U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: **Supplement #:**	BLA 761089 SUPPL-31
Drug Name:	Ajovy (fremanezumab-vfrm) - 120 mg and 225 mg vs Placebo - injection, solution
Indication(s):	Episodic Migraine
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.
Date(s):	Submit Date: 02/05/2025. Goal date: 08/05/2025.
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
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Keywords: Link to keywords: ANCOVA, Double-blind, Intend-to-Treat (ITT), Mixed-model Repeated Measures (MMRM), Odds Ratio, Per Protocol, Sensitivity Analyses, Subgroup Analyses.	

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1 EXECUTIVE SUMMARY

Study TV48125-CNS-30083 demonstrated that fremanezumab (administered at 225 mg and 120 mg, with the latter dose adjusted based on patient weight) is superior to placebo in the treatment of episodic migraine.

The study met its primary endpoint, which was the mean change from baseline in the monthly average number of migraine days over the 12-week period following the first dose of the study drug. The difference in least square means between the fremanezumab and placebo groups was -1.03 (p-value = 0.0210).

Several key secondary efficacy endpoints were also statistically significant. The monthly average number of headache days of at least moderate severity showed a least square means difference (fremanezumab – placebo) of -1.1 (p-value = 0.0172).

The proportion of patients achieving at least a 50% reduction in the monthly average number of migraine days was 47.2% in the fremanezumab group, compared to 27.0% in the placebo group; this resulted in an odds ratio of 2.482 (p-value = 0.0016).

The monthly average number of days of use of any acute headache medication showed a least square means difference (fremanezumab – placebo) of -1.1 (p-value = 0.0016).

Due to the fixed sequence testing procedure, and the non-significant 12-week PeDMIDAS mean change from baseline, the 12-week PedsQL endpoint results are considered inferentially uninterpretable.

2 INTRODUCTION

2.1 Drug Development

Fremanezumab is a humanized immunoglobulin G2 (IgG2) Δa/kappa monoclonal antibody (mAb) derived from a murine precursor. In September 2018, fremanezumab was approved in the United States of America (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab has also been approved in the European Union (EU) and a number of countries worldwide.

2.2 Studies Submitted

1. TV48125-CNS-30083: A randomized, double blind, placebo, controlled, parallel group study to assess the safety and efficacy of fremanezumab versus placebo for the preventative treatment of episodic migraine (EM) in pediatric patients, ages 6 to less than 18 years of age.

2. TV48125-CNS-30084: A multicenter, open-label study evaluating the long-term safety, tolerability, and efficacy of monthly subcutaneous administration of fremanezumab for the preventive treatment of episodic and chronic migraine in pediatric patients 6 to 17 years of age.

2.3 Overview

The trial TV48125-CNS-30083, assessing efficacy and safety, is being reviewed in this document.

Table 1: List of All Studies Included in Analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
TV48125-CNS-30083	A randomized, double blind, placebo, controlled, parallel group study to assess the safety and efficacy of fremanezumab versus placebo	12 weeks	~ 28 days after the final dose	237 randomized: 36 and 87 in frmenaezumab 120 mg and 225 mg respectively 112 in placebo.	Patients with Episodic Migraine (EM), ages 6 to less than 18 years of age.

2.3.1 History of Drug Development

The fremanezumab global clinical development program for migraine, encompassing two Phase 3 (TV48125-CNS-30049 and TV48125-CNS-30050), one long-term safety (TV48125-CNS-30051), and two supportive Phase 2b trials (LBR-101-021 and LBR-101-022), demonstrated superior efficacy of fremanezumab over placebo. This efficacy was observed at the proposed dosing regimens of 225 mg monthly (with a 675 mg starting dose for chronic migraine [CM] patients) and 675 mg quarterly, in adult patients with episodic migraine [EM] and CM.

The global Phase 3 program (HALO) in adults with migraine in conjunction with the supportive Phase 2b trials served as the basis for the marketing authorizations described above.

Following the approvals in the US and EU, additional trials in difficult to treat migraine population, including those who have failed 2 to 4 classes of prior preventive medication (TV48125-CNS-30068; FOCUS) and migraine patients with comorbid major depressive disorder (TV48125-MH-40142; UNITE), with fremanezumab were conducted within the migraine development program. Results from these trials demonstrated consistent efficacy and safety profile as shown in the HALO trials.

The fremanezumab pediatric migraine development program consists of a completed Phase 1 open-label trial (TV48125-CNS-10141) evaluating single 75 mg subcutaneous doses in patients aged 6-11, two ongoing Phase 3 double-blind placebo-controlled efficacy/safety trials (TV48125-CNS-30082 [CM] and TV48125-CNS-30083 [EM]), and one ongoing open-label safety extension trial (TV48125-CNS-30084 [EM and CM]). Trial TV48125-CNS-30083 aimed to determine the safety and efficacy of fremanezumab for migraine prevention in pediatric episodic migraine (EM) patients.

2.4 Data Sources

The links to various documents are presented in the following links:

A. Electronic submission

B. Reviewer's Guide

C. Location of protocol, report, statistical analysis plan (SAP)

D. Location of the SAS codes

   Note: The sponsor submitted updated version of their codes here.

E. Location of the ADaM datasets (adrg.pdf contains the details of the dataset and the programs)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality are adequate and followed the statistical analysis plan (SAP). The statistical reviewer was able to replicate the sponsor's finding using the provided datasets and SAS code. The primary and secondary analysis results, along with the corresponding SAS code, have been verified by the statistical reviewer. The results presented are based on the full analysis set (FAS).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Design

This was a 4-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial designed to evaluate the efficacy, safety, and tolerability of 2 different doses (dependent on participants' body weight) of subcutaneous fremanezumab and placebo among male and female participants aged 6 to 17 years, inclusive.

The enrollment target was approximately 230 EM patients, with approximately 20% of those patients in the 6-through 11-year-old age group. Randomization was 1:1 between fremanezumab and placebo. Randomization was stratified by country, sex, puberty status, and preventive medication use at baseline (Yes/No).

The study included a 28-day baseline and 12-week treatment period. Patients received three monthly SC blinded treatments (approximately 28 days apart), starting at Visit 2 (Day 1), with final assessments at Visit 5 (EOT), 28 days post-treatment. Acute migraine medications, excluding opioids and barbiturates, are permitted. Eligible patients completing this study was offered enrollment in a 9-month open-label safety extension (TV48125-CNS-30084) with a 5-month follow-up.

