# Clinical trial results:
# A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Chronic Migraine in Pediatric Patients 6 to 17 Years of Age

## Summary

| | |
|---|---|
| EudraCT number | 2019-002053-33 |
| Trial protocol | DE FI NL PL IT |
| Global end of trial date | 29 November 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 June 2025 |
| First version publication date | 08 June 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | TV48125-CNS-30082 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04464707 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Teva Branded Pharmaceutical Products R&D, Inc. |
| Sponsor organisation address | 145 Brandywine Parkway, West Chester, United States, 19380 |
| Public contact | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., MedInfo@tevaeu.com |
| Scientific contact | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., MedInfo@tevaeu.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001877-PIP01-15 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 29 November 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 November 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 November 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effectiveness of fremanezumab as compared to placebo for the preventive treatment of chronic migraine (CM).

Protection of trial subjects:

This trial was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6), ISO 14155: Clinical investigation of medical devices for human subjects – Good clinical practice, and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 September 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 31 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | Finland: 30 |
| Country: Number of subjects enrolled | Israel: 25 |
| Country: Number of subjects enrolled | Italy: 44 |
| Country: Number of subjects enrolled | Netherlands: 12 |
| Country: Number of subjects enrolled | Poland: 30 |
| Country: Number of subjects enrolled | United States: 99 |
| Worldwide total number of subjects | 292 |
| EEA total number of subjects | 137 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|---|---|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 36 |
| Adolescents (12-17 years) | 256 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 494 participants were screened; of which 292 participants were randomized and included in the analysis.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Participants received placebo matched to fremanezumab subcutaneously (SC) for 3 months (Days 1, 29, and 57).

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo matched to fremanezumab was administered per schedule specified in the arm description.

| | |
|---|---|
| **Arm title** | Fremanezumab Dose A |

Arm description:

Participants weighing <threshold weight received fremanezumab SC at Dose A for 3 months (Days 1, 29, and 57).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fremanezumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Fremanezumab was administered per schedule specified in the arm description.

| | |
|---|---|
| **Arm title** | Fremanezumab Dose B |

Arm description:

Participants weighing ≥threshold weight received fremanezumab SC at Dose B for 3 months (Days 1, 29, and 57).

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Fremanezumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Fremanezumab was administered per schedule specified in the arm description.

| **Number of subjects in period 1** | Placebo | Fremanezumab Dose A | Fremanezumab Dose B |
|---|---|---|---|
| Started | 143 | 26 | 123 |
| Received at Least 1 Dose of Study Drug | 143 | 26 | 123 |
| Completed | 139 | 25 | 120 |
| Not completed | 4 | 1 | 3 |
| Consent withdrawn by subject | - | - | 2 |
| Adverse event, non-fatal | 1 | - | - |
| Protocol Deviation | 1 | - | - |
| Withdrawal by Parent/Guardian | - | 1 | - |
| Lost to follow-up | 2 | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo matched to fremanezumab subcutaneously (SC) for 3 months (Days 1, 29, and 57). | |
| Reporting group title | Fremanezumab Dose A |
| Reporting group description: | |
| Participants weighing <threshold weight received fremanezumab SC at Dose A for 3 months (Days 1, 29, and 57). | |
| Reporting group title | Fremanezumab Dose B |
| Reporting group description: | |
| Participants weighing ≥threshold weight received fremanezumab SC at Dose B for 3 months (Days 1, 29, and 57). | |

