Network Meta-Analysis: Chronic Migraine

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January 16th, 2026

Executive summary
A frequentist network meta-analysis was conducted using placebo-controlled trial data to compare galcanezumab with erenumab, eptinezumab, and Botox A for reduction in monthly migraine days in chronic migraine.

Key findings
- All active treatments reduced monthly migraine days compared with placebo.
- Eptinezumab showed the largest average reduction, followed by erenumab, galcanezumab, and Botox A.
- Galcanezumab showed comparable efficacy to other CGRP monoclonal antibodies and ranked third based on P-scores.

1 Objective

To compare galcanezumab with erenumab, eptinezumab, and Botox A for the reduction of monthly migraine days in chronic migraine.

2 Data

The dataset includes study-level treatment effects from randomized controlled trials in patients with chronic migraine. Treatment effects are reported as mean differences in the reduction of monthly migraine days from baseline to Week 12 versus placebo. Treatments include galcanezumab, erenumab, eptinezumab, Botox A, and placebo. Negative values indicate fewer migraine days relative to placebo.

Two study contrasts without reported standard errors were excluded from the analysis. One study included three treatment arms, contributing multiple treatment–placebo contrasts. Table 1 summarizes the characteristics of the data included in the analysis.

Table 1: Summary of available data

Data characteristics	Value
Number of studies	12
Number of treatment–placebo contrasts	12
Treatments included	Galcanezumab, Erenumab, Eptinezumab, Botox A

3 Methods

3.1 Analysis approach

Study-level treatment effects were structured as treatment–placebo contrasts using placebo as the common comparator. Contrasts without reported standard errors were excluded from the analysis. One study included three treatment arms; as within-study correlation information was not available, each treatment–placebo contrast from this study was treated as an independent comparison. A frequentist network meta-analysis was conducted using a common-effect model.

3.2 Heterogeneity assessment

Between-study variability was assessed to evaluate the consistency of evidence across the network.

3.3 Sensitivity analysis

One study contrast was identified as inconsistent during data review. Excluding this contrast reduced variability across studies and did not change the overall treatment ranking (Appendix Table 5).

4 Results

4.1 Evidence network

Figure 1 shows the evidence network linking galcanezumab, erenumab, eptinezumab, and Botox A through placebo-controlled trials. No direct head-to-head comparisons between active treatments were available; therefore, indirect comparisons were informed via the shared placebo comparator.

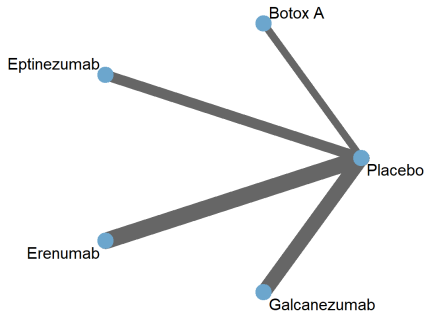

Figure 1: Evidence network

Notes: Nodes represent treatments; edges represent direct comparisons. Edge thickness reflects the number of studies contributing to each comparison.

4.2 Pooled treatment effects versus placebo

Figure 2 and Table 2 summarize the average reduction in monthly migraine days for each treatment compared with placebo. Negative values indicate fewer migraine days.

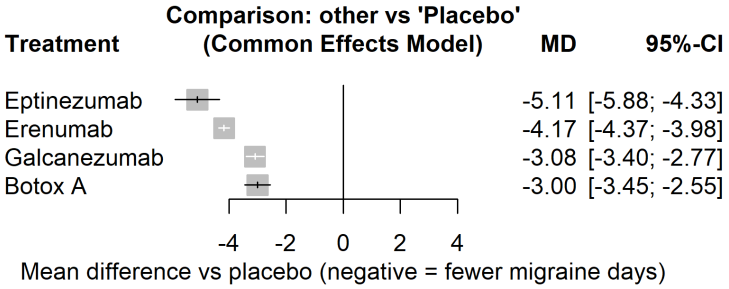

Figure 2: Pooled treatment effects versus placebo (common-effect model).

All active treatments reduced the number of monthly migraine days compared with placebo. Eptinezumab showed the largest average reduction, followed by erenumab, galcanezumab, and Botox A. The results indicate that galcanezumab provides a meaningful reduction in migraine days and performs comparably to other CGRP-targeted treatments.

Table 2: Pooled treatment effects versus placebo

Treatment	MD	SE	Lower	Upper
Eptinezumab	-5.11	0.39	-5.88	-4.33
Erenumab	-4.17	0.10	-4.37	-3.98
Galcanezumab	-3.08	0.16	-3.40	-2.77
Botox A	-3.00	0.23	-3.45	-2.55

Notes: MD = mean difference in monthly migraine days versus placebo. Negative values indicate fewer migraine days. Lower and Upper denote the bounds of the 95% confidence interval.

4.3 Treatment ranking

Figure 3 and Table 3 present the relative ranking of treatments based on P-scores, where higher values indicate a greater likelihood of better performance in reducing monthly migraine days.

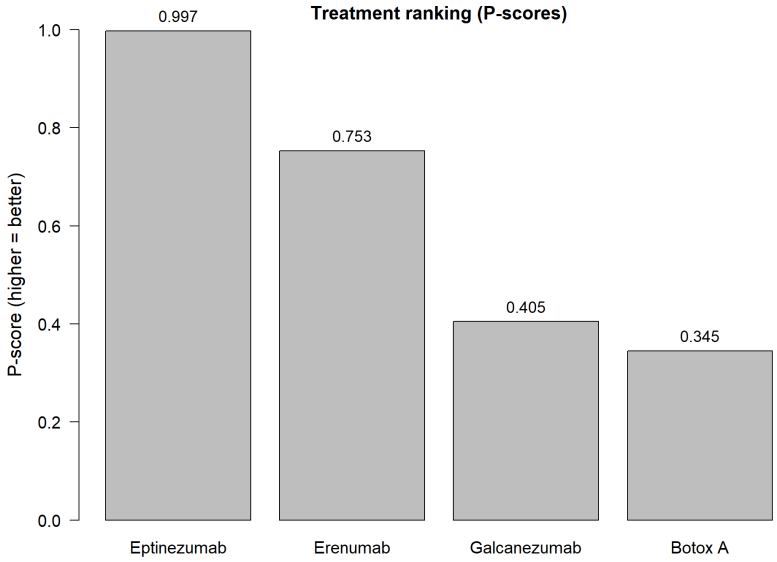

Figure 3: Treatment ranking based on P-scores

Notes: P-scores summarise the relative likelihood that a treatment performs better than others in reducing monthly migraine days. Higher values indicate better relative performance.

Eptinezumab ranked highest, followed by erenumab, galcanezumab, and Botox A. These rankings reflect relative average treatment effects estimated across the available evidence. Galcanezumab ranked competitively among CGRP-targeted therapies. All pairwise treatment comparisons from the network meta-analysis are provided in Appendix Table 4.

Table 3: Treatment ranking based on P-scores

Treatment	P-score
Eptinezumab	0.997
Erenumab	0.753
Galcanezumab	0.405
Botox A	0.345

Notes: P-scores summarise the relative likelihood that a treatment performs better than others in reducing monthly migraine days. Higher values indicate better relative performance.

4.4 Heterogeneity and sensitivity analysis

The base-case analysis exhibited substantial heterogeneity driven by one inconsistent contrast. Excluding this contrast reduced heterogeneity and did not materially change the ordering of treatments (Appendix Table 5).

A Appendix

A.1 League table

Appendix Table 4 presents all pairwise treatment comparisons.

Table 4: League table of pooled mean differences (common-effect NMA).

	Botox A	Eptinezumab	Erenumab	Galcanezumab	Placebo
Botox A	–				-3.00 [-3.45; -2.55]
Eptinezumab	2.11 [1.21; 3.00]	–			-5.11 [-5.88; -4.33]
Erenumab	1.17 [0.68; 1.66]	-0.94 [-1.73; -0.14]	–		-4.17 [-4.37; -3.98]
Galcanezumab	0.08 [-0.46; 0.63]	-2.02 [-2.86; -1.18]	-1.09 [-1.46; -0.71]	–	-3.08 [-3.40; -2.77]
Placebo	-3.00 [-3.45; -2.55]	-5.11 [-5.88; -4.33]	-4.17 [-4.37; -3.98]	-3.08 [-3.40; -2.77]	–

Notes: Each cell reports the mean difference (95% confidence interval) for the row treatment compared against the column treatment. Negative values indicate fewer monthly migraine days for the row treatment.

A.2 Base-case versus sensitivity comparison

Table 5: Sensitivity analysis: base-case versus outlier-excluded results.

	Base-case				**Sensitivity (excluding outlier)**			
Treatment	MD	SE	Lower	Upper	MD	SE	Lower	Upper
Botox A	-3.00	0.23	-3.45	-2.55	-3.00	0.23	-3.45	-2.55
Eptinezumab	-5.11	0.39	-5.88	-4.33	-5.11	0.39	-5.88	-4.33
Erenumab	-4.17	0.10	-4.37	-3.98	-4.17	0.10	-4.37	-3.98
Galcanezumab	-3.08	0.16	-3.40	-2.77	-3.78	0.17	-4.12	-3.45

Notes: Results are reported as mean differences (MD) in monthly migraine days relative to placebo. Negative values indicate fewer monthly migraine days (favouring active treatment). Lower and Upper denote the lower and upper bounds of the 95% confidence interval, respectively. The sensitivity analysis excludes a single outlying study contrast identified in the heterogeneity assessment.

A.3 R code

The following R script reproduces the analyses, tables, and figures reported in this document.

```
############################################################
# Frequentist NMA  Chronic Migraine
############################################################
# Author: Lilac Zihui Zhao
# Date: 16/01/2026
#
# Outputs (base-case):
# - fig_network.png
# - fig_forest_vs_placebo.png
# - fig_ranking_pscore.png
# - table_summary_stats.tex
```

```r
# - table_effects_vs_placebo.tex
# - table_league.tex
# - table_ranking_pscore.tex
#
# Outputs (sensitivity):
# - table_base_vs_sensitivity.tex
############################################################

# Packages
library(readxl)
library(dplyr)
library(netmeta)
library(knitr)

####################################
# Load data
####################################
df_raw <- read_excel("C:/Users/big_d/Dropbox/DS/Chronic_Migraine_dataset.xlsx")

####################################
# Data cleaning
####################################
df <- df_raw %>%
  mutate(
    trt = as.character(trt),
    study = as.character(study),
    na = as.numeric(na),
    TE = as.numeric(y),
    seTE = suppressWarnings(as.numeric(se))
  ) %>%
  filter(trt != "Placebo") %>%
  transmute(
    studlab = study,
    treat1 = trt,
    treat2 = "Placebo",
    TE = TE,
    seTE = seTE,
    num_of_arms = na
  ) %>%
  filter(!is.na(seTE), seTE > 0) %>%
  mutate(
    # Multi-arm trials: no covariance available, so treat each contrast as
        independent
    studlab = ifelse(num_of_arms > 2, paste0(studlab, "_", make.names(treat1)),
        studlab)
  )


####################################
# Summary Statistics
####################################
n_studies <- n_distinct(df$studlab)
n_contrasts <- nrow(df)
treatments <- paste(sort(unique(df$treat1)), collapse = ", ")

summary_table <- data.frame(
  Characteristic = c("Number of studies",
                     "Number of treatment--placebo contrasts",
                     "Treatments included"),
```

```r
  Value = c(n_studies,
            n_contrasts,
            treatments)
)


###################################
# Base-case NMA (common-effect)
###################################
nma <- netmeta(
  TE, seTE,
  treat1, treat2,
  studlab,
  data = df,
  sm = "MD",
  reference.group = "Placebo",
  common = TRUE,
  random = FALSE
)

summary(nma)


#################################
# Ranking (P-scores)
#################################
rnk <- netrank(nma, small.values = "good")

ps <- rnk$ranking.common

table_rank <- data.frame(
  Treatment = names(ps),
  Pscore = as.numeric(ps)
) %>%
  filter(!is.na(Pscore), Treatment != "", Treatment != "Placebo") %>%
  arrange(desc(Pscore)) %>%
  mutate(Pscore = round(Pscore, 3))


#########################################################################
# Sensitivity NMA (exclude outlier study label starting "Cleverley")
#########################################################################
df_sens <- df %>% filter(!grepl("^Cleverley", studlab))

nma_sens <- netmeta(
  TE, seTE,
  treat1, treat2,
  studlab,
  data = df_sens,
  sm = "MD",
  reference.group = "Placebo",
  common = TRUE,
  random = FALSE
)

summary(nma_sens)
```

```r

####################################
# Figures (base-case)
####################################

################
# Network plot
################
png("fig_network.png", 1800, 1200, res = 200)
netgraph(nma, points = TRUE, cex.points = 4, thickness = "number.of.studies",
       col.points = "skyblue3", col = "grey40", cex = 1.2, multiarm =
           FALSE,number=FALSE)
dev.off()

#################################################################
# Forest plot vs placebo (sorted by pooled effect vs placebo)
#################################################################
sv <- nma$TE.common[, "Placebo"]

png("fig_forest_vs_placebo.png", 2000, 1400, res = 220)
par(mar = c(5, 6, 6, 4))
forest(
  nma,
  ref = "Placebo",
  sortvar = sv,
  digits = 2,
  xlab = "Mean difference vs placebo (negative = fewer migraine days)"
)
dev.off()

################################
# Ranking plot (P-scores)
################################
png("fig_ranking_pscore.png", width = 2000, height = 1400, res = 220)

op <- par(no.readonly = TRUE)
par(mar = c(10, 6, 5, 2) + 0.1, xpd = NA)

bp <- barplot(
  table_rank$Pscore,
  names.arg = table_rank$Treatment,
  las = 1,
  cex.names = 1.1,
  cex.axis = 1.1,
  cex.lab = 1.2,
  ylim = c(0, 1),
  ylab = "P-score (higher = better)",
  main = "Treatment ranking (P-scores)"
)

text(
  x = bp,
  y = table_rank$Pscore,
  labels = sprintf("%.3f", table_rank$Pscore),
  pos = 3,
  cex = 1.0
)

par(op)
```

```r
dev.off()

###################################
# Tables (base-case)
###################################

#################################
# Effects vs placebo table
#################################
TE_mat <- nma$TE.common
SE_mat <- nma$seTE.common # important: SE matrix

ref <- "Placebo"
trts <- setdiff(rownames(TE_mat), ref)

table_eff <- data.frame(
  Treatment = trts,
  MD = as.numeric(TE_mat[trts, ref]),
  SE = as.numeric(SE_mat[trts, ref])
)
table_eff$Lower <- table_eff$MD - 1.96 * table_eff$SE
table_eff$Upper <- table_eff$MD + 1.96 * table_eff$SE

table_eff <- table_eff %>%
  mutate(across(where(is.numeric), ~ round(.x, 2)))

writeLines(
  kable(
    table_eff,
    format = "latex",
    booktabs = TRUE,
    caption = "Pooled mean differences versus placebo (common-effect NMA). Negative values indicate fewer monthly migraine days.",
    label = "tab:effects_vs_placebo"
  ),
  "table_effects_vs_placebo.tex"
)

################
# League table
################
lg <- netleague(nma, digits = 2)

writeLines(
  kable(
    as.data.frame(lg$common),
    format = "latex",
    booktabs = TRUE,
    caption = "League table of pooled mean differences (row vs column; common-effect NMA).",
    label = "tab:league"
  ),
  "table_league.tex"
)

################################
# Ranking (P-scores) table
################################
table_rank_tex <- table_rank %>%
```

```r
  mutate(Pscore = round(Pscore, 3))

writeLines(
  kable(
    table_rank_tex,
    format = "latex",
    booktabs = TRUE,
    caption = "Treatment ranking based on P-scores (higher indicates better
        performance).",
    label = "tab:ranking_pscore"
  ),
  "table_ranking_pscore.tex"
)

###################################
# Sensitivity comparison table
###################################
TE2 <- nma_sens$TE.common
SE2 <- nma_sens$seTE.common
trts2 <- setdiff(rownames(TE2), ref)

table_sens <- data.frame(
  Treatment = trts2,
  MD_sens = as.numeric(TE2[trts2, ref]),
  SE_sens = as.numeric(SE2[trts2, ref])
)
table_sens$Lower_sens <- table_sens$MD_sens - 1.96 * table_sens$SE_sens
table_sens$Upper_sens <- table_sens$MD_sens + 1.96 * table_sens$SE_sens

compare_tbl <- merge(table_eff, table_sens, by = "Treatment")
compare_tbl <- compare_tbl %>% mutate(across(where(is.numeric), ~ round(.x, 2)))

writeLines(
  kable(
    compare_tbl,
    format = "latex",
    booktabs = TRUE,
    caption = "Sensitivity analysis: base-case vs excluding outlier study.",
    label = "tab:base_vs_sensitivity"
  ),
  "table_base_vs_sensitivity.tex"
)

cat("\nSaved figures:\n",
    " - fig_network.png\n",
    " - fig_forest_vs_placebo.png\n",
    " - fig_ranking_pscore.png\n\n",
    "Saved LaTeX tables:\n",
    " - table_summary_stats.tex\n",
    " - table_effects_vs_placebo.tex\n",
    " - table_league.tex\n",
    " - table_ranking_pscore.tex\n",
    " - table_base_vs_sensitivity.tex\n", sep = "")
```