An interim analysis with blinded sample size re-estimation was conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients had completed at least 3 months of treatment or had withdrawn from the study early. There was no Data Monitoring Committee in this study.

3.2.1.2 Primary Endpoint

The primary efficacy endpoint is the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug. The primary efficacy measure was derived from headache variables collected daily using an electronic diary device.

3.2.1.3 Secondary Efficacy Endpoints

A. Mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug.
B. Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug.
C. Mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug.
D. Mean change from baseline (day 1) in migraine-related disability score, as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of study drug.

E. Mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 weeks after administration of the first dose of study drug.

A fixed-sequence (hierarchical) testing procedure will be implemented to control the Type 1 error rate at 0.05. The sequence is same as described above.

3.2.2 Statistical Methodologies

3.2.2.1 Sample Size Calculation

The sample size planned is approximately 220 patients (110 evaluable patients completing the study per treatment group). Assuming a treatment difference of 1.8 days (reduction in monthly average number of migraine days) and a common SD of 4.31, a sample size of 110 patients per treatment group gives at least 87% power for the study to succeed at an alpha level of 0.05. Assuming a 4% discontinuation rate, approximately 230 patients (115 patients per treatment group) will be randomized.

3.2.2.2 Efficacy Analysis

Primary efficacy was analyzed using ANCOVA, with treatment, sex, puberty status, region, baseline weight, and preventative medication use as fixed effects, and baseline migraine days as a covariate. Treatment policy strategy is used for all intercurrent events. Efficacy variables (days/hours) are prorated to 28 days for patients with ≥10 e-diary days post-dose; those with <10 days are treated as missing. Multiple imputation (MI) will be used for sensitivity analyses on the primary variable.

Continuous secondary efficacy endpoints were analyzed using the same ANCOVA model as the primary endpoint. Responder proportions were analyzed via logistic regression with treatment, sex, weight, region, puberty, preventative medication, and baseline migraine days as factors. Odds ratios, 95% CIs, placebo differences, and nominal p-values were reported.

3.2.2.3 Sensitivity Analysis

1. **MMRM Analysis:** The MMRM model includes baseline value, treatment, demographics, baseline medication, month, and treatment-by-month interaction as fixed effects, and patient as a random effect. An unstructured covariance matrix is used; if convergence fails, simpler structures are applied in this order: heterogeneous Toeplitz, Toeplitz, or compound symmetry with a robust sandwich estimator (Liang & Zeger, 1986). For a model-based estimator of the covariance (i.e., unstructured, heterogeneous Toeplitz, or Toeplitz) for making inferences between treatment groups, especially at a particular visit, the Kenward-Roger degrees of freedom will be employed (Kenward & Roger, 1997).

2. **Multiple Imputation:** Monthly missing e-diary data (<10 days) were imputed using a Missing Not at Random (MNAR) mechanism. To account for potential biases, patients in

the active treatment groups who prematurely discontinued due to adverse events or lack of efficacy were reassigned to the placebo group for imputation purposes. 100 complete datasets were generated using a multiple imputation procedure. Within each imputed dataset, monthly values were prorated for patients with partial e-diary data. The average number of migraine days and the change from baseline were calculated across the 100 imputed datasets. Treatment group comparisons were performed using an ANCOVA model on each imputed dataset. Finally, the final least squares means, treatment differences, associated p-values, and 95% confidence intervals were generated, summarizing the results across all 100 imputed datasets.

3. The ANCOVA analysis will be repeated as a sensitivity analysis using the actual stratification factors in the model.

3.2.2.4 Subgroup Analysis

The ANCOVA method will be applied to the following subgroups for the change from baseline values in the number of migraine days and the monthly average number of headache days of at least moderate severity.

- patients receiving or not receiving any concomitant preventive treatment at baseline.
- patients in different race groups (Caucasian, non-Caucasian)
- patients by age group (6-11 years, 12-17 years)
- patients by weight group
- patients by puberty status
- patients by sex
- patients by region

The model to be used in exploring the consistency of a treatment effect (i.e., TEV-48125 – placebo) across the subgroup levels will have treatment, subgroup, and treatment-by-subgroup interaction as fixed effects, and a baseline covariate that corresponds to the respective endpoint (i.e., response variable in the model).

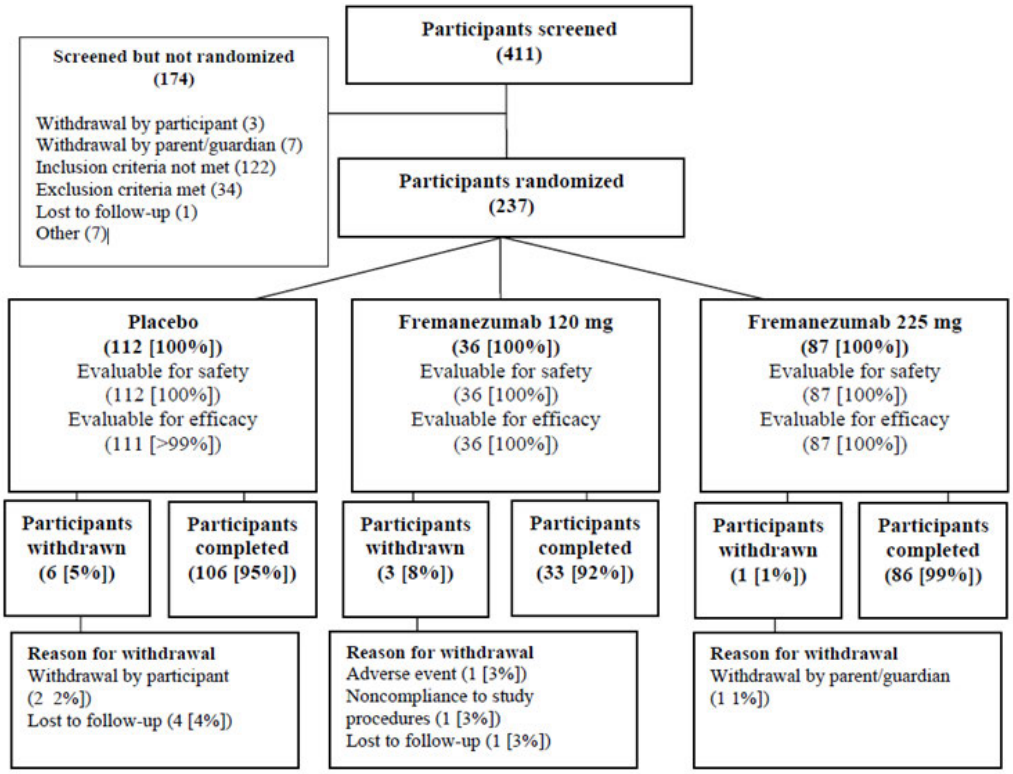
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Participant Disposition