| Reporting group values | Placebo | Fremanezumab Dose A | Fremanezumab Dose B |
|---|---|---|---|
| Number of subjects | 143 | 26 | 123 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 14.3 | 11.7 | 15.2 |
| standard deviation | ± 2.46 | ± 2.60 | ± 1.75 |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 102 | 15 | 97 |
| Male | 41 | 11 | 26 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 123 | 21 | 101 |
| Black or African American | 4 | 0 | 4 |
| Asian | 0 | 0 | 2 |
| Other | 2 | 1 | 2 |
| Missing | 14 | 4 | 14 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 8 | 2 | 12 |
| Not Hispanic or Latino | 135 | 23 | 109 |
| Unknown or Not Reported | 0 | 1 | 2 |
| Number of Migraine Days Per Month | | | |
| A migraine day was defined as a day with any of the following: A day with at least 2 hours of headache with ≥2 migraine symptom(s) or day demonstrating a headache treated with migraine medications (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol etc.), or a headache associated with aura. The number of migraine days during baseline was calculated using headache diary data collected in the run-in period and normalized to a 28-day equivalent using formula: (Total migraine days during run-in/Total days with assessments recorded in the diary for the run-in period) × 28. | | | |
| Units: migraine days per month | | | |
| arithmetic mean | 15.7 | 12.3 | 14.4 |
| standard deviation | ± 5.02 | ± 6.42 | ± 5.32 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 292 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 214 | | |
| Male | 78 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 245 | | |
| Black or African American | 8 | | |
| Asian | 2 | | |
| Other | 5 | | |
| Missing | 32 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 22 | | |
| Not Hispanic or Latino | 267 | | |
| Unknown or Not Reported | 3 | | |
| Number of Migraine Days Per Month | | | |
| A migraine day was defined as a day with any of the following: A day with at least 2 hours of headache with ≥2 migraine symptom(s) or day demonstrating a headache treated with migraine medications (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol etc.), or a headache associated with aura. The number of migraine days during baseline was calculated using headache diary data collected in the run-in period and normalized to a 28-day equivalent using formula: (Total migraine days during run-in/Total days with assessments recorded in the diary for the run-in period) × 28. | | | |
| Units: migraine days per month<br>arithmetic mean<br>standard deviation | <br><br>- | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo matched to fremanezumab subcutaneously (SC) for 3 months (Days 1, 29, and 57). | |
| Reporting group title | Fremanezumab Dose A |
| Reporting group description: | |
| Participants weighing <threshold weight received fremanezumab SC at Dose A for 3 months (Days 1, 29, and 57). | |
| Reporting group title | Fremanezumab Dose B |
| Reporting group description: | |
| Participants weighing ≥threshold weight received fremanezumab SC at Dose B for 3 months (Days 1, 29, and 57). | |
| Subject analysis set title | Fremanezumab |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Participants received fremanezumab SC for 3 months (Days 1, 29, and 57). | |
| Subject analysis set title | Fremanezumab |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Participants weighing < threshold will receive Dose A subcutaneously monthly for 3 months.<br>Participants weighing ≥ threshold will receive Dose B subcutaneously monthly for 3 months. | |

### Primary: Mean Change From Baseline in Monthly Average Number of Migraine Days During 12-Week Period After the First Dose of Study Drug

| | |
|---|---|
| End point title | Mean Change From Baseline in Monthly Average Number of Migraine Days During 12-Week Period After the First Dose of Study Drug[1] |
| End point description: | |
| A migraine day was defined as a day with any of the following: A day (0:00 to 23:59) with at least 2 hours of headache with ≥2 migraine symptom(s) or day (0:00 to 23:59) demonstrating a headache treated with migraine medications (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol etc.), or a headache associated with aura.<br><br>Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over 12-week period/number of days with assessments recorded in electronic diary (e-diary) for 12-week period) * 28. Least square (LS) mean was calculated using analysis of covariance (ANCOVA). The full analysis set (FAS) included all randomized participants who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on primary endpoint. Efficacy analysis was planned to be collected and evaluated combined for both fremanezumab dose treatment groups. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (Day -28 to Day -1), up to Week 12 | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| End point values | Placebo | Fremanezumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 140 | 149 | | |
| Units: days/month | | | | |
| least squares mean (standard error) | -3.7 (± 0.78) | -3.8 (± 0.80) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Placebo v Fremanezumab |
| Number of subjects included in analysis | 289 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8484 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.48 |
| upper limit | 1.22 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.69 |

**Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)**

| End point title | Number of Participants With Treatment-Emergent Adverse Events (TEAEs) |
|---|---|

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious AEs (SAEs) were defined as death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized participant and required medical intervention to prevent 1 of the outcomes listed in this definition. AEs were considered TEAEs if onset occurred on or after the first dose date. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. The safety analysis set included all randomized participants who received at least 1 dose of study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Month 3

| End point values | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 26 | 123 | |
| Units: participants | 77 | 16 | 71 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Shift From Baseline to Last Assessment in Electrocardiogram (ECG) Findings (Assessed by Investigator)

| End point title | Number of Participants With Shift From Baseline to Last Assessment in Electrocardiogram (ECG) Findings (Assessed by Investigator) |
|---|---|

End point description:

The number of participants with a shift from Baseline (Normal, Abnormal CS [Clinically Significant], or Abnormal NCS [Not Clinically Significant]) in any of the following ECG parameters is reported by treatment group: Heart rate, PR interval, QRS interval, RR interval, QT interval, QT interval corrected using the Bazett's formula (QTcB), and QT interval corrected using the Fridericia formula (QTcF). Last assessment was defined as the last observed postbaseline interpretation. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. The safety analysis set included all randomized participants who received at least 1 dose of study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to last assessment (up to Month 3)

| End point values | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 26 | 123 | |
| Units: participants | | | | |
| Normal/Normal | 127 | 25 | 110 | |
| Abnormal NCS/Normal | 5 | 0 | 3 | |
| Abnormal CS/Normal | 0 | 0 | 0 | |
| Normal/Abnormal NCS | 7 | 0 | 7 | |
| Abnormal NCS/Abnormal NCS | 3 | 1 | 2 | |
| Abnormal CS/Abnormal NCS | 0 | 0 | 0 | |
| Normal/Abnormal CS | 0 | 0 | 0 | |
| Abnormal NCS/Abnormal CS | 0 | 0 | 0 | |
| Abnormal CS/Abnormal CS | 0 | 0 | 0 | |
| Missing | 1 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Shift From Baseline to Last Assessment in ECG Findings (Assessed by Cardiologist)

| End point title | Number of Participants With Shift From Baseline to Last Assessment in ECG Findings (Assessed by Cardiologist) |
|---|---|

End point description:

The number of participants with a shift from Baseline (Normal or Abnormal) in any of the following ECG parameters is reported by treatment group: Heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB, and QTcF. Last assessment was defined as the last observed postbaseline interpretation. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. The safety analysis set included all randomized participants who received at least 1 dose of study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to last assessment (up to Month 3)

| End point values | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 26 | 123 | |
| Units: participants | | | | |
| Normal/Normal | 118 | 22 | 109 | |
| Abnormal/Normal | 7 | 0 | 1 | |
| Normal/Abnormal | 12 | 1 | 6 | |
| Abnormal/Abnormal | 5 | 3 | 5 | |
| Missing | 1 | 0 | 2 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Any One or More Potentially Clinically Significant (PCS) Vital Signs Abnormalities

| End point title | Number of Participants With Any One or More Potentially Clinically Significant (PCS) Vital Signs Abnormalities |
|---|---|

End point description:

The PCS abnormal vital signs findings included any one of the following: Pulse rate ≥120 beats per minute (bpm) and increase from baseline of ≥15 bpm, or ≤50 bpm and decrease from baseline of ≥15 bpm; or ≤60 bpm and decrease from baseline of ≥15 bpm; and Respiratory rate <15 breaths/minute. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. The safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' = participants with at least one Baseline and post-baseline vital sign assessment.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Month 3

| End point values | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 142 | 26 | 122 | |
| Units: participants | 5 | 2 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With PCS Abnormal Laboratory (Serum Chemistry, Hematology, Coagulation, and Urinalysis) Results

| End point title | Number of Participants With PCS Abnormal Laboratory (Serum Chemistry, Hematology, Coagulation, and Urinalysis) Results |
|---|---|

End point description:

Serum chemistry tests with PCS abnormal findings included: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both ≥2*upper limit of normal (ULN); and bilirubin ≥34.2 micromole/liter (umol/L). Hematology tests with PCS abnormal findings included: hemoglobin ≤100 grams (g)/L, leukocytes ≤3*10^9 cells/L, and eosinophils/leukocytes ≥10%. Coagulation parameter test with PCS abnormal findings included: prothrombin international normalized ratio (INR) >1.5. Urinalysis laboratory tests with PCS abnormal findings included: urine protein ≥2 units (U) increase from baseline. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. The safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' and 'n'= participants with at least one Baseline and post-baseline assessment of the specified laboratory parameters.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Month 1, and Month 3

| End point values | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 142 | 26 | 122 | |
| Units: participants | | | | |
| Serum chemistry abnormality (n=142,26,121) | 6 | 1 | 5 | |
| Hematology abnormality (n=140,25,121) | 6 | 2 | 5 | |
| Coagulation abnormality (n=142,25,121) | 1 | 0 | 2 | |
| Urinalysis abnormality (n=140,26,122) | 2 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Abnormal Physical Examination Findings as Identified by the Investigator

| End point title | Number of Participants With Abnormal Physical Examination |
|---|---|

| | |
|---|---|
| | Findings as Identified by the Investigator |

End point description:

A complete physical examination included the following organ systems: general appearance; head, eyes, ears, nose, and throat (HEENT); chest and lungs; cardiovascular; abdomen; musculoskeletal; skin; lymph nodes; neurological, and extremities/back. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. The safety analysis set included all randomized participants who received at least 1 dose of study drug.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline up to Month 3

| **End point values** | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 26 | 123 | |
| Units: participants | 11 | 0 | 9 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Suicidal Ideation or Suicidal Behavior as Assessed by the Columbia Suicide Severity Rating Scale (C-SSRS)

| | |
|---|---|
| End point title | Number of Participants With Suicidal Ideation or Suicidal Behavior as Assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) |

End point description:

C-SSRS is a questionnaire to assess suicidal ideation and suicidal behavior. Suicidal behavior was defined as a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Suicidal ideation was defined as a "yes" answer to any one of 5 suicidal ideation questions: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent, any self-injurious behavior with no suicidal intent. The safety analysis set included all randomized participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' = participants with both Baseline and Month 3 assessment.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline and Month 3

| **End point values** | Placebo | Fremanezumab Dose A | Fremanezumab Dose B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 26 | 123 | |
| Units: participants | | | | |
| Baseline | 2 | 0 | 1 | |
| Month 3 | 1 | 0 | 0 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean 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 Study Drug

| End point title | Mean 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 Study Drug[2] |
|---|---|

End point description:

Participants recorded any headache medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken each day in their electronic headache diary device. Acute headache medication included triptans and ergot compounds, NSAIDs, or paracetamol. Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over 12-week period/number of days with assessments recorded in e-diary for 12-week period) * 28. LS mean was calculated using ANCOVA. The FAS included all randomized participants who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint. Efficacy analysis was planned to be collected and evaluated combined for both fremanezumab dose treatment groups.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day -28 to Day -1), up to Week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| End point values | Placebo | Fremanezumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 140 | 149 | | |
| Units: days/month | | | | |
| least squares mean (standard error) | -2.2 (± 0.46) | -2.0 (± 0.47) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants 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

| End point title | Number of Participants 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[3] |
|---|---|

End point description:

A migraine day was defined as a calendar day where the participant reported either of the following: A calendar day (00:00 to 23:59) demonstrating at least 2 consecutive hours of a headache that was

accompanied by ≥1 migraine symptom(s) or a calendar day (00:00 to 23:59) demonstrating a headache of any duration that was treated with acute headache medications (NSAIDs, paracetamol or triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over 12-week period/number of days with assessments recorded in e-diary for 12-week period) * 28. LS mean was calculated using ANCOVA. The FAS included all randomized participants who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint. Efficacy analysis was planned to be collected and evaluated combined for both fremanezumab dose treatment groups.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day -28 to Day -1) up to Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| **End point values** | Placebo | Fremanezumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 140 | 149 | | |
| Units: participants | 28 | 30 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During 12-Week Period After the First Dose of Study Drug

| End point title | Mean Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During 12-Week Period After the First Dose of Study Drug[4] |
|---|---|

End point description:

A headache day of at least moderate severity was defined as a calendar day (00:00 to 23:59) where the participant reported either of the following: A day with headache pain that lasted ≥2 hours with a peak severity of at least moderate severity or a day where the participant used acute headache medication (triptans, ergots, NSAIDs, or paracetamol) to treat a headache of any severity or duration. Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over 12-week period/number of days with assessments recorded in e-diary for 12-week period) * 28. LS mean was calculated using ANCOVA. The FAS included all randomized participants who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint. Efficacy analysis was planned to be collected and evaluated combined for both fremanezumab dose treatment groups.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day -28 to Day -1), up to Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| End point values | Placebo | Fremanezumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 140 | 149 | | |
| Units: days/month | | | | |
| least squares mean (standard error) | -3.8 (± 0.76) | -3.1 (± 0.78) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline in Migraine-related Disability Score at Week 12, as Measured by the Pediatric Migraine Disability Assessment (PedMIDAS) Questionnaire

| End point title | Mean Change From Baseline in Migraine-related Disability Score at Week 12, as Measured by the Pediatric Migraine Disability Assessment (PedMIDAS) Questionnaire[5] |
|---|---|

End point description:

PedMIDAS includes 3 subscales: impact of headache on school performance (scores range 0-92), disability at home (scores range 0-92), social/sport functioning (scores range 0-92). Subscales are added to get the total score with a range 0 to 276. Total score was used for grading of disability, with 4 score categories of 0 to 10, 11 to 30, 31 to 50, and 51-276 interpreted as disability grades 1 (little/no disability), 2 (mild disability), 3 (moderate disability), and 4 (severe disability). Higher total scores indicated severe disability. LS mean was calculated using ANCOVA. Change from baseline score is reported with a range of -276 to 276 with higher scores indicating more severe disability. FAS included all randomized participants who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on primary endpoint. Efficacy analysis was planned to be collected and evaluated combined for both fremanezumab dose treatment groups.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 12

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| End point values | Placebo | Fremanezumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 140 | 149 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -33.5 (± 7.97) | -26.2 (± 8.17) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline in Quality of Life at Week 12, as Measured by Pediatric Quality of Life Inventory (PedsQL) Questionnaire

| End point title | Mean Change From Baseline in Quality of Life at Week 12, as Measured by Pediatric Quality of Life Inventory (PedsQL) Questionnaire[6] |
|---|---|

End point description:

PedsQL 4.0 (23-item instrument) evaluates quality of life (QoL) in 4 areas of functioning: physical, emotional, social, and school. For child and adolescent self-report (8-18 years) and parent report forms, a 5-point Likert scale was used to rate severity (0=never a problem;1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). For younger children (5-7 years), a 3-point Likert scale, anchored with a happy and sad face, was used (0=not at all a problem; 2=sometimes a problem; 4=a lot of a problem). PedsQL yields a total QoL score and 2 summary scores: Physical Health Summary Score and Psychosocial Health Summary Score. To obtain scores, items were reverse scored, transformed to a 0 to 100 scale (0=100, 1=75, 2=50, 3=25, 4=0), and averaged; total scores near 0 indicated lower QoL, while scores approaching 100 indicated higher QoL. Analysis was done on FAS. Efficacy analysis was collected and evaluated combined for both fremanezumab dose groups.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 12

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| **End point values** | Placebo | Fremanezumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 140 | 149 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Child-Physical Health Summary Score | 8.0 (± 2.11) | 6.5 (± 2.20) | | |
| Child-Psychosocial Health Summary Score | 7.7 (± 1.36) | 6.6 (± 1.40) | | |
| Child-Total Scale Score | 7.6 (± 1.43) | 6.2 (± 1.48) | | |
| Parent-Physical Health Summary Score | 12.0 (± 3.43) | 4.7 (± 3.80) | | |
| Parent-Psychosocial Health Summary Score | 11.6 (± 2.40) | 4.9 (± 2.65) | | |
| Parent-Total Scale Score | 11.7 (± 2.47) | 4.8 (± 2.73) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Developing Anti-drug Antibodies (ADAs) Throughout the Study

| End point title | Number of Participants Developing Anti-drug Antibodies (ADAs) Throughout the Study[7] |
|---|---|

End point description:

Number of participants who developed ADAs were reported. The FAS included all randomized participants who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint. Here, 'Overall number of participants analyzed' = Participants who had Baseline and at least 1 postbaseline ADA assessment.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Month 3

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting statistics for the specified arms only.

| End point values | Fremanezumab Dose A | Fremanezumab Dose B | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 121 | | |
| Units: participants | 1 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Baseline up to Month 3 | |
| Adverse event reporting additional description: | |
| The safety analysis set included all randomized participants who received at least 1 dose of study drug. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo matched to fremanezumab SC for 3 months (Days 1, 29, and 57). | |
| Reporting group title | Fremanezumab Dose B |
| Reporting group description: | |
| Participants weighing ≥threshold weight received fremanezumab SC at Dose B for 3 months (Days 1, 29, and 57). | |
| Reporting group title | Fremanezumab Dose A |
| Reporting group description: | |
| Participants weighing <threshold weight received fremanezumab SC at Dose A for 3 months (Days 1, 29, and 57). | |

| Serious adverse events | Placebo | Fremanezumab Dose B | Fremanezumab Dose A |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 143 (3.50%) | 4 / 123 (3.25%) | 0 / 26 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | 3 / 123 (2.44%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status migrainosus | | | |
| subjects affected / exposed | 0 / 143 (0.00%) | 1 / 123 (0.81%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 143 (0.70%) | 0 / 123 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | 0 / 123 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Neurosis | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | 0 / 123 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | 0 / 123 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Placebo | Fremanezumab Dose B | Fremanezumab Dose A |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 143 (27.27%) | 30 / 123 (24.39%) | 8 / 26 (30.77%) |
| Nervous system disorders | | | |
| Migraine | | | |
| subjects affected / exposed | 4 / 143 (2.80%) | 2 / 123 (1.63%) | 2 / 26 (7.69%) |
| occurrences (all) | 4 | 2 | 3 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 20 / 143 (13.99%) | 13 / 123 (10.57%) | 3 / 26 (11.54%) |
| occurrences (all) | 31 | 15 | 4 |
| Injection site pain | | | |
| subjects affected / exposed | 14 / 143 (9.79%) | 12 / 123 (9.76%) | 5 / 26 (19.23%) |
| occurrences (all) | 25 | 14 | 7 |

| | | | |
|---|---|---|---|
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 15 / 143 (10.49%)<br>20 | 10 / 123 (8.13%)<br>14 | 3 / 26 (11.54%)<br>3 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 June 2019 | The primary reasons for this amendment were to improve the feasibility of the diary compliance requirement, clarify the exclusion criterion for nerve stimulation or device, and clarify the timing of injection site reaction assessment. |
| 05 December 2019 | The primary reason for this amendment was to update the protocol with the dose to be used for participants <45.0 kg following the completion of the Phase 1 pediatric pharmacokinetic study (TV48125-CNS-10141). |
| 03 February 2020 | The primary reason for this amendment was to update the sponsor's address. |
| 20 April 2020 | The primary reason for this amendment was to revise an exclusion criterion to exclude participants with a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome. |
| 27 June 2020 | The primary reason for this amendment was to revise the protocol in accordance with the Grounds for Non-Acceptance received from the Voluntary Harmonization Procedure (VHP). Major changes to the protocol included: - Inclusion criterion was revised to specify that some countries may allow participants aged 15 to 17 years to give written informed consent, per local regulations. - Exclusion criterion was revised to specify that exclusion of a participant based on clinically significant psychiatric condition was at the discretion of the investigator. - Exclusion criterion was revised to exclude those with a known active coronavirus disease of 2019 (COVID-19) infection; to exclude participants taking a combined estrogen and progestogen hormonal contraceptive; and to exclude participants concomitantly using lamotrigine. - An exclusion of participants with an estimated glomerular filtration rate of <90 milliliters (mL)/minute/1.73 square meter (m^2) was added as another means of evidence of renal disease. - Exclusion criteria was added to ensure participants with a known hypersensitivity were not enrolled in the study. - Additional information on the selected weight cutoff for the pediatric population has been added for investigator awareness. - Additional information on the pediatric population pharmacokinetic model to determine the dose for participants weighing <45 kg was added for investigator awareness. |
| 27 July 2020 | The primary reason for this amendment was to revise the protocol in accordance with the conditions for approval of the clinical trial application received from the VHP. |
| 20 August 2020 | The primary reason for this amendment was to provide guidance for remote assessments to minimize the time that participants and caregivers were required to spend at the study site. This consideration was triggered by the COVID-19 pandemic; however, remote assessments could be carried out on a regular basis to provide flexibility for participants, caregivers, and site staff. Patient reported outcomes assessed in this study, including the PedMIDAS, PedsQL, and Patients Global Impression of Improvement (PGI-I), as well as the C-SSRS, were valid to be conducted remotely, as confirmed by the scale authors. Instructions on remote data collection were available in the site operational manual. |
| 09 December 2021 | The primary reason for this amendment was to revise the protocol to allow combined oral progestin and estrogen contraceptives, expand the body mass index (BMI) upper limit to 120% of the 95th percentile in order to reflect the real-world participant population, and to clarify potential sample size changes subsequent to the planned interim analysis. |

| | |
|---|---|
| 24 September 2023 | The primary reason for this protocol amendment was to reduce the trial population size and relaxation of the inclusion criteria. Consequently, there was reduction in statistical power and a removal of the interim analysis. In alignment with the new protocol template, the terms "study(ies)" and "patient(s)" were updated to "trial(s)" and "participant(s)", respectively, throughout the document. In addition, where appropriate the term "test investigational medicinal product (IMP)" was used for the Teva product under study and the term for "placebo" was updated to "placebo IMP". |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported