Executive Summary of Network Meta-Analysis of Galcanezumab for Chronic Migraine

Meha Patel

June 11, 2025

Galcanezumab was evaluated using a network meta-analysis (NMA) approach to assess its effectiveness in reducing monthly migraine days compared to other treatments such as Eptinezumab, Erenumab, and Botox A.

1 Objectives

The goals of this network meta-analysis were to:

1. Compare the efficacy of Galcanezumab versus key comparators in reducing monthly migraine days in patients with chronic migraine.
2. Rank treatments based on relative effectiveness using network-derived estimates.
3. Assess the certainty of evidence supporting treatment comparisons through the evaluation of network consistency and heterogeneity.

2 Methods

Network meta-analysis was selected as the preferred analytical approach as it allows simultaneous comparison of multiple treatments using both direct evidence (from head-to-head trials) and indirect evidence (through common comparators), thus maximizing use of available evidence while preserving randomization. Specifically, a frequentist network meta-analysis was performed using the netmeta package in R, using the mean difference in monthly migraine days as the primary outcome measure. Both common-effects and random-effects models were fitted, with random-effects results presented as primary given the presence of heterogeneity. Treatment rankings were assessed using P scores, representing the mean degree of certainty that each treatment performs better than the comparators.

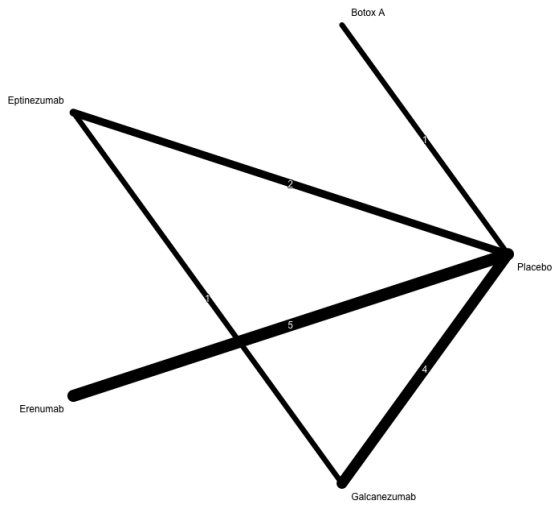

Figure 1: Network diagram showing evidence structure for chronic migraine treatments. Node size reflects number of participants; line thickness indicates number of studies per comparison.

3 Findings

3.1 Network Characteristics

The analysis included 11 studies comprised of 13 pairwise comparisons across 5 treatments (Figure 1). The network included both two-arm and multi-arm trials, with one three-arm study (Crisp) providing a direct comparison between Eptinezumab and Galcanezumab. The evidence base consisted of 5 distinct study designs connecting all treatments through direct and indirect comparisons. The network demonstrates good connectivity with placebo as a central hub, allowing robust indirect comparisons between active treatments. The line thickness in the network diagram reflects the relative amount of evidence for each comparison, with the thickest connections representing the most number of studies conducted.

3.2 Treatment Effects

Compared to the placebo, all active treatments demonstrated statistically significant reductions in monthly migraine days:

- **Eptinezumab:** -4.48 days (95% CI: -6.45 to -2.50)
- **Erenumab:** -4.20 days (95% CI: -5.40 to -3.00)
- **Botox A:** -3.00 days (95% CI: -5.69 to -0.31)
- **Galcanezumab:** -1.98 days (95% CI: -3.37 to -0.60)

Key Pairwise Comparisons with Galcanezumab (Figure 2):

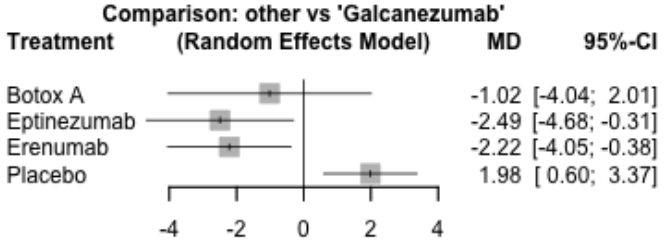

Figure 2: Forest plot comparing all treatments versus Galcanezumab (random effects model). Values < 0 favor the comparator; values > 0 favor Galcanezumab

- **Eptinezumab vs. Galcanezumab:** -2.49 days (95% CI: -4.68 to -0.31), favoring Eptinezumab
- **Erenumab vs. Galcanezumab:** -2.22 days (95% CI: -4.05 to -0.38), favoring Erenumab
- **Botox A vs. Galcanezumab:** -1.02 days (95% CI: -4.04 to 2.01), no significant difference
- **Placebo vs. Galcanezumab:** +1.98 days (95% CI: 0.60 to 3.37), favoring Galcanezumab

Galcanezumab demonstrated statistically significant superiority only versus placebo. All active treatments achieved reductions exceeding the 2-day threshold generally considered clinically meaningful for chronic migraine prevention.

3.3 Treatment Rankings

P-scores (Random Effects Model): P-scores measure the mean certainty that one treatment is better than another, averaged across all other treatments in the network, with values ranging from 0 (certainly worst) to 1 (certainly best).

1. **Eptinezumab:** 0.85 (highest efficacy)
2. **Erenumab:** 0.80
3. **Botox A:** 0.53
4. **Galcanezumab:** 0.32
5. **Placebo:** 0.00 (lowest efficacy)

The P-score analysis indicates Eptinezumab has an 85% probability of being superior to a randomly selected comparator, while Galcanezumab has a 32% probability, positioning it fourth among the five treatments evaluated.

4 Clinical Context

These findings align with previous systematic reviews demonstrating the efficacy of CGRP inhibitors and botulinum toxin for chronic migraine prevention. The observed treatment hierarchy is consistent with head-to-head trial data where available, particularly the direct comparison between Eptinezumab and Galcanezumab from the Crisp study. While Galcanezumab demonstrated statistically significant efficacy versus placebo, its relative ranking suggests other CGRP inhibitors may offer superior efficacy for reducing monthly migraine days. However, the substantial heterogeneity observed indicates that treatment effects may vary considerably across patient subgroups, and individual patient factors including tolerability, administration preferences, and comorbidities should inform treatment selection alongside efficacy considerations.

A Network Meta-Analysis Technical Details

A.1 R Statistical Code

A.1.1 Package Installation and Data Import

```r
# Import and install necessary packages
install.packages("readxl")
install.packages("netmeta")
install.packages("tidyverse")
library(tidyverse)
library(readxl)
library(netmeta)
library(dplyr)

# Set a consistent theme for all plots for reporting purposes
library(ggplot2)
theme_set(theme_minimal())

# Import dataset from excel file in local directory
my_data <- read_excel("/Users/admin/Downloads/Chronic_Migraine_Dataset.
    xlsx")

# Display the first few rows of the dataset
head(my_data)

# Check the structure of the dataset
str(my_data)
```

Listing 1: Required R packages and data import

A.1.2 Data Preparation and Cleaning

```r
# Convert se to numeric since it represents standard error
my_data$se <- as.numeric(my_data$se)

# Check for missing values in the columns of interest
missing_values <- my_data %>%
  summarise(across(c(y, se, trt, study), ~ sum(is.na(.))))
print(missing_values)

# Filter out rows with NA values in the columns of interest
my_data <- my_data %>%
  filter(!is.na(y), !is.na(se), !is.na(trt), !is.na(study))

# Check data
print(my_data)
```

Listing 2: Data preprocessing and quality checks

A.1.3 Multi-arm Trial Processing (Crisp Study)

```r
# Subset crisp study from full dataset to run pairwise analysis
# since it has 3 arms
crisp_data <- my_data %>% filter(study == "Crisp")
print(crisp_data)

# Create placebo reference for multi-arm trial
placebo_row <- data.frame(
  study = "Crisp",
  trt = "Placebo",
  y = 0,          # Placebo is the reference, so y = 0
  se = 0,         # se is usually NA for reference arm
  n = 100         # or the actual sample size for Placebo
)

# Append the new row to crisp_data
crisp_long <- bind_rows(crisp_data, placebo_row)
print(crisp_long)

# Run pairwise function from netmeta package on crisp study
pw_crisp <- pairwise(
  treat = trt,
  TE = y,
  seTE = se,
  studlab = study,
  data = crisp_long,
  sm = "MD"
)
print(pw_crisp)
```

Listing 3: Handling three-arm trial data using pairwise function

A.1.4 Contrast Data Preparation

```r
# Subset original full dataset into contrast dataset by removing
# placebo rows and crisp study, will append crisp pairwise later
contrast_data <- my_data %>%
  filter(trt != "Placebo", study != "Crisp") %>%
  mutate(
    trt1 = trt,
    trt2 = "Placebo"
  ) %>%
  select(study, trt1, trt2, y, se, na)

print(contrast_data)

# Check for any NA entries
sum(is.na(contrast_data))

# Combine the two data frames, adding crisp pairwise to contrast dataset
final_contrast_data <- bind_rows(
  contrast_data,
  pw_crisp %>% select(study = studlab, trt1 = treat1, trt2 = treat2,
```

```
                        y = TE, se = seTE)
)

# Drop any columns not needed for nma
final_contrast_data <- final_contrast_data %>%
  select(study, trt1, trt2, y, se)

print(final_contrast_data)
```

Listing 4: Creating contrast format dataset for network meta-analysis

A.1.5 Data Quality Assurance

```
# Check for NA or Inf in your columns
summary(final_contrast_data)
str(final_contrast_data)

# Remove any rows with zero standard errors
sum(final_contrast_data$se == 0)
final_contrast_data <- final_contrast_data %>% filter(se > 0)

# Check for finite values
sapply(final_contrast_data, function(x) sum(!is.finite(x)))

# Check network connectivity
netconnection(final_contrast_data$trt1, final_contrast_data$trt2)

# Check for duplicate comparisons
any(duplicated(final_contrast_data[, c("study", "trt1", "trt2")]))

# Final validation
sum(final_contrast_data$se <= 0)
summary(final_contrast_data)
```

Listing 5: Final data validation before network meta-analysis

A.1.6 Network Meta-Analysis Execution

```
# Run network meta-analysis
nma_object <- netmeta(
  TE = y,         # Treatment Effect
  seTE = se,      # Standard Error
  treat1 = trt1,
  treat2 = trt2,
  studlab = study,
  data = final_contrast_data,
  sm = "MD",      # Mean Difference
  details.chkmultiarm = TRUE
)

# View the summary of results
summary(nma_object)
```

```r

# Extract key results
nma_object$TE.random      # Mean differences
nma_object$lower.random   # Lower CI bounds
nma_object$upper.random   # Upper CI bounds
```

Listing 6: Primary network meta-analysis model

A.1.7 Treatment Rankings and Visualizations

```r
# Calculate treatment rankings
netrank(nma_object)

# Create network graph
netgraph(nma_object)
ggsave("fig_graph_plot.pdf")

# Plot treatment rankings
plot(netrank(nma_object))
ggsave("fig_rank_plot.pdf")

# Create forest plot comparing all treatments to galcanezumab
forest(nma_object, reference.group = "Galcanezumab")
ggsave("fig_forest_plot.pdf")

# Generate league table for all pairwise comparisons
netleague(nma_object)
```

Listing 7: P-scores, rankings, and network plots

A.1.8 Network Assessment and Diagnostics

```r
# Design decomposition
decomp.design(nma_object)

# Network contribution matrix
netcontrib(nma_object)

# Node-splitting for inconsistency assessment
netsplit(nma_object)
ggsave("fig_split_plot.pdf")
```

Listing 8: Inconsistency assessment and network diagnostics

A.2 References

A.2.1 Primary Statistical References

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A.2.2 Methodological References

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6. **Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G.** Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8(10):e76654.

7. **Dias S, Welton NJ, Caldwell DM, Ades AE.** Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*. 2010;29(7-8):932-944.

A.2.3 Health Technology Assessment References

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A.2.4 Software and Computing References

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A.2.5 Network Meta-Analysis Guidance

13. **Hutton B, Salanti G, Caldwell DM, et al.** The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine*. 2015;162(11):777-784.

14. **Jansen JP, Fleurence R, Devine B, et al.** Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value in Health*. 2011;14(4):417-428.