1. A total of 411 participants with EM were screened for enrollment. In this trial, 237 participants with EM were randomly assigned to treatment (36 and 87 participants in the fremanezumab treatment groups [120 mg or 225 mg, respectively] and 112 participants in the placebo treatment group).
2. However, 2 subjects (1 assigned to fremanezumab 225 mg and 1 assigned to placebo) were excluded from all analysis sets due to concern with data reliability after GCP noncompliance at a particular site (14368) that was subsequently terminated from continuing to participate in the trial.
3. Of the total 235 randomized participants included in the analysis sets, 100% received at least 1 dose of trial drug; and 225 (96%) participants completed the trial.

4. Of note, the safety profile of the 2 participants excluded from analysis had been examined and found to be consistent with the fremanezumab known safety profile.

Figure 1: Participant Disposition (All Participants)



Source: Summary 15.1, Listing 16.2.1.01, and Listing 16.2.1.03.
PK=pharmacokinetics.
Note: Numbers in parentheses are numbers of participants. The denominator for calculating percentages is the number of participants in the ITT analysis set.
A total of 16 participants had failed initial screening and re-screened. 12 of 16 participants had randomized during re-screening and are counted in the ITT set.
The other 4 participants had failed the re-screening and are counted as screen failures.

The ITT set includes all randomized patients, excluding two due to GCP non-compliance, and is used for all trial summaries. The FAS, for primary and secondary analyses, includes ITT patients with at least one dose and ≥10 post-baseline diary days. The per-protocol set, a subset of FAS, includes patients with no major protocol deviations and ≥75% diary compliance.

Table 2: Disposition of Participants

Analysis Group, n (%)	Placebo	Fremanezumab 120 mg	Fremanezumab 225 mg	All Fremanezumab	Total
ITT analysis set	112 (100)	36 (100)	87 (100)	123 (100)	235 (100)
Full analysis set	111 (>99)	36 (100)	87 (100)	123 (100)	234 (>99)
Per protocol analysis set	87 (78)	28 (78)	69 (79)	97 (79)	184 (78)

Analysis Group, n (%)	Placebo	Fremanezumab 120 mg	Fremanezumab 225 mg	All Fremanezumab	Total
Completed trial	106 (95)	33 (92)	86 (99)	119 (97)	225 (96)
Discontinued trial	6 (5)	3 (8)	1 (1)	4 (3)	10 (4)
Adverse event	0	1 (3)	0	1 (< 1)	1 (<1)
Noncompliance	0	1 (3)	0	1 (< 1)	1 (<1)
Withdrawal by subject	2 (2)	0	0	0	2 (<1)
Withdrawal by parent/ guardian	0	0	1	1	1
Lost to follow-up	4 (4)	1 (3)	0	1 (<1)	5 (2)

Source: Summary 15.1, Listings 16.2.1.01 and 16.2.1.03.
ITT=Intent-to-treat; n=number of participants included in analysis.
Note: The denominator for calculating percentages is the number of participants in the ITT analysis set. Sixteen (16) participants failed the initial screening and were subsequently re-screened. Out of these 16 participants, 14 were randomized during the re-screening.
Note: The total N may appear as though 2 participants are missing from the analysis sets, however 2 participants from 1 site were excluded from all analysis sets due to GCP non-compliance but kept in the raw data sets.

3.2.3.2 Demographic Characteristics

The treatment groups (i.e, fremanezumab and placebo) were well matched with respect to demographic characteristics for the ITT analysis set (Table 5). The average age of the participants was 13.3 years (range 6 to 17 years). The majority (77%) of participants were white. Slightly more than half of participants were female (55%).

Table 3: Demographic Information (ITT analysis set)

Demographic variables	Placebo (N=112)	Fremanezumab 120 mg (N=36)	Fremanezumab 225 mg (N=87)	All Fremanezumab (N=123)	Total (N=235)
Age, years					
Mean	13.4	11.0	14.2	13.3	13.3
SD	2.99	2.27	2.34	2.74	2.86
Median	14.0	11.0	15.0	13.0	13.0
Min, max	6.0, 17.0	6.0, 17.0	9.0, 17.0	6.0, 17.0	6.0, 17.0
Age in Categories, n (%)					
6 - 11 years	32 (29)	19 (53)	13 (15)	32 (26)	64 (27)
12 - 17 years	80 (71)	17 (47)	74 (85)	91 (74)	171 (73)
Age in categories, n (%)					
6 - 11 years	32 (29)	19 (53)	13 (15)	32 (26)	64 (27)

Demographic variables	Placebo (N=112)	Fremanezumab 120 mg (N=36)	Fremanezumab 225 mg (N=87)	All Fremanezumab (N=123)	Total (N=235)
12 - 14 years	31 (28)	15 (42)	29 (33)	44 (36)	75 (32)
15 - 17 years	49 (44)	2 (6)	45 (52)	47 (38)	96 (41)
Sex, n (%)					
Male	48 (43)	20 (56)	37 (43)	57 (46)	105 (45)
Female	64 (57)	16 (44)	50 (57)	66 (54)	130 (55)
Race, n (%)					
White	84 (75)	28 (78)	68 (78)	96 (78)	180 (77)
Black Or African American	4 (4)	1 (3)	4 (5)	5 (4)	9 (4)
Asian	0	0	2 (2)	2 (2)	2 (< 1)
American Indian Or Alaska Native	0	0	0	0	0
Native Hawaiian Or Other Pacific Islander	0	0	0	0	0
Other	3 (3)	2 (6)	0	2 (2)	5 (2)
Missing	21 (19)	5 (14)	13 (15)	18 (15)	39 (17)
Race by subgroups, n (%)					
Caucasian	84 (75)	28 (78)	68 (78)	96 (78)	180 (77)
Non-Caucasian	7 (6)	3 (8)	6 (7)	9 (7)	16 (7)
Missing	21 (19)	5 (14)	13 (15)	18 (15)	39 (17)
Ethnicity, n (%)					
Not Hispanic or Latino	102 (91)	31 (86)	75 (86)	106 (86)	208 (89)
Hispanic or Latino	9 (8)	4 (11)	8 (9)	12 (10)	21 (9)
Missing	1 (< 1)	1 (3)	4 (5)	5 (4)	6 (3)
Weight, kg					
Mean	52.054	35.317	59.715	52.574	52.327
SD	15.7616	6.0188	12.1665	15.4591	15.5727
SE	1.4893	1.0031	1.3044	1.3939	1.0159
Median	50.85	36.350	56.00	51.3	51.00
Min, max	19.80, 88.00	20.50, 44.60	15.00, 102.60	20.50, 102.6	19.80, 102.6
Weight in categories (kg), n (%)					
< 45	33 (29)	36 (100)	0	36 (29)	69 (29)
≥ 45	79 (71)	0	87 (100)	87 (71)	166 (71)
Preventative medication use, n (%)					
Yes	25 (22)	8 (22)	17 (20)	25 (20)	50 (21)

Demographic variables	Placebo (N=112)	Fremanezumab 120 mg (N=36)	Fremanezumab 225 mg (N=87)	All Fremanezumab (N=123)	Total (N=235)
No	87 (78)	28 (78)	70 (80)	98 (80)	185 (79)
Time since initial migraine diagnosis (years)					
Mean	4.4	3.8	4.7	4.4	4.4
SD	3.11	2.67	3.05	2.96	3.03
SE	0.29	0.45	0.33	0.27	0.20
Median	4.0	3.5	4.0	4.0	4.0
Min, max	0.0, 14.0	0.0, 11.0	0.0, 13.0	0.0, 13.0	0.0, 14.0
Triptans/ergots use during baseline, n (%)					
Yes	49 (44)	12 (33)	40 (46)	52 (42)	101 (43)
No	63 (56)	24 (67)	47 (54)	71 (58)	134 (57)
Migraine with aura, n (%)					
Yes	30 (27)	9 (25)	32 (37)	41 (33)	71 (30)
No	82 (73)	27 (75)	55 (63)	82 (67)	164 (70)

Source: Summary 15.1.2.1, Listing 16.2.4.01.
BMI=body mass index; min=minimum; max=maximum; SD=standard deviation; n=number of participants included in analysis; N=total number of participants in the treatment group; SE=standard error.
Note: Patients with CRF values UNKNOWN or NOT REPORTED were counted into the 'Missing' category.

3.2.3.3 Baseline Characteristics

Baseline efficacy variables were generally similar between participants in each treatment group for the ITT analysis set (Table 6).

Table 4: Baseline Efficacy Variables (ITT analysis set)

Baseline characteristic	Placebo (N=112)	Fremanezumab 120 mg (N=36)	Fremanezumab 225 mg (N=87)	All Fremanezumab (N=123)
Number of migraine days (days)				
Mean	7.5	7.6	7.9	7.8
SD	2.84	2.92	3.21	3.12
Median	7.5	7.5	7.5	7.5
Min, max	0.0, 14.0	1.0, 15.2	1.3, 17.6	1.0, 17.6
Number of headache days of at least moderate severity (days)				
Mean	7.9	8.0	8.3	8.2
SD	2.8	3.19	3.11	3.12

Baseline characteristic	Placebo (N=112)	Fremanezumab 120 mg (N=36)	Fremanezumab 225 mg (N=87)	All Fremanezumab (N=123)
Median	7.8	8.1	8.3	8.3
Min, max	0.9, 14.0	0.0, 15.2	0.0, 14.0	0.0, 15.2
Number of days of any acute headache medication (days)				
Mean	5.6	6.1	5.7	5.8
SD	3.38	3.36	3.68	3.58
Median	5.5	6.5	5.6	5.8
Min, max	0.0, 14.0	0.0, 15.2	0.0, 14.0	0.0, 15.2
Number of days of use of acute headache medications (days)				
n	25	8	17	25
Mean	6.1	5.6	5.7	5.6
SD	3.97	3.48	3.74	3.58
Median	6.8	4.5	5.8	5.1
Min, max	0.0, 14.0	0.0, 11.0	0.0, 12.0	0.0, 12.0
Number of headache days of any severity (days)				
Mean	8.2	8.3	8.6	8.5
SD	2.8	3.14	3.13	3.12
Median	7.9	8.5	8.4	8.4
Min, max	0.9, 14.0	0.0, 15.2	0.0, 17.6	0.0, 17.6
Number of days with nausea or vomiting (days)				
Mean	3.7	3.8	4.1	4.0
SD	2.99	3.56	3.82	3.73
Median	3.1	2.6	3.2	3.1
Min, max	0.0, 11.0	0.0, 11.7	0.0, 16.0	0.0, 16.0
Number of days with photophobia and phonophobia (days)				
Mean	5.9	5.5	5.6	5.6
SD	3.45	3.92	4.01	3.97
Median	6.0	6.0	5.0	5.0
Min, max	0.0, 13.5	0.0, 14.0	0.0, 17.6	0.0, 17.6
Migraine Disability Assessment (PedMIDAS) Total Score				

Baseline characteristic	Placebo (N=112)	Fremanezumab 120 mg (N=36)	Fremanezumab 225 mg (N=87)	All Fremanezumab (N=123)
n	111	36	87	123
Mean	46.5	45.3	44.0	44.4
SD	43.59	32.93	23.59	26.52
Median	34.0	39.5	39.0	39.0
Min, max	5.0, 261.0	1.0, 155.0	0.0, 133.0	0.0, 155.0
Migraine-specific Quality of Life (PedsQL) Reported by Child Total Score				
n	110	36	86	122
Mean	72.7	72.1	71.9	72.0
SD	13.67	14.47	12.61	13.12
Median	72.8	75.0	72.8	72.8
Min, max	28.3, 100.0	41.3, 94.6	44.6, 100.0	41.3, 100.0
Migraine-specific Quality of Life (PedsQL) Reported by Parent Total Score				
n	38	29	23	52
Mean	73.1	73.4	74.9	74.0
SD	15.28	14.71	16.37	15.33
Median	73.4	75.0	70.7	71.7
Min, max	31.5, 97.8	42.4, 96.7	48.9, 100.0	42.4, 100.0

Source: Summary 15.1.2.5, Listings 16.2.6.03, 16.2.6.04, and 16.2.6.05.
ITT=intent-to-treat; max=maximum; min=minimum; n=number of participants included in analysis; N=total number of participants in the treatment group; NSAIDs=Non-steroidal anti-inflammatory drugs; PedMIDAS=Pediatric Migraine Disability Assessment; PedsQL=Pediatric Quality of Life Inventory; SD=standard deviation; SE=standard error.
Note: All data collected in the baseline period were used in the analyses while only the first 28 days of diary data were used for eligibility evaluation.
Note: For PedMIDAS total score, larger scores reflect greater disability.
Note: PedsQL domains are on a scale of 0 to 100, with higher scores indicating better quality of life. If a participant's ability to complete the questionnaire was impaired, their parent could also have completed it on their behalf. Parent and child questionnaires are summarized separately.

3.2.4 Results and Conclusions

3.2.4.1 Analysis Efficacy

3.2.4.1.1 Analysis of Primary Efficacy Variables

The primary efficacy variable, the mean change from baseline in monthly average migraine days over 12 weeks post-first dose, was analyzed with ANCOVA, including treatment, sex, puberty status, region, weight, and baseline medication use as fixed effects, and baseline endpoint days as a covariate. The results showed statistically significant differences between placebo and

fremanezumab in the FAS, with the fremanezumab group experiencing a greater reduction in migraine days. (Table 7).

Table 5: Change from Baseline in Monthly Average Number of Migraine Days During 12-Week Period After the First Dose of Trial Drug by Treatment Group (Full Analysis Set)

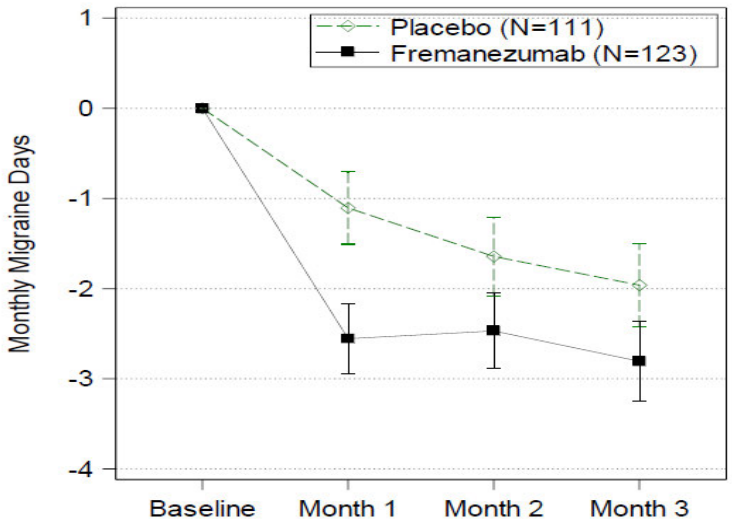
Statistic	Placebo (N=111)	Fremanezumab (N=123)
LS mean (SE)	-1.4 (0.39)	-2.5 (0.38)
95% confidence interval	-2.22, -0.67	-3.22, -1.72
Comparison with placebo		
LS mean (SE)	-	-1.0 (0.44)
95% confidence interval	-	-1.90, -0.16
p-value	-	0.0210

Source: Summary 15.2.1, Listing 16.2.6.01 and 16.2.6.03.
ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares; SE=standard error of the mean.
Note: LS mean (SE), 95% CI, and p-value represent the results obtained from the ANCOVA model with treatment, sex, puberty status, region, weight category, and baseline preventive migraine medication use (yes/no) as fixed effects and the baseline number of migraine days as a covariate.
Verified by Statistical Reviewer.

Sensitivity Analyses

Sensitivity analysis using MMRM yielded nominally statistically significant differences between treatment groups during the 12-week period. Additionally, the MMRM analysis revealed nominally statistically significant differences at Month 1, and numerical trend favoring fremanezumab at Months 2 and 3.

Figure 2: Line Plot of LS Mean (± SE) Change from Baseline in Monthly Average Number of Migraine Days During 12-Week Period by Treatment Group Using MMRM (Full Analysis Set)



The sensitivity analysis using ANCOVA with multiple imputation for missing data under MNAR yielded similar results as the primary analysis, as only 1 subject terminated with reasons of

adverse event or lack of efficacy. ANCOVA with actual stratification values instead of stratification used in randomization showed consistent results.

3.2.4.1.2 Analysis of Secondary Efficacy Variables

3.2.4.1.2.1 Mean Change from Baseline (28-Day Baseline Period) in Monthly Average Number of Headache Days of at Least Moderate Severity During the 12-week Period after the First Dose of Trial Drug

The mean change from baseline in monthly average headache days of at least moderate severity over the 12-week period post-first dose showed statistically significant differences between placebo and fremanezumab in the FAS, with the fremanezumab group experiencing a greater reduction in moderate or severe headache days (Table 8).

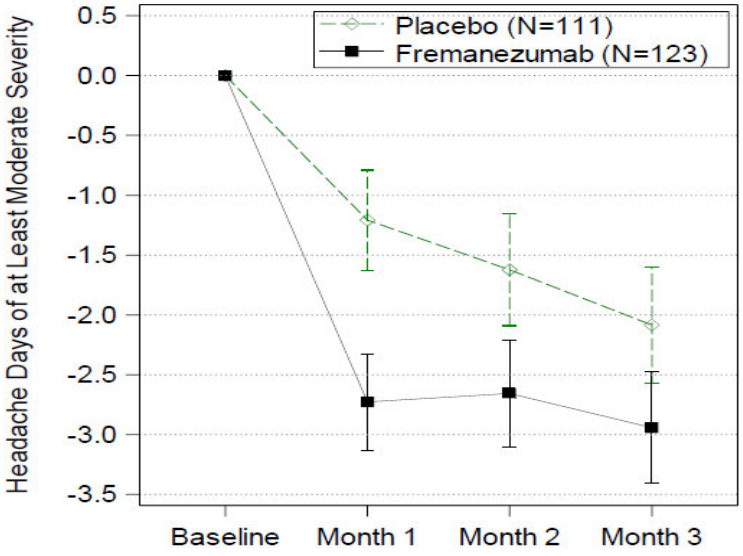
Table 6: Mean Change from Baseline (28-Day Baseline Period) in Monthly Average Number of Headache Days of at Least Moderate Severity During the 12-Week after the First Dose of Trial Drug Period by Treatment Group (Full Analysis Set)

Statistic	Placebo (N=111)	Fremanezumab (N=123)
LS mean (SE)	-1.5 (0.42)	-2.6 (0.40)
95% confidence interval	-2.32, -0.66	-3.42, -1.83
Comparison with placebo		
LS mean (SE)	-	-1.1 (0.47)
95% confidence interval	-	-2.06, -0.20
p-value	-	0.0172

ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares; SE=standard error of the mean.
Note: LS mean (SE), 95% CI, and p-value represent the results obtained from the ANCOVA model with treatment, sex, puberty status, region, weight category, and baseline preventive migraine medication use (yes/no) as fixed effects and the baseline number of migraine days as a covariate.
Verified by Statistical Reviewer.

Sensitivity Analysis
Sensitivity analyses also showed nominally statistically significant differences ($p < 0.05$) between treatment groups for the FAS and PP analysis sets. Specifically, the MMRM analysis revealed: for the FAS, nominally significant differences at Month 1 and overall, and numerical differences at Months 2 and 3; and for the PP, nominally significant differences at Months 1, 2, and overall, and numerical differences at Month 3, see Figure 5.

Figure 3: Line Plot of LS Mean (± SE) Change from Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During 12-Week Period by Treatment Group Using MMRM (Full Analysis Set)



3.2.4.1.2.2 Proportion of Patients Reaching at Least 50% Reduction in the Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Trial Drug

The proportion of participants achieving at least a 50% reduction in monthly average migraine days over 12 weeks post-first dose was statistically significantly different between placebo and fremanezumab (nominally significant at each month) in the FAS. Participants in the fremanezumab group had over twice the odds of experiencing a 50% reduction in migraine days (Table 9).

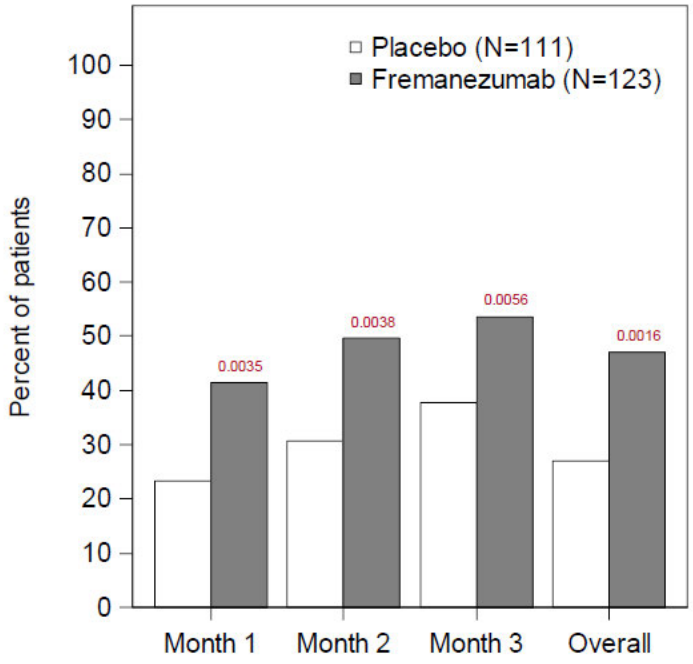
Table 7: Proportion of Patients Reaching at Least 50% Reduction in the Monthly Average Number of Migraine Days During the 12-week Period After the First Dose of Trial Drug by Month and Treatment Group (Full Analysis Set)

Time point	Placebo (N=111)	Fremanezumab (N=123)	Odds Ratio (95% CI)
Month 1, n			2.387 (1.332, 4.279). p-values = 0.0035
Yes	26 (23.4)	51 (41.5)	
No	85 (76.6)	70 (56.9)	
Month 2, n			2.237 (1.297, 3.860). p-values = 0.0038
Yes	34 (30.6)	61 (49.6)	
No	74 (66.7)	59 (48.0)	
Month 3, n			2.213 (1.261, 3.885). p-values = 0.0056
Yes	42 (37.8)	66 (53.7)	
No	62 (55.9)	46 (37.4)	
Overall, n			2.482 (1.409, 4.371). p-values = 0.0016
Yes	30 (27.0)	58 (47.2)	
No	81 (73.0)	65 (52.8)	

n=Number of patients with data available.

Note: Percentage based on N (number of patients in population).
Note: The odds ratio, 95% confidence interval and p-value are from a logistic regression model with the following factors: treatment, sex, region, puberty status, weight category, and preventive migraine medication use at baseline (Yes/No).
Note: The early discontinued participants are considered as non-responder for overall analysis.
Verified by Statistical Reviewer.

Figure 4: Proportion of Patients Reaching at Least 50% Reduction from Baseline in the Monthly Average Number of Migraine Days During the 12-week Period After the First Dose of Trial Drug by Month and Treatment Group –Logistic Regression Results (Full Analysis Set)



3.2.4.1.2.3 Mean Change from Baseline (28-Day Baseline Period) in the Monthly Average Number of Days of Use of Any Acute Headache Medications During the 12-Week Period After the First Dose of Trial Drug

In the FAS analysis, fremanezumab significantly reduced the mean change from baseline in monthly acute headache medication use compared to placebo (Table 10 and Figure 7).

Table 8: Mean Change from Baseline in the Monthly Average Number of Days of Use of Any Acute Headache Medications During the 12-Week Period After the First Dose of Trial Drug by Treatment Group (Full Analysis Set)

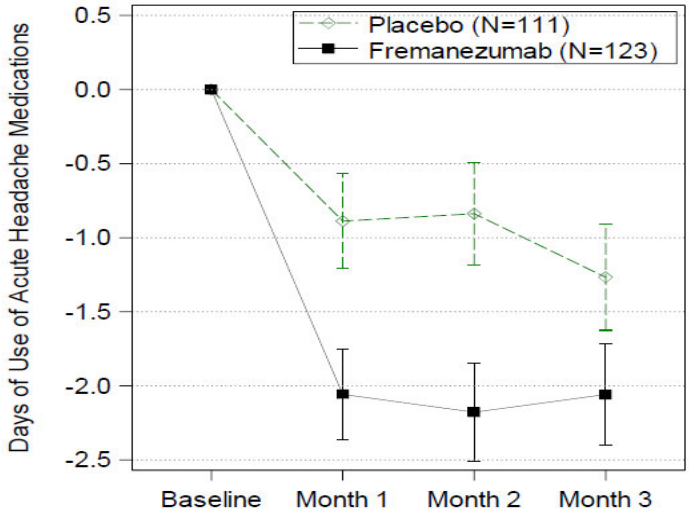
Statistic	Placebo (N=111)	Fremanezumab (N=123)
LS mean (SE)	-1.0 (0.30)	-2.1 (0.29)
95% confidence interval	-1.56, -0.36	-2.64, -1.48
Comparison with placebo		
LS mean (SE)	-	-1.1 (0.34)
95% confidence interval - -	-	-1.77, -0.42
p-value	-	0.0016

ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares; SE=standard error of the mean.
Note: LS mean (SE), 95% CI, and p-value represent the results obtained from the ANCOVA model with treatment, sex, puberty status, region, weight category, and baseline preventive migraine medication use (yes/no) as fixed effects and the baseline number of migraine days as a covariate.
Verified by Statistical Reviewer.

Sensitivity Analysis

Sensitivity analyses confirmed the findings, showing nominally statistically significant differences ($p < 0.05$) between fremanezumab and placebo for both FAS and PP analyses. Specifically, MMRM analyses revealed nominally significant differences at Months 1, 2, and overall, with numerical differences at Month 3, for both FAS and PP sets.

Figure 5:Line Plot of LS Mean (± SE) Change from Baseline in Monthly Average Number of Days of Use of Any Acute Headache Medications During 12-Week Period After the First Dose of Trial Drug by Treatment Group Using MMRM (Full Analysis Set)



3.2.4.1.2.4 Mean Change from Baseline (Day 1) in Migraine-Related Disability Score, as Measured by the Pediatric Migraine Disability Assessment (PedMIDAS) Questionnaire, at 12 Weeks After the First Dose of Trial Drug

In the FAS analysis, the mean change from baseline in migraine-related disability score at week-12 showed no statistically significant difference between placebo and fremanezumab, although a trend suggested slightly lower scores in the fremanezumab group. Due to the pre-defined hierarchical testing procedure, subsequent endpoints were not to be interpreted inferentially.

Table 9: Mean Change from Baseline at Week 12 After the First Dose of Trial Drug in PedMIDAS Questionnaire by Treatment Group (Full Analysis Set)

Statistic	Placebo (N=111)	Fremanezumab (N=123)
LS mean (SE)	-15.3 (3.37)	-21.6 (3.29)
95% confidence interval	-21.98, -8.68	-28.07, -15.10
Comparison with placebo		

LS mean (SE)	-	-6.3 (3.79)
95% confidence interval - -	-	-13.72, 1.21
p-value	-	0.1001

LS=least squares; PedMIDAS= Pediatric Migraine Disability Assessment; SE=standard error of the mean.
Note: For PedMIDAS total score, larger scores reflect greater disability.

3.2.4.2 Statistical and Analytical Issues

Analysis of covariates, handling of dropouts and missing data, and multiplicity control were performed according to the statistical analysis plan (SAP).

The primary efficacy analysis revealed a significant effect of site 53452. When this site was excluded from the analysis, the resulting p-value increased to 0.052, exceeding the significance threshold of 0.05. This is not a significant concern.

The analysis excluded participants with fewer than 10 days of e-diary data, raising potential concerns regarding selection bias. Despite repeated recommendations to avoid this exclusion, the sponsor did not do so. However, there is only placebo subject had fewer than 10 days of e-diary data, and the exclusion does not have meaningful impact on the results.

The sponsor redefined the primary endpoint, monthly migraine days, for consistency with previous studies. However, the new derivation (appendix B of SAP) omits probable migraine (defined as at least 2 hours duration with at least one migraine symptom) and is inconsistent with the migraine day definition in Section 6.2 of SAP. This discrepancy was raised as an Information Request (IR), in which clinical reviewer acknowledged that the new derivation is acceptable.

3.3 Evaluation of Safety

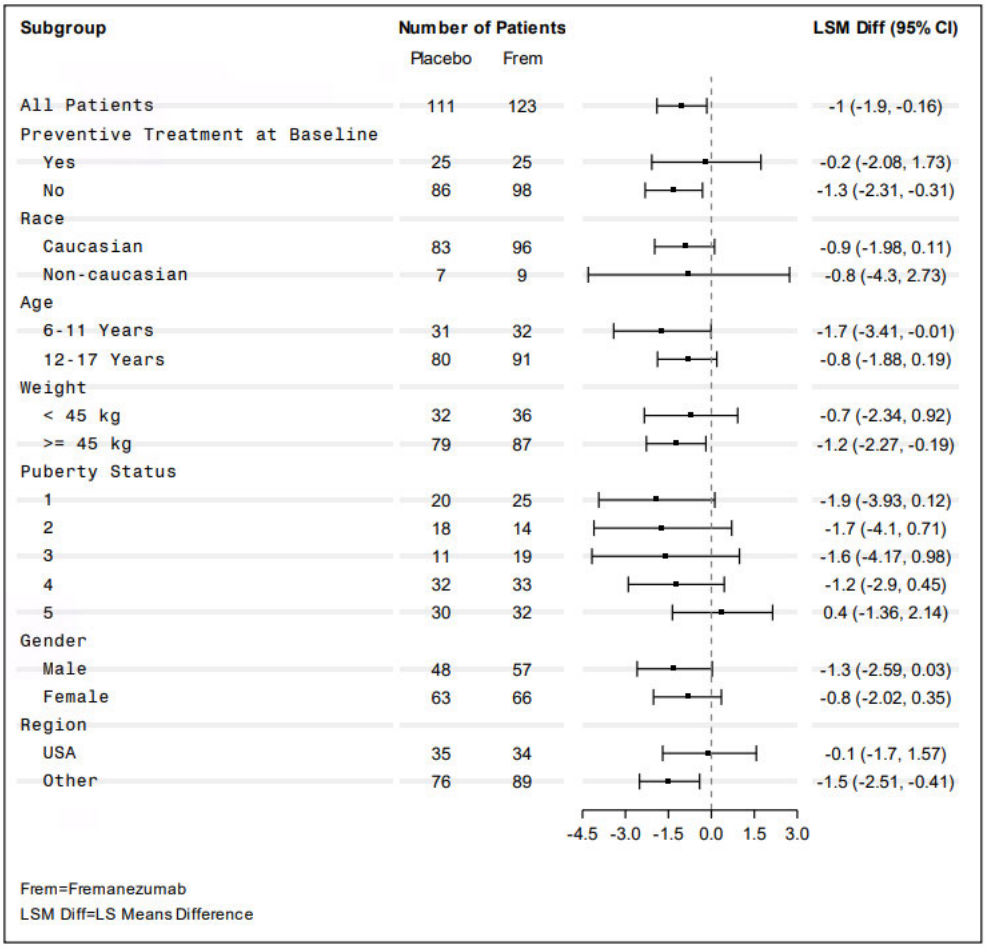
Please refer to the clinical team's review for a detailed analysis of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The results of subgroup analyses by concomitant preventative medication at baseline, different race groups, age groups, weight groups, puberty status, sex, and region for primary endpoint on the FAS dataset are described in the following forest plot, see Figure 8.

In most of the subgroups the treatment group shows a trend of numerically more reduction in monthly average number of migraine days than placebo from baseline (except for subgroup puberty status of stage 5). The region subgroup of USA, and preventative treatment at baseline subgroup showed a point estimate close to zero.

Figure 6: Forest Plot for Subgroup Analysis on Primary Endpoint: Mean Change from Baseline in Monthly Average Number of Migraine Days During 12-Week Period by Treatment Group Using ANCOVA (Full Analysis Set)



4.1 Gender, Race, Age, and Geographic Region

4.1.1 Race

Subgroup analysis for race on the primary endpoint based on the full analysis set and similar ANCOVA model as the primary analysis is not significant in both the race groups i.e., Caucasian, and non-Caucasian. Similar results were seen for the sensitivity analysis using the MMRM model in both the race groups.

Statistic	Placebo	Fremanezumab
	Race = Caucasian	
n	83	96
LS mean (SE)	-1.8 (0.39)	-2.7 (0.36)

Statistic	Placebo	Fremanezumab
95% confidence interval	-2.57, -1.04	-3.45, -2.03
Comparison with placebo		
LS mean (SE)	-	-0.9 (0.53)
95% confidence interval - -	-	-1.98, 0.11
p-value	-	0.0801
Race = non-Caucasian		
n	7	9
LS mean (SE)	-1.8 (1.34)	-2.6 (1.18)
95% confidence interval	-4.47, 0.82	-4.93, -0.29
Comparison with placebo		
LS mean (SE)	-	-0.8 (1.78)
95% confidence interval - -	-	-4.30, 2.73
p-value	-	0.6612

4.1.2 Age Groups

Subgroup analysis for age group on the primary endpoint based on the full analysis set and similar ANCOVA model as the primary analysis is barely significant (p-value 0.0488) in 6-11 years age group and not significant in 12-17 years age group.

Statistic	Placebo	Fremanezumab
Age = 6-11 Years		
n	31	32
LS mean (SE)	-1.7 (0.61)	-3.4 (0.60)
95% confidence interval	-2.88, -0.46	-4.57, -2.19
Comparison with placebo		
LS mean (SE)	-	-1.7 (0.86)
95% confidence interval	-	-3.41, -0.01
p-value	-	0.0488
Age = 12-17 Years		
n	80	91
LS mean (SE)	-1.8 (0.38)	-2.7 (0.36)
95% confidence interval	-2.58, -1.07	-3.37, -1.96
Comparison with placebo		
LS mean (SE)	-	-0.8 (0.53)
95% confidence interval	-	-1.88, 0.19
p-value	-	0.1096

4.1.3 Gender

Subgroup analysis for gender on the primary endpoint based on the full analysis set and similar ANCOVA model as the primary analysis is not significant for both male and female subgroups.

Statistic	Placebo	Fremanezumab
Gender = Male		
n	48	57
LS mean (SE)	-2.2 (0.49)	-3.5 (0.45)
95% confidence interval	-3.16, -1.23	-4.36, -2.58
Comparison with placebo		
LS mean (SE)	-	-1.3 (0.67)
95% confidence interval	-	-2.59, 0.03
p-value	-	0.0555
Gender = Female		
n	63	66
LS mean (SE)	-1.5 (0.43)	-2.3 (0.42)
95% confidence interval	-2.31, -0.63	-3.14, -1.48
Comparison with placebo		
LS mean (SE)	-	-0.8 (0.60)
95% confidence interval	-	-2.02, 0.35
p-value	-	0.1647

4.1.4 Region

Subgroup analysis for region on the primary endpoint based on the full analysis set and similar ANCOVA model as the primary analysis is not significant for USA and significant for “Other” region.

Statistic	Placebo	Fremanezumab
Region = USA		
n	35	34
LS mean (SE)	-1.9 (0.58)	-2.0 (0.59)
95% confidence interval	-3.02, -0.75	-3.11, -0.79
Comparison with placebo		
LS mean (SE)	-	-0.1 (0.83)
95% confidence interval	-	-1.70, 1.57
p-value	-	0.9377
Region = Other		
n	76	89
LS mean (SE)	-1.7 (0.39)	-3.2 (0.36)
95% confidence interval	-2.50, -0.97	-3.90, -2.48
Comparison with placebo		
LS mean (SE)	-	-1.5 (0.53)
95% confidence interval	-	-2.51, -0.41
p-value	-	0.0066

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues that impact the overall conclusions were identified. Missing data and intercurrent events were limited and did not significantly impact the study results.

5.2 Collective Evidence

Trial TV48125-CNS-30083 confirmed that Fremanezumab effectively reduced the monthly average number of migraine and headache days in pediatric patients aged 6-17. Compared to placebo, the Fremanezumab group showed a significantly greater reduction in the monthly average number of days using acute headache medication. Additionally, participants on Fremanezumab had two times higher odds of achieving at least a 50% reduction in the monthly average number of migraine days during the 12-week study period. The trial also suggested a trend for rapid onset of efficacy, with effects seen as early as 4 weeks after the first dose, which aligns with Fremanezumab's established efficacy profile in adults. The results are generally consistent across subgroups.

5.3 Conclusions and Recommendations

The results of trial TV48125-CNS-30083 support the preventative treatment of the proposed indication of episodic migraine in pediatric patients 6 to 17 years of age.

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/s/

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