



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 Episodic Migraine in Pediatric Patients 6 to 17 Years of Age

Summary

EudraCT number	2019-002055-42
Trial protocol	DE FI PL NL IT
Global end of trial date	13 March 2024

Results information

Result version number	v1
This version publication date	26 September 2024
First version publication date	26 September 2024

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30083
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04458857
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)	EMA-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	18 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2024
Global end of trial reached?	Yes
Global end of trial date	13 March 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 efficacy of fremanezumab as compared to placebo for the preventive treatment of episodic migraine (EM).

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) and 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	15 July 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	Germany: 11
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Finland: 36
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	United States: 70
Worldwide total number of subjects	235
EEA total number of subjects	135

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)	64
Adolescents (12-17 years)	171
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 411 participants were screened; of which 235 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
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Arm title	Placebo
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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
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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
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Arm description:

Participants weighing $\geq$ threshold weight received fremanezumab SC at dose B for 3 months (Days 1, 29, and 57).

Arm type	Experimental
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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	112	36	87
Received at least 1 dose of study drug	112	36	87
Completed	106	33	86
Not completed	6	3	1
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	-	1	-
Non-compliance with study drug	-	1	-
Lost to follow-up	4	1	-
Withdrawal by parent/guardian	-	-	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	112	36	87
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	13.4	11.0	14.2
standard deviation	± 2.99	± 2.27	± 2.34
Sex: Female, Male			
Units: participants			
Female	64	16	50
Male	48	20	37
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	1	4
White	84	28	68
More than one race	0	0	0
Unknown or Not Reported	24	7	13
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	9	4	8
Not Hispanic or Latino	102	31	75
Unknown or Not Reported	1	1	4
Number of Migraine Days			
A migraine day was defined as a calendar day where the participant reported either of the following: A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache that was accompanied by ≥1 migraine symptom(s) or a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine specific medications (non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol or triptans and ergot compounds).			
Units: days			

arithmetic mean	7.5	7.6	7.9
standard deviation	± 2.84	± 2.92	± 3.21

Reporting group values	Total		
Number of subjects	235		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	130		
Male	105		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	9		
White	180		
More than one race	0		
Unknown or Not Reported	44		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	21		
Not Hispanic or Latino	208		
Unknown or Not Reported	6		
Number of Migraine Days			
A migraine day was defined as a calendar day where the participant reported either of the following: A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache that was accompanied by ≥1 migraine symptom(s) or a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine specific medications (non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol or triptans and ergot compounds).			
Units: days			
arithmetic mean			
standard deviation	-		

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).	

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 calendar day where a participant reported either of the following: A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache that was accompanied by ≥1 migraine symptom(s) or a calendar day demonstrating a headache of any duration that was treated with migraine specific 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. Least square (LS) mean was calculated using analysis of covariance (ANCOVA). Full analysis set (FAS): 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 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: Efficacy analysis was planned to be evaluated combined for fremanezumab low and high dose treatment groups.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	111	123		
Units: days/month				
least squares mean (standard error)	-1.4 (± 0.39)	-2.5 (± 0.38)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fremanezumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.021
Method	ANCOVA
Parameter estimate	LS mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.44

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

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)
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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
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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	112	36	87	
Units: participants	55	20	48	

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)
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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
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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	112	36	87	
Units: participants				
Normal/Normal	92	32	74	
Abnormal NCS/Normal	13	0	4	
Abnormal CS/Normal	0	0	0	
Normal/Abnormal NCS	2	2	6	
Abnormal NCS/Abnormal NCS	4	1	3	
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	1	0	

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)
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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
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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	112	36	87	
Units: participants				
Normal/Normal	88	29	72	
Abnormal/Normal	14	0	5	
Normal/Abnormal	2	4	4	
Abnormal/Abnormal	6	2	6	
Missing	2	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With One or More Potentially Clinically Significant Vital Signs Abnormalities

End point title	Number of Participants With One or More Potentially Clinically Significant Vital Signs Abnormalities
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End point description:

