Clinical trial results:
A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study With an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients With Inadequate Response to Prior Preventive Treatments

Summary

EudraCT number	2017-002441-30
Trial protocol	DK GB SE BE DE CZ FI NL ES IT
Global end of trial date	29 May 2019

Results information

Result version number	v2 (current)
This version publication date	19 March 2020
First version publication date	19 October 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30068

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03308968
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	41 Moores Road, Frazer, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2018
Global end of trial reached?	Yes
Global end of trial date	29 May 2019
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 demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous injections to adult participants with migraine with documented inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (for example; Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2017
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	Belgium: 50
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Czech Republic: 188
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Finland: 85
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Netherlands: 23
Country: Number of subjects enrolled	Poland: 66
Country: Number of subjects enrolled	Sweden: 37
Country: Number of subjects enrolled	United States: 120
Worldwide total number of subjects	838
EEA total number of subjects	716

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	807
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 838 participants were randomized in a 1:1:1 ratio to placebo, fremanezumab quarterly, or fremanezumab monthly treatment groups.

Period 1

Period 1 title	Double-Blind Period (12 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

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

Dosage and administration details:

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

Arm title	Fremanezumab Quarterly

Arm description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was administered per dose and schedule specified in the arm.

Arm title	Fremanezumab Monthly

Arm description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was administered per dose and schedule specified in the arm.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly
Started	279	276	283
DB Modified ITT (mITT) analysis set	278	276	283
Completed	264	271	272
Not completed	15	5	11
Consent withdrawn by subject	2	2	3
Non-compliance to study procedures	1	1	-
Adverse event, non-fatal	3	1	4
Other than specified	1	-	2
Lost to follow-up	1	-	-
Protocol deviation	6	-	2
Lack of efficacy	1	1	-

Period 2

Period 2 title	Open-Label Period (12 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Arm type	Placebo
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was administered per dose and schedule specified in the arm.

Arm title	Fremanezumab Quarterly

Arm description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was administered per dose and schedule specified in the arm.

Arm title	Fremanezumab Monthly

Arm description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Arm type	Experimental

Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was administered per dose and schedule specified in the arm.

Number of subjects in period 2	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly
Started	264	271	272
OL mITT analysis set	263	271	272
Completed	253	259	260
Not completed	11	12	12
Consent withdrawn by subject	5	5	7
Non-compliance to study procedures	-	-	1
Adverse event, non-fatal	4	1	1
Other than specified	1	2	1
Lost to follow-up	-	1	1
Lack of efficacy	1	2	-
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.	
Reporting group title	Fremanezumab Quarterly
Reporting group description:	
DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.	
Reporting group title	Fremanezumab Monthly
Reporting group description:	
DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.	

Reporting group values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly
Number of subjects	279	276	283
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	46.8	45.8	45.9
standard deviation	± 11.10	± 10.97	± 11.05
Sex: Female, Male Units: Subjects			
Female	233	229	238
Male	46	47	45
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	11	6	7
Not Hispanic or Latino	255	260	264
Unknown or Not Reported	13	10	12
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	1	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	262	262	262

Other	1	2	1
Unknown or Not Reported	13	10	12

Number of Migraine Days During the 28 Day Baseline Period			
A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine; a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications. 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.			
Units: days			
arithmetic mean	14.3	14.1	14.1
standard deviation	± 6.12	± 5.61	± 5.58
Number of Headache Days of at Least Moderate Severity During the 28 Day Baseline Period			
Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of at least moderate severity was defined as a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific acute medications (triptans and ergot compounds). 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.			
Units: days			
arithmetic mean	12.8	12.4	12.7
standard deviation	± 5.92	± 5.84	± 5.82

Reporting group values	Total		
Number of subjects	838		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	700		
Male	138		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	24		
Not Hispanic or Latino	779		
Unknown or Not Reported	35		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	4		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	786		
Other	4		
Unknown or Not Reported	35		

Number of Migraine Days During the 28 Day Baseline Period			
A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine; a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications. 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.			
Units: days arithmetic mean standard deviation	- 		
Number of Headache Days of at Least Moderate Severity During the 28 Day Baseline Period			
Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of at least moderate severity was defined as a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific acute medications (triptans and ergot compounds). 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.			
Units: days arithmetic mean standard deviation	- 		

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Fremanezumab Quarterly

Reporting group description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Fremanezumab Monthly

Reporting group description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Placebo

Reporting group description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Fremanezumab Quarterly

Reporting group description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Fremanezumab Monthly

Reporting group description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

DB period: Participants with CM or EM received 3 injections of placebo 1.5 mL SC on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56.

Subject analysis set title	Fremanezumab Quarterly
Subject analysis set type	Safety analysis

Subject analysis set description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2

months (on Days 28 and 56).

Subject analysis set title	Fremanezumab Monthly
Subject analysis set type	Safety analysis

Subject analysis set description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).

Primary: DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab

End point title	DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab

End point description:

A migraine day was defined as when at least 1 of the following occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion was missing; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)*28. Change was calculated as post-baseline value – baseline value. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on primary endpoint.

End point type	Primary

End point timeframe:

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

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: days/month				
least squares mean (standard error)	-0.6 (± 0.34)	-3.7 (± 0.34)	-4.1 (± 0.34)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using analysis of covariance (ANCOVA) method with treatment, sex, region, special group of treatment failure (yes or no), migraine classification (that is; CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The stratification factors (as randomized) were used in the model.

Comparison groups	Placebo v Fremanezumab Quarterly

Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.84
upper limit	-2.42
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using ANCOVA method with treatment, sex, region, special group of treatment failure (yes or no), migraine classification (that is; CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The stratification factors (as randomized) were used in the model.

Comparison groups	Placebo v Fremanezumab Monthly
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.19
upper limit	-2.78
Variability estimate	Standard error of the mean
Dispersion value	0.36

Secondary: DB Period: Percentage of Participants Reaching at Least 50 Percent (%) Reduction From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab

End point title	DB Period: Percentage of Participants Reaching at Least 50 Percent (%) Reduction From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab

End point description:

A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion was missing; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was

treated with migraine-specific medications (triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)*28. DB mITT analysis set included participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on the primary endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: percentage of participants				
number (not applicable)	9	34	34	

Statistical analyses

No statistical analyses for this end point

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

End point title	DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 12-Week Period After the First Dose of Fremanezumab

End point description:

A headache day of at least moderate severity: a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day demonstrating a headache of any duration that was treated with migraine-specific acute medications. Monthly averages were derived and normalized to 28 days equivalent by the following formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in the e-diary over the relevant period) * 28. LS mean calculated using ANCOVA model with treatment, gender, region, special group of treatment failure(yes/no), migraine classification (EM/CM), and treatment*migraine classification as fixed effects and baseline number of headache days of at least moderate severity and years since onset of migraine as covariates. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on primary endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: days/month				
least squares mean (standard error)	-0.6 (± 0.33)	-3.9 (± 0.34)	-4.2 (± 0.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab

End point title	DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab

End point description:

A migraine day was defined as when at least 1 of following occurred: A calendar day demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with/without aura; at least 4 consecutive hours of a headache meeting criteria for probable migraine; a headache of any duration that was treated with migraine-specific drugs. Monthly averages were derived and normalized to 28 days equivalent by:(number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)*28. LS mean calculated using ANCOVA model with treatment, gender, region, special group of treatment failure(yes/no), migraine classification(EM/CM), and treatment*migraine classification as fixed effects, and baseline number of migraine days, years since onset of migraines as covariates. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on

End point type	Secondary

End point timeframe:

Baseline (Day -28 to Day -1), up to Week 4

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: days/month				
least squares mean (standard error)	-0.6 (± 0.35)	-4.1 (± 0.35)	-4.1 (± 0.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Participants Reaching at Least 50% Reduction From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab

End point title	DB Period: Percentage of Participants Reaching at Least 50% Reduction From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab

End point description:

A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with

or without aura; a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion was missing; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)*28. DB mITT analysis set included participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day -28 to Day-1), up to Week 4

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: percentage of participants				
number (not applicable)	10	38	36	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Monthly Average Number of Days of Use of Any Acute Headache Medications During the 12-Week Period After the First Dose of Fremanezumab

End point title	DB Period: Change From Baseline in Monthly Average Number of Days of Use of Any Acute Headache Medications During the 12-Week Period After the First Dose of Fremanezumab

End point description:

Baseline data and the mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after administration of the first dose of study drug (based on Week 0 to 12 data) is reported. Least Squares (LS) mean calculated using analysis of covariance (ANCOVA) model with treatment, gender, region, special group of treatment failure (yes/no), migraine classification (EM/CM), and treatment*migraine classification as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. DB mITT analysis set included participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on the primary endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: days/month				
least squares mean (standard error)	-0.6 (± 0.32)	-3.7 (± 0.32)	-3.9 (± 0.32)	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 4-Week Period After the First Dose of Fremanezumab

End point title	DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 4-Week Period After the First Dose of Fremanezumab

End point description:

A headache day of at least moderate severity: a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day demonstrating a headache of any duration that was treated with migraine-specific acute medications. Monthly averages were derived and normalized to 28 days equivalent by following formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in the e-diary over the relevant period) * 28. LS mean calculated using ANCOVA model with treatment, gender, region, special group of treatment failure (yes/no), migraine classification (EM/CM), and treatment*migraine classification as fixed effects, and baseline number of headache days of at least moderate severity and years since onset of migraines as covariates. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on primary endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day -28 to Day -1), up to Week 4

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	276	283	
Units: days/month				
least squares mean (standard error)	-0.5 (± 0.34)	-4.2 (± 0.35)	-4.5 (± 0.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Adverse Events (AEs) and Who Did Not Complete the Study Due to AEs

End point title	DB Period: Number of Participants With Adverse Events (AEs) and Who Did Not Complete the Study Due to AEs

End point description:

An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severe AE was defined as inability to carry out usual activities. Treatment-related AEs were defined as AEs with possible, probable, definite, or missing relationship to study drug. Serious AEs 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. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	277	276	285	
Units: participants				
Any AEs	134	151	129	
AEs leading to withdrawal from study	3	1	4	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With AEs and Who Did Not Complete the Study Due to AEs

End point title	OL Period: Number of Participants With AEs and Who Did Not Complete the Study Due to AEs

End point description:

An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severe AE was defined as inability to carry out usual activities. Treatment-related AEs were defined as AEs with possible, probable, definite, or missing relationship to study drug. Serious AEs 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. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	262	271	274	
Units: participants				
Any AEs	137	149	155	
AEs leading to withdrawal from study	4	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results

End point title	DB Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results

End point description:

Criteria for potentially clinically significant abnormal serum chemistry values included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and lactate dehydrogenase (LDH) (units/liter [U/L]): greater than or equal to (≥) 3*upper limit of normal (ULN); Blood Urea Nitrogen (BUN): ≥10.71 millimoles/liter (mmol/L); creatinine: ≥177 micromoles/liter (µmol/L); bilirubin (total): ≥34.2 µmol/L; and uric acid: ≥625 µmol/L (men), and ≥506 µmol/L (women). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	272	268	280	
Units: participants	1	3	4	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results

End point title	OL Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results

End point description:

Criteria for potentially clinically significant abnormal serum chemistry values included: ALT, AST, ALP, GGT, and LDH (U/L): ≥3*ULN; BUN: ≥10.71 mmol/L; creatinine: ≥177 µmol/L; bilirubin (total): ≥34.2 µmol/L; and uric acid: ≥625 µmol/L (men), and ≥506 µmol/L (women). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	268	273	
Units: participants	2	3	2	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

End point title	DB Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

End point description:

Criteria for potentially clinically significant abnormal hematology values included: hemoglobin: less than (<) 115 grams/liter (g/L) (in men) or less than or equal to (≤) 95 g/L (in women), hematocrit: <0.37 L/L (in men) or <0.32 L/L (in women), leukocytes: ≥20*10^9/L or ≤3*10^9/L, eosinophils: >=10%, platelets: ≥700*10^9/L or ≤75*10^9/L, and absolute neutrophil count (ANC): ≤1*10^9/L. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	271	268	278	
Units: participants	11	12	3	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

End point title	OL Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

End point description:

Criteria for potentially clinically significant abnormal hematology values included: hemoglobin: <115 g/L (in men) or ≤95 g/L (in women), hematocrit: <0.37 L/L (in men) or <0.32 L/L (in women), leukocytes: ≥20*10^9/L or ≤3*10^9/L, eosinophils: >=10%, platelets: ≥700*10^9/L or ≤75*10^9/L, and ANC: ≤1*10^9/L. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	258	268	273	
Units: participants	7	10	4	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results

End point title	DB Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results

End point description:

Criteria for potentially clinically significant abnormal coagulation values included: prothrombin international normalized ratio (INR): greater than (>) 1.5. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	269	267	277	
Units: participants	2	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results

End point title	OL Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results

End point description:

Criteria for potentially clinically significant abnormal coagulation values included: prothrombin INR: >1.5. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	270	272	
Units: participants	3	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results

End point title	DB Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results

End point description:

Criteria for potentially clinically significant abnormal urinalysis values included: urine glucose (milligrams/deciliter [mg/dL]): ≥2 unit increase from baseline, ketones (mg/dL): ≥2 unit increase from baseline, urine total protein (mg/dL): ≥2 unit increase from baseline, and haemoglobin ≥2 unit increase from baseline. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	277	276	285	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results

End point title	OL Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results

End point description:

Criteria for potentially clinically significant abnormal urinalysis values included: urine glucose (mg/dL): ≥2 unit increase from baseline, ketones (mg/dL): ≥2 unit increase from