# Supplementary Material

# Optimal Dose of Erenumab for Preventive Treatment of Episodic Migraine: A Systematic Review and Meta-Analysis

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### S1. Full electronic search strategy

((((“Migraine”) OR "Migraine Disorders") OR "Migraine without Aura") OR "Migraine with Aura")AND ((((((Erenumab) OR AMG334) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial ) NOT (animals NOT humans).

### S2. Bayesian ranking results of network meta-analysis

| Treatment | Rank of possibility (%) (The first sensitivity analysis) | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| **The reduction of MMD from baseline** | | | |
| Erenmab 140 mg | **96** | 4 | 0 |
| Erenmab 70 mg | 4 | 96 | 0 |
| Placebo | 0 | 0 | **100** |
| **The reduction of MSMD from baseline** | | | |
| Erenmab 140 mg | **100** | 0 | 0 |
| Erenmab 70 mg | 0 | 100 | 0 |
| Placebo | 0 | 0 | **100** |
| **The rate of patients achieving ≥50% reduction in MMD** | | | |
| Erenmab 140 mg | **98** | 2 | 0 |
| Erenmab 70 mg | 2 | 98 | 0 |
| Placebo | 0 | 0 | **100** |
| **The reduction of MPFID-EA from baseline** | | | |
| Erenumab 140 mg | **96** | 4 | 0 |
| Erenumab 70 mg | 4 | 96 | 0 |
| Placebo | 0 | 0 | **100** |
| **The reduction of MPFID-PI from baseline** | | | |
| Erenumab 140 mg | **97** | 3 | 0 |
| Erenumab 70 mg | 3 | 97 | 0 |

| | | | |
|---|---|---|---|
| Placebo | 0 | 0 | **100** |
| **The frequency of AE** | | | |
| Erenumab 140 mg | 6 | 35 | **59** |
| Erenumab 70 mg | 5 | 55 | 40 |
| Placebo | **89** | 10 | 1 |
| **The frequency of SAE** | | | |
| Erenumab 140 mg | 16 | 26 | **58** |
| Erenumab 70 mg | 30 | 41 | 29 |
| Placebo | **54** | 33 | 13 |

The number in each cell represents the posterior probability of the row-defining treatment being ranked at the column-defining position. The numbers with biggest probability of ranking first and last are in bold and underscored.

**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; **AE**=Adverse Events; **SAE**=Serious Adverse Events.

## S3. Node-splitting analysis of inconsistency

| Outcome | Direct effect | Indirect effect | Network effect | P value |
|---|---|---|---|---|
| **MMD** | 0.24 [-1.09, 1.44] | 0.5 [-1.79, 2.78] | 0.36 [-0.32, 0.99] | 0.79 |
| **MSMD** | 0.28 [-0.93, 1.31] | 1.06 [-1, 2.97] | 0.46 [-0.32, 1.14] | 0.33 |
| **50% Responds** | -0.21 [-0.88, 0.51] | -0.35 [-1.6, 0.93] | -0.27 [-0.63, 0.11] | 0.79 |
| **MPFID-EA** | 0.39 [-4.71, 5.49] | 2.88 [-4.43, 10.31] | 1 [-1.99, 4.28] | 0.45 |
| **MPFID-PI** | 0.74 [-3.72, 5.29] | 2.2 [-4.42, 8.78] | 1.09 [-1.41, 3.77] | 0.61 |
| **AE** | 0.06 [-0.3, 0.43] | -0.14 [-0.84, 0.56] | 0.02 [-0.28, 0.32] | 0.59 |
| **SAE** | 0.27 [-1.48, 1.99] | -0.85 [-4.98, 2.99] | 0.16 [-1.17, 1.53] | 0.58 |

**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; **AE**=Adverse Events; **SAE**=Serious Adverse Events.

## S4. Comparisons of the fit of fixed and random models using deviance information criteria (DIC)

| Outcome | Model | DIC | Accepted Model |
|---|---|---|---|
| **MMD** | Random | 19.2647045 | Fixed |
| | Fixed | 17.628238 | |
| **MSMD** | Random | 23.2069084 | Random |
| | Fixed | 25.5114377 | |
| **50% Responds** | Random | 18.3565065 | Fixed |
| | Fixed | 16.5591554 | |
| **MPFID-EA** | Random | 13.6663505 | Fixed |
| | Fixed | 13.5668407 | |
| **MPFID-PI** | Random | 12.518146 | Fixed |
| | Fixed | 11.0484003 | |
| **AE** | Random | 18.5301946 | Fixed |
| | Fixed | 17.3593887 | |

| | | | |
|---|---|---|---|
| **SAE** | Random | 20.714574 | Fixed |
| | Fixed | 19.7241294 | |

The DIC is a Bayesian model evaluation criterion that measures model fit adjusted with complexity of the model; smaller DIC values correspond to more preferable models.

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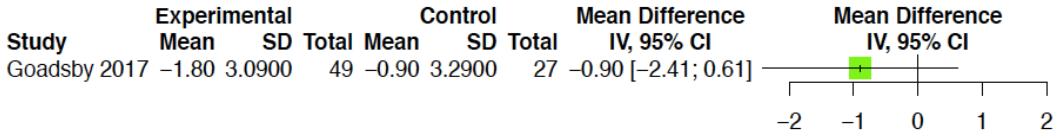
## S5. Convergence diagnostics

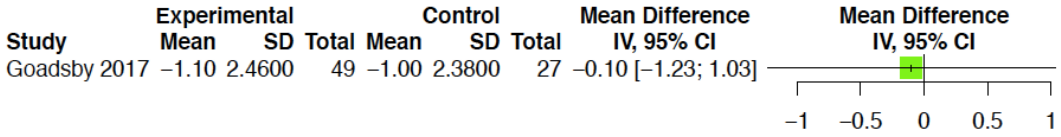
| Outcome | Convergence |
|---|---|
| **MMD** | 1.000212031 |
| **MSMD** | 1.000144947 |
| **50% Responds** | 1.000041676 |
| **MPFID-EA** | 1.000310727 |
| **MPFID-PI** | 1.000257072 |
| **AE** | 1.000050375 |
| **SAE** | 1.000377173 |

**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; **AE**=Adverse Events; **SAE**=Serious Adverse Events.

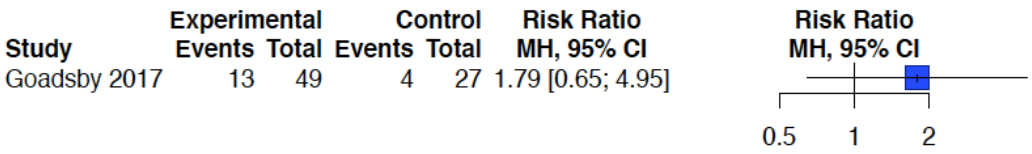
## S6. Forest plot of monthly migraine days; 70mg erenumab versus placebo; CI, confidence interval



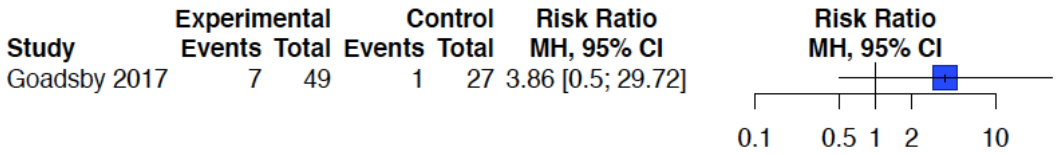

## S7. Forest plot of monthly acute migraine-specific medication treatment days; 70mg erenumab versus placebo; CI, confidence interval



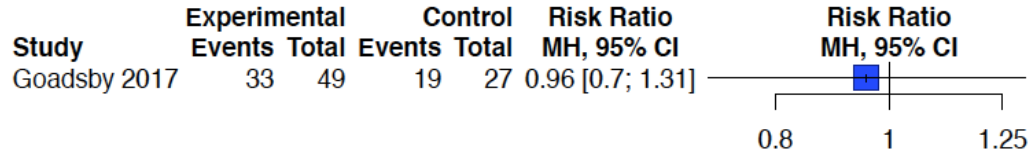

## S8. Forest plot of 50% response rate; 70mg erenumab versus placebo; CI, confidence interval



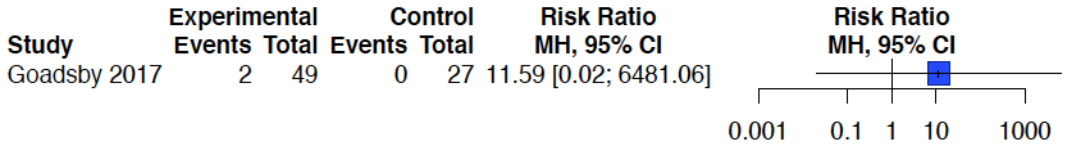
**S9. Forest plot of 75% response rate; 70mg erenumab versus placebo; CI, confidence interval**



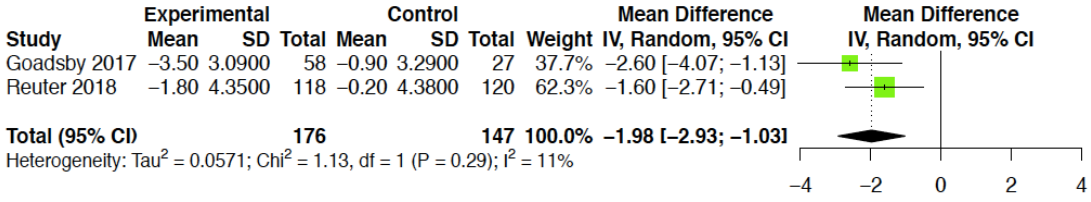

**S10. Forest plot of adverse events; 70mg erenumab versus placebo; CI, confidence interval**



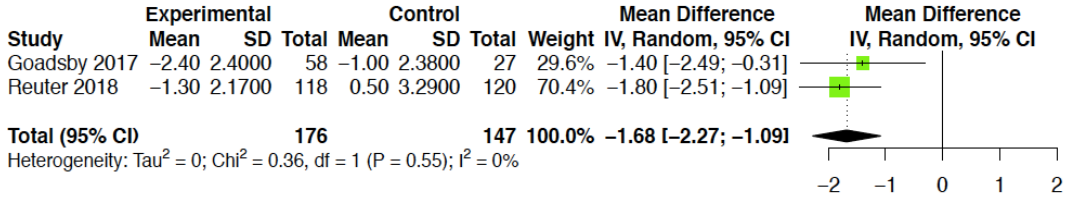

**S11. Forest plot of serious adverse events; 70mg erenumab versus placebo; CI, confidence interval**



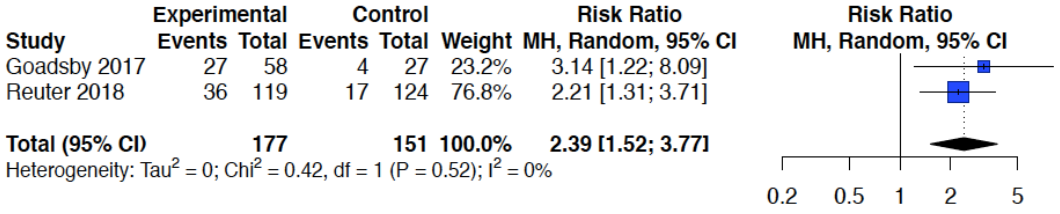

**S12. Forest plot of monthly migraine days; 140mg erenumab versus placebo; CI, confidence interval**



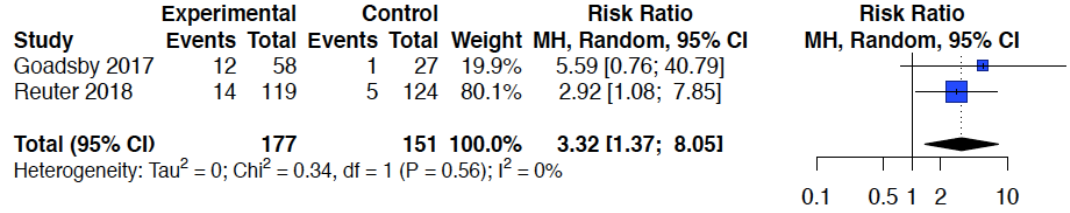

**S13. Forest plot of monthly acute migraine-specific medication treatment days; 140mg erenumab versus placebo; CI, confidence interval**



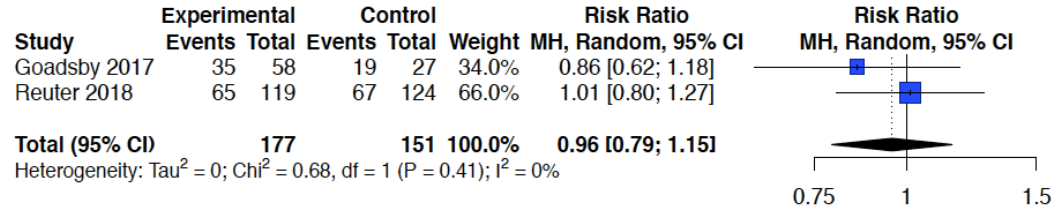
**S14. Forest plot of 50% response rate; 140mg erenumab versus placebo; CI, confidence interval**



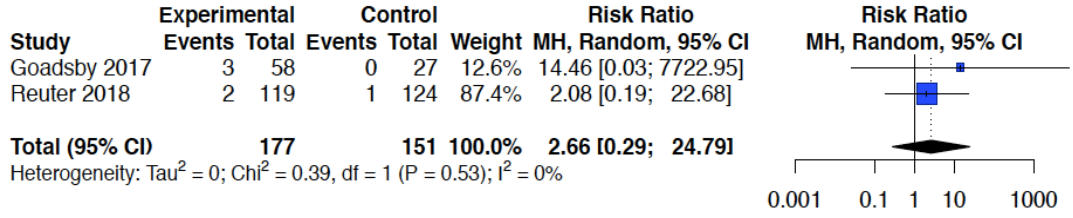

**S15. Forest plot of 75% response rate; 140mg erenumab versus placebo; CI, confidence interval**




**S16. Forest plot of adverse events; 140mg erenumab versus placebo; CI, confidence interval**




**S17. Forest plot of serious adverse events; 140mg erenumab versus placebo; CI, confidence interval**



# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | 2 |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3-4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3-4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 4 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 4 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 4 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 5 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 5-6 |
| Synthesis of results | 21 | Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency | 5-6 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 4 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 5-6 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 7 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 9 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 10 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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