Potentially clinically significant abnormal vital signs findings included: Pulse rate ≥ 120 beats per minute (bpm) and increase from baseline of ≥ 15 bpm, or ≤ 50 bpm and decrease from baseline of ≥ 15 bpm; Systolic blood pressure ≤ 85 millimeters of mercury (mmHg) and decrease from baseline of ≥ 20 mmHg; Diastolic blood pressure ≥ 100 mmHg and increase from baseline of ≥ 15 mmHg; 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
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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	112	35	87	
Units: participants	14	3	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Abnormal

Laboratory (Serum Chemistry, Hematology, Coagulation, and Urinalysis) Results

End point title	Number of Participants With Potentially Clinically Significant Abnormal Laboratory (Serum Chemistry, Hematology, Coagulation, and Urinalysis) Results
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End point description:

Potentially clinically significant abnormal findings included- Serum chemistry tests: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both $\geq 2 \times$ upper limit of normal (ULN); and bilirubin ≥ 34.2 micromole/liter (umol/L). Hematology tests: hemoglobin ≤ 100 grams (g)/L, leukocytes $\leq 3 \times 10^9$ cells/L, neutrophils $\leq 1 \times 10^9$ cells/L, eosinophils/leukocytes $\geq 10\%$, and platelets $\geq 700 \times 10^9$ cells/L or $\leq 75 \times 10^9$ cells/L. Coagulation parameter test: prothrombin international normalized ratio (INR) > 1.5 . Urinalysis laboratory tests: 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
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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	111	35	87	
Units: participants				
Serum chemistry abnormality (n=111,35,87)	2	1	3	
Hematology abnormality (n=110,34,87)	6	2	3	
Coagulation abnormality (n=110,35,87)	3	0	1	
Urinalysis abnormality (n=111,35,87)	1	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
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End point description:

A complete physical examination included the following organ systems: general appearance; head, eyes, ears, nose, and throat (HEENT); chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Only the organ systems with abnormal physical findings in at least one treatment group have been reported. 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 physical examination.

End point type	Secondary
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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	109	34	87	
Units: participants				
General Appearance	0	0	1	
HEENT	1	0	1	
Musculoskeletal	2	0	1	
Skin	5	1	2	
Neurological	1	0	0	
Extremities/Back	0	0	1	

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)
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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 ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants with both Baseline and Month 3 assessment.

End point type	Secondary
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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	105	33	86	
Units: participants				
Baseline	0	1	0	
Month 3	1	0	0	

Statistical analyses

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 ^[2]
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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 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 evaluated combined for both fremanezumab dose treatment groups.

End point type	Secondary
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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: Efficacy analysis was planned to be evaluated combined for fremanezumab low and high dose treatment groups.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	111	123		
Units: days/month				
least squares mean (standard error)	-1.5 ($\pm$ 0.42)	-2.6 ($\pm$ 0.40)		

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]
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End point description:

A migraine day was defined as a calendar day where the participant reported either of the following: A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache that was accompanied by ≥ 1 migraine symptom(s) or a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine specific 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. 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 evaluated combined for both fremanezumab dose treatment groups.

End point type	Secondary
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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: Efficacy analysis was planned to be evaluated combined for fremanezumab low and high dose treatment groups.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	111	123		
Units: participants	111	123		

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 ^[4]
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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 evaluated combined for both fremanezumab dose treatment groups.

End point type	Secondary
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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: Efficacy analysis was planned to be evaluated combined for fremanezumab low and high dose treatment groups.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	111	123		
Units: days/month				
least squares mean (standard error)	-1.0 (± 0.30)	-2.1 (± 0.29)		

Statistical analyses

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]
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End point description:

PedMIDAS questionnaire is a 6-item instrument developed to assess headache-related disability. It has been validated in participants aged 4 through 18 years and includes questions related to the impact of headache on school performance, disability at home (for example, inability to do chores or homework), and social/sport functioning. Total score: that is, the sum of 6 questions, was used for grading of disability, with scores of 0 to 10, 11 to 30, 31 to 50, and >50 interpreted as disability grades 1 (little or no disability), 2 (mild disability), 3 (moderate disability), and 4 (severe disability), respectively. Higher scores indicated severe disability. LS mean was calculated using ANCOVA. 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 evaluated combined for both fremanezumab dose treatment groups.

End point type	Secondary
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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: Efficacy analysis was planned to be evaluated combined for fremanezumab low and high dose treatment groups.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	111	123		
Units: units on a scale				
least squares mean (standard error)	-15.3 (± 3.37)	-21.6 (± 3.29)		

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]
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End point description:

PedsQL 4.0 (23-item health-related quality of life [QoL]) evaluates QoL in 4 areas: physical, emotional, social, and school functioning. For child and adolescent (8-18 years) and parent, a 5-point Likert scale was used to rate item 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 a 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 population: FAS. Efficacy analysis was planned to be evaluated combined for both fremanezumab dose groups.

End point type	Secondary
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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: Efficacy analysis was planned to be evaluated combined for fremanezumab low and high dose treatment groups.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	111	123		
Units: units on a scale				
least squares mean (standard error)				
Child-Physical Health Summary Score	8.3 (± 1.61)	7.8 (± 1.57)		
Child-Psychosocial Health Summary Score	5.3 (± 1.38)	4.7 (± 1.35)		
Child-Total Scale Score	6.2 (± 1.37)	5.7 (± 1.33)		
Parent-Physical Health Summary Score	7.3 (± 2.69)	7.3 (± 2.35)		
Parent-Psychosocial Health Summary Score	6.8 (± 2.28)	4.3 (± 1.96)		
Parent-Total Scale Score	7.2 (± 2.28)	5.2 (± 1.97)		

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]
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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
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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 end point 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	35	87		
Units: participants	1	1		

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

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

Reporting group title	Fremanezumab Dose B
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Reporting group description:

Participants weighing $\geq$ threshold weight received fremanezumab SC at dose B for 3 months (Days 1, 29, and 57).

Reporting group title	Fremanezumab Dose A
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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	3 / 112 (2.68%)	1 / 87 (1.15%)	1 / 36 (2.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 87 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 112 (0.89%)	0 / 87 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Immune thrombocytopenia			

subjects affected / exposed	1 / 112 (0.89%)	0 / 87 (0.00%)	0 / 36 (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			
Hepatitis infectious mononucleosis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 87 (1.15%)	0 / 36 (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

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	26 / 112 (23.21%)	29 / 87 (33.33%)	8 / 36 (22.22%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 112 (1.79%)	0 / 87 (0.00%)	2 / 36 (5.56%)
occurrences (all)	3	0	3
Dizziness			
subjects affected / exposed	0 / 112 (0.00%)	5 / 87 (5.75%)	0 / 36 (0.00%)
occurrences (all)	0	5	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	6 / 112 (5.36%)	11 / 87 (12.64%)	1 / 36 (2.78%)
occurrences (all)	9	18	2
Injection site pain			
subjects affected / exposed	6 / 112 (5.36%)	6 / 87 (6.90%)	0 / 36 (0.00%)
occurrences (all)	10	9	0
Injection site swelling			
subjects affected / exposed	1 / 112 (0.89%)	5 / 87 (5.75%)	1 / 36 (2.78%)
occurrences (all)	1	6	1
Vaccination site pain			
subjects affected / exposed	1 / 112 (0.89%)	0 / 87 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	8 / 112 (7.14%)	8 / 87 (9.20%)	3 / 36 (8.33%)
occurrences (all)	10	10	4
Upper respiratory tract infection			
subjects affected / exposed	5 / 112 (4.46%)	4 / 87 (4.60%)	2 / 36 (5.56%)
occurrences (all)	6	5	2
COVID-19			
subjects affected / exposed	6 / 112 (5.36%)	5 / 87 (5.75%)	2 / 36 (5.56%)
occurrences (all)	6	5	2

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, to clarify the exclusion criterion for nerve stimulation or device, and to 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 (120 mg SC monthly) following the completion of the Phase 1 pediatric pharmacokinetic study (TV48125-CNS-10141).
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.
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 Patient 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, to expand the body mass index (BMI) upper limit to 120% of the 95th percentile in order 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 amendment was to reduce the size of the study population and to update the inclusion criteria in order to help with enrollment and study completion. - Updated study timelines according to new projections and reduced study population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported