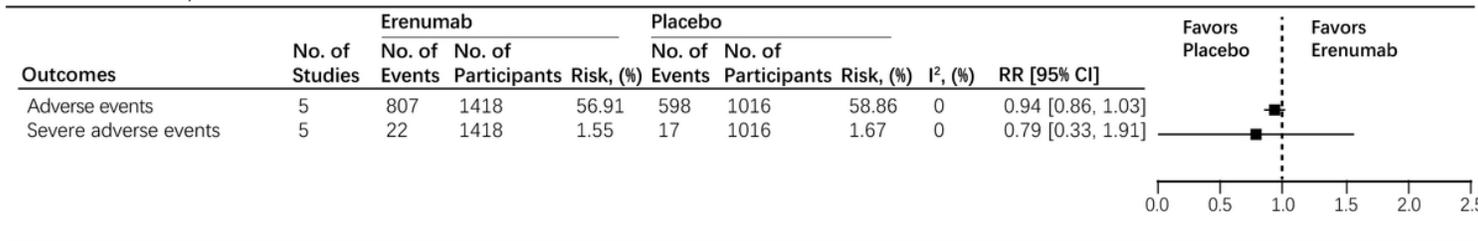


Figure 3

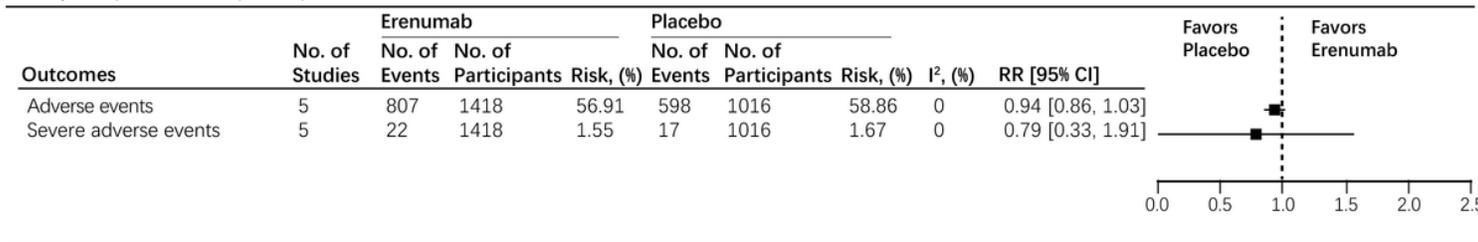
Efficacy endpoints in all participants. MMD=Monthly Migraine Days; MSMD=Monthly Acute Migraine-Specific Medication Treatment Days; MPFID-EA=Migraine Physical Function Impact Diary-Everyday Activities; MPFID-PI=Migraine Physical Function Impact Diary-Physical Impairment; HIT=Headache Impact Test; CI=Confidence Interval; RR=Risk Ratio; MD=Mean Difference; SD=Standard Difference.



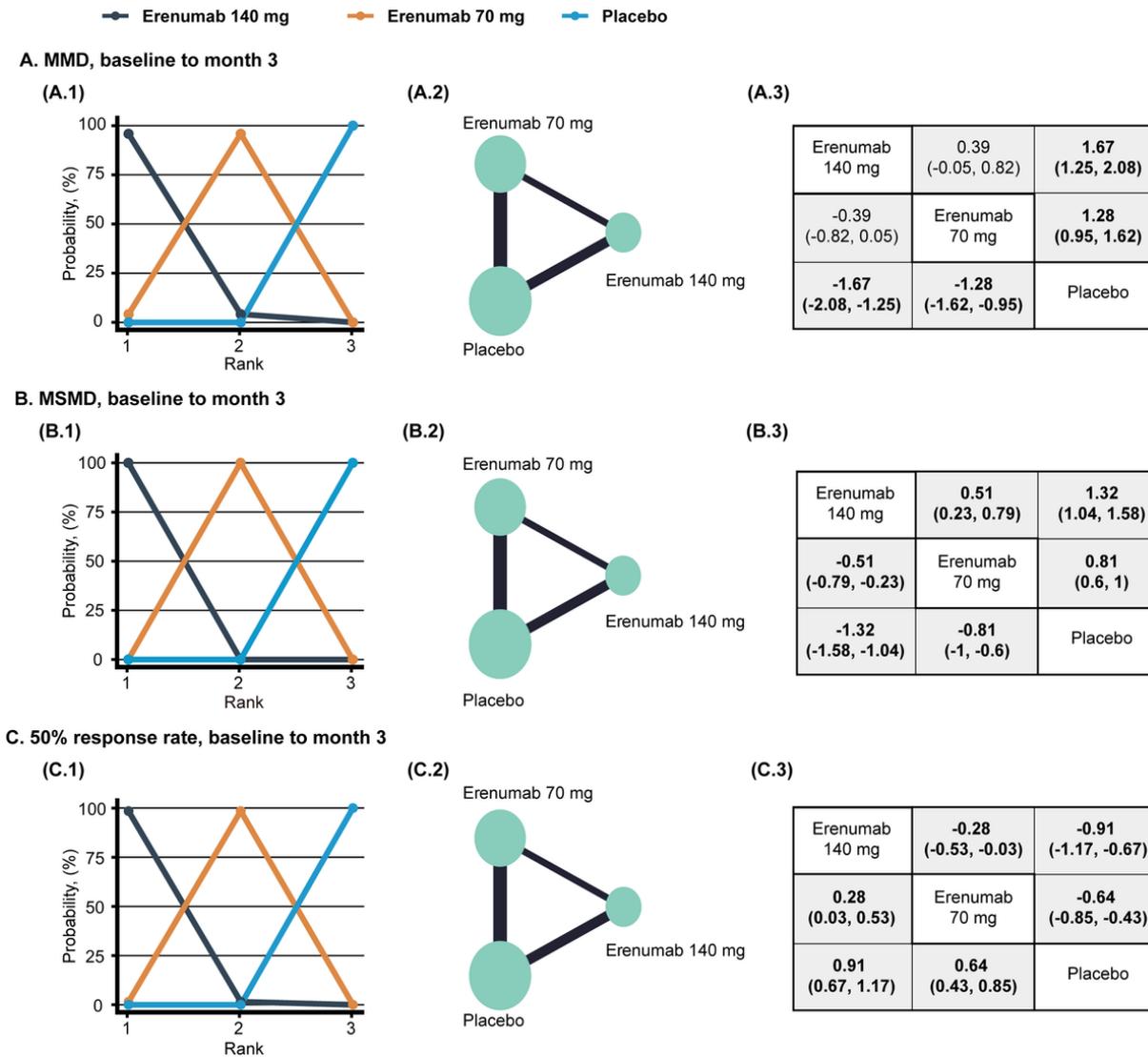
**Figure 3**  
 Efficacy endpoints in all participants. MMD=Monthly Migraine Days; MSMD=Monthly Acute Migraine-Specific Medication Treatment Days; MPPID-EA=Migraine Physical Function Impact Diary-Everyday Activities; MPPID-PI=Migraine Physical Function Impact Diary-Physical Impairment; HIT=Headache Impact Test; CI=Confidence Interval; RR=Risk Ratio; MD=Mean Difference; SD=Standard Difference.



**Figure 4**  
 Safety endpoints in all participants. CI=Confidence Interval; RR=Risk Ratio.

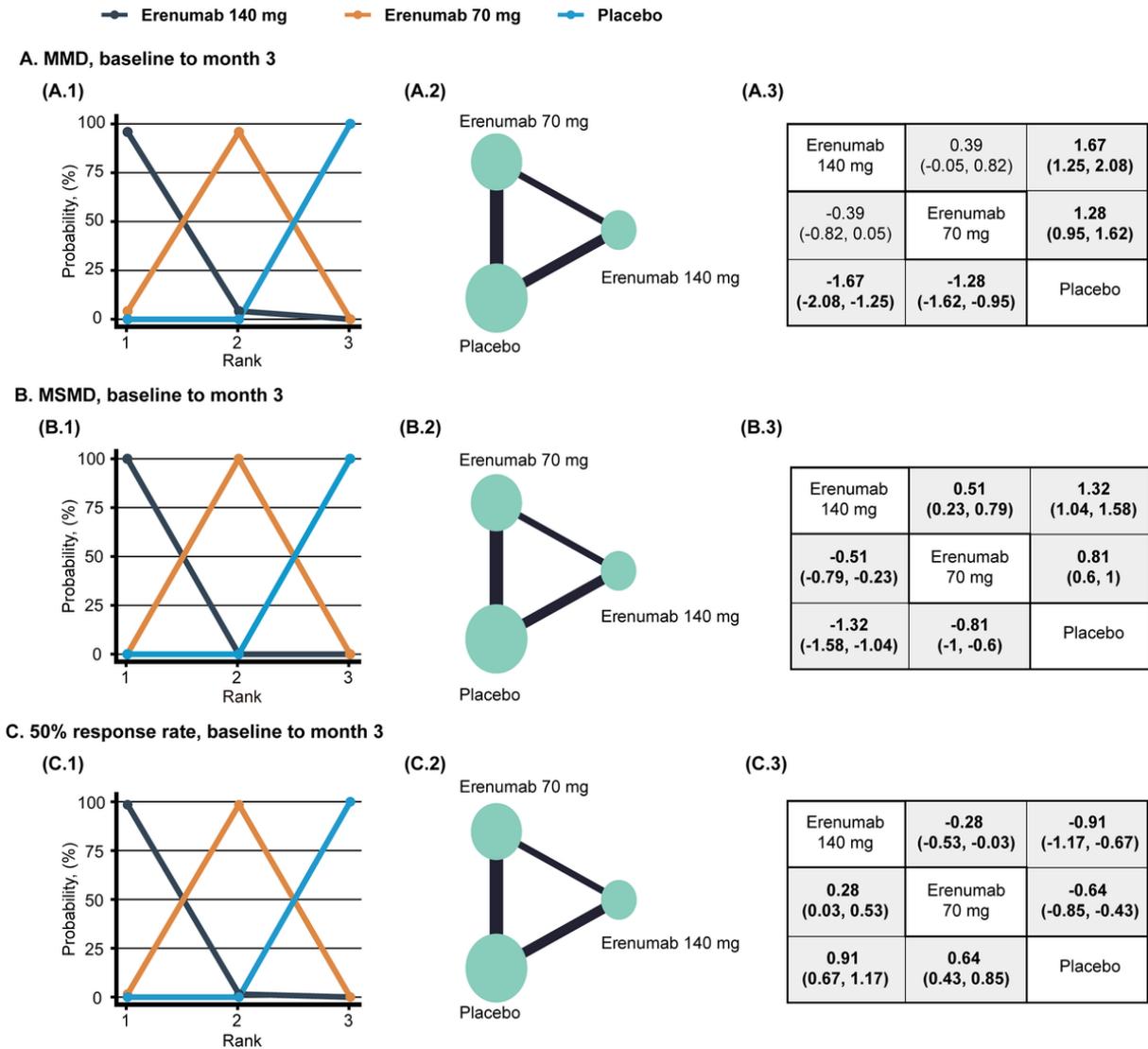


**Figure 4**  
 Safety endpoints in all participants. CI=Confidence Interval; RR=Risk Ratio.



**Figure 5**

Network diagrams of comparisons on reduced migraine frequency in the placebo, erenumab 70mg, erenumab 140mg groups of patients with episodic migraine. (1) Rank probability plot. (2) Network diagrams of comparisons. The edges represent direct comparisons observed in the included trials. The size of the nodes was proportional to the number of patients assigned to the treatment protocol, and the thickness of the edges was proportional to the sample size of the included studies. (3) Mean difference/ log odds ratio (95% credible intervals) between column and row treatment regimens. Statistically significant results, where the 95% credible interval does not include 0, are in bold. A, monthly migraine days (MMD) (Mean Difference). B, monthly acute migraine-specific medication treatment days (MSMD) (Mean Difference). C, 50% response rate (Log Odds Ratio).



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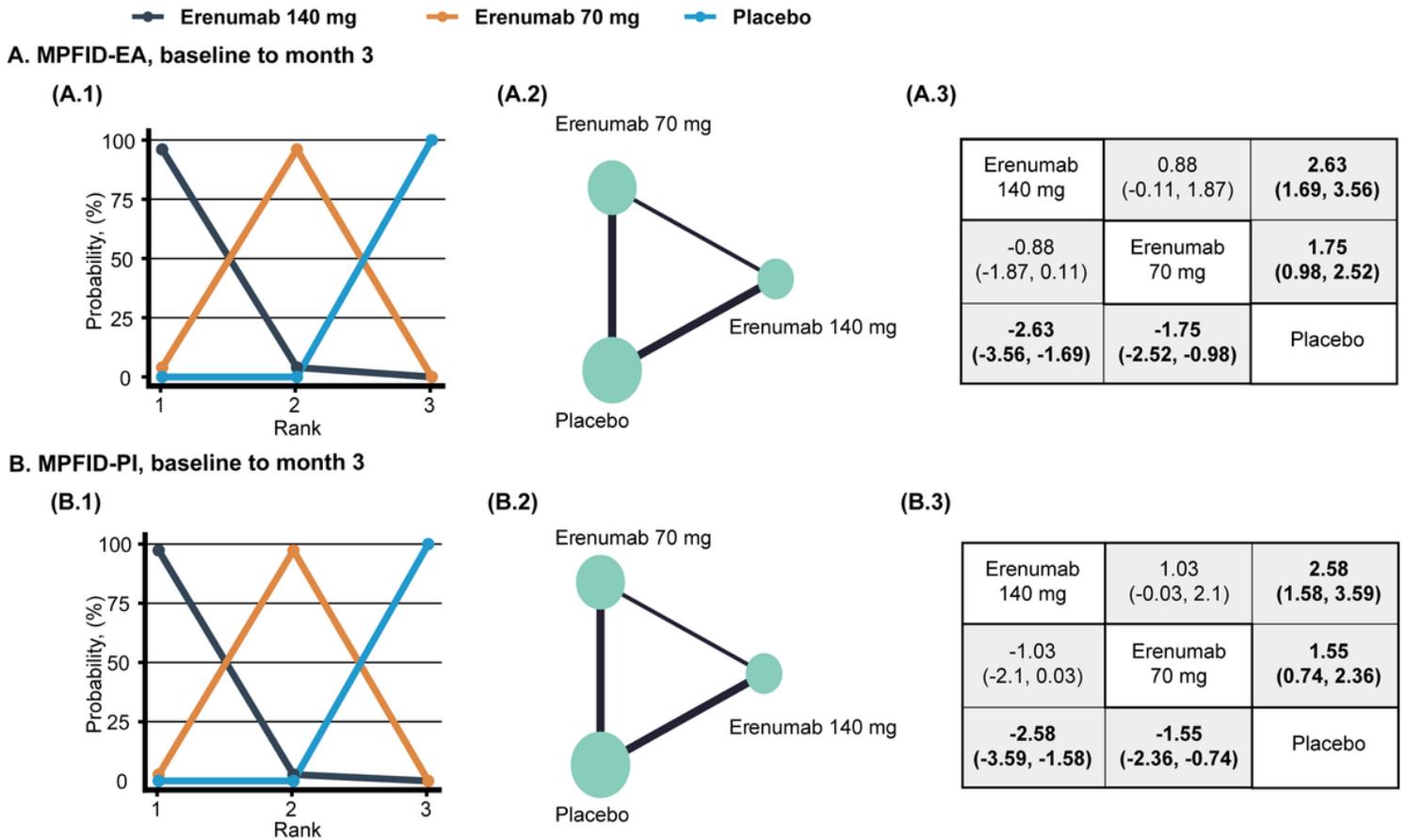
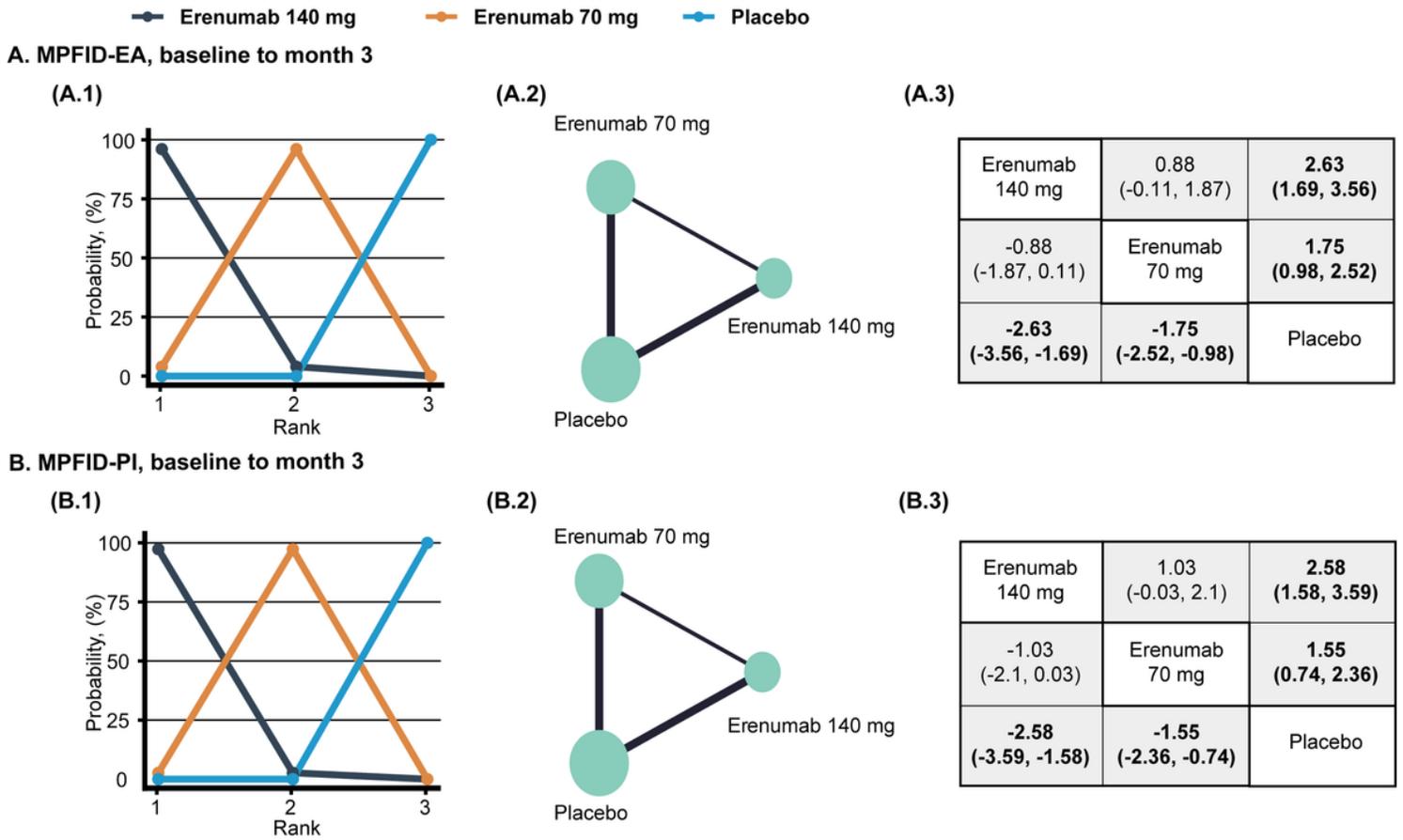


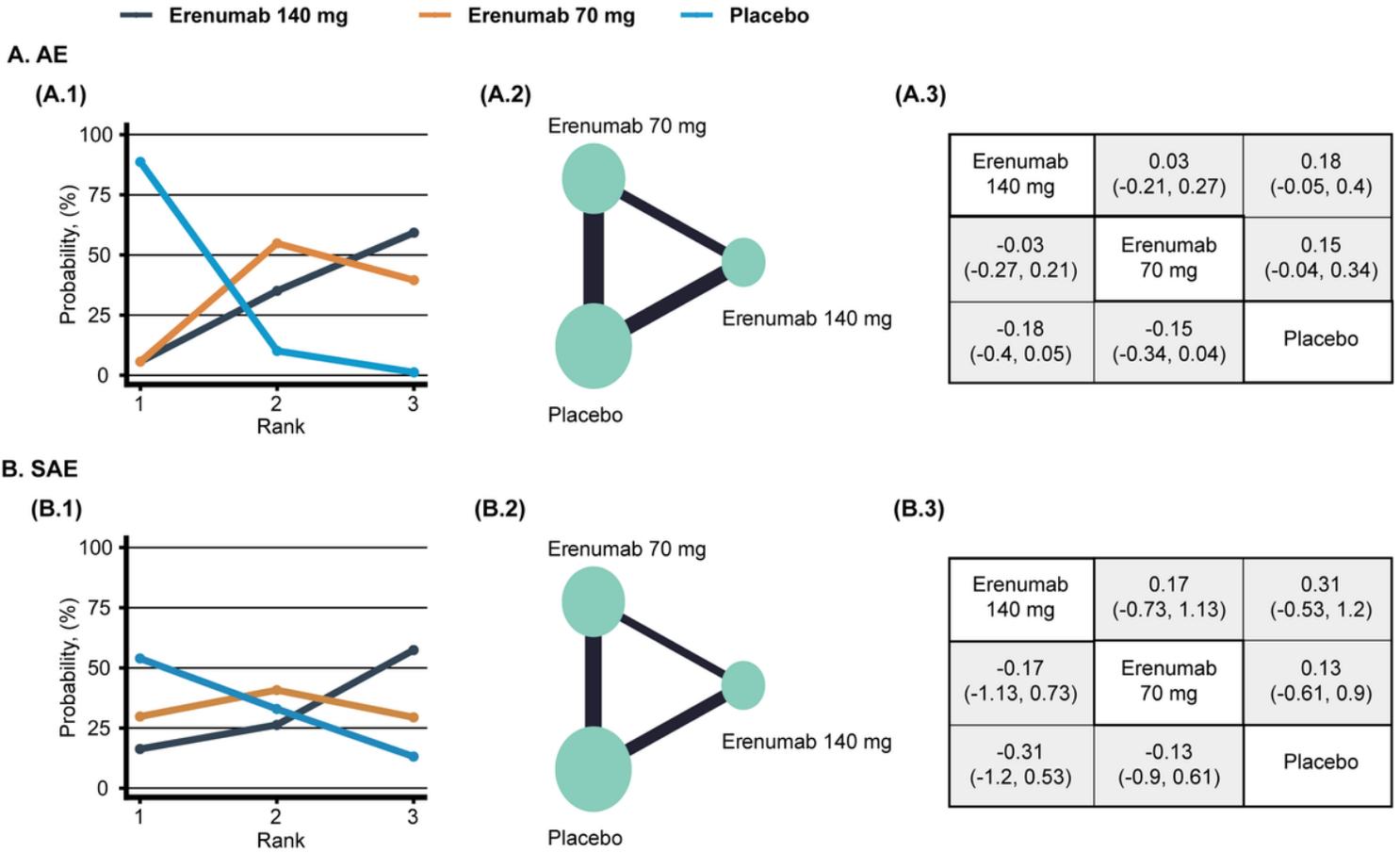
Figure 6

Network diagrams of comparisons on improved functional outcome in the placebo, erenumab 70mg, erenumab 140mg groups of patients with episodic migraine. (1) Rank probability plot. (2) Network diagrams of comparisons. The edges represent direct comparisons observed in the included trials. The size of the nodes was proportional to the number of patients assigned to the treatment protocol, and the thickness of the edges was proportional to the sample size of the included studies. (3) Mean difference (95% credible intervals) between column and row treatment regimens. Statistically significant results, where the 95% credible interval does not include 0, are in bold. A, migraine physical function impact diary-everyday activities (MPFID-EA) (Mean Difference). B, migraine physical function impact diary-physical impairment (MPFID-PI) (Mean Difference).



**Figure 6**

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**Figure 7**  
 Network diagrams of comparisons on safety endpoints in the placebo, erenumab 70mg, erenumab 140mg groups of patients with episodic migraine. (1) Rank probability plot. (2) Network diagrams of comparisons. The edges represent direct comparisons observed in the included trials. The size of the nodes was proportional to the number of patients assigned to the treatment protocol, and the thickness of the edges was proportional to the sample size of the included studies. (3) Log odds ratio (95% credible intervals) between column and row treatment regimens. Statistically significant results, where the 95% credible interval does not include 0, are in bold. A, adverse events (AE) (Log Odds Ratio). B, serious adverse events (SAE) (Log Odds Ratio).

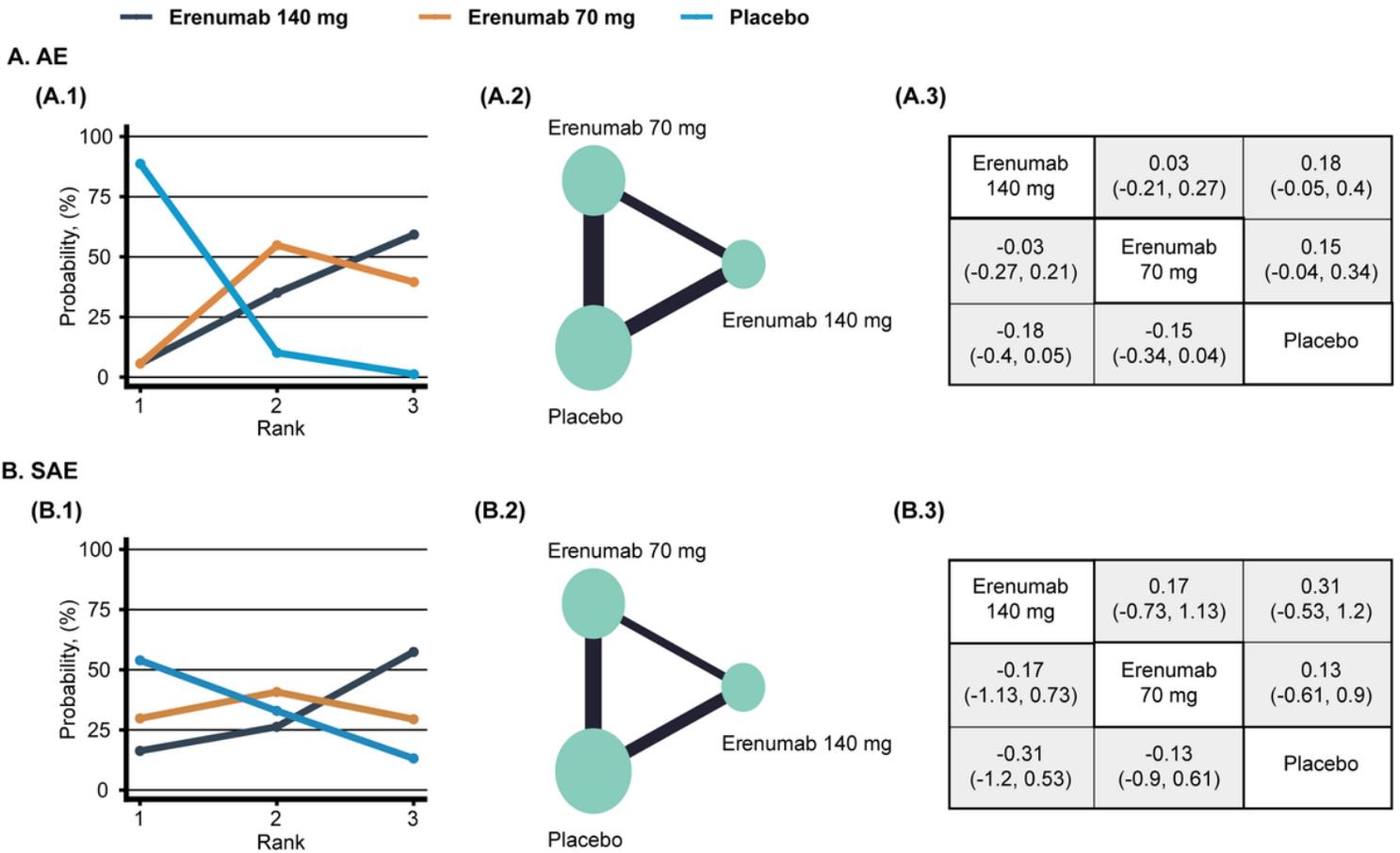


Figure 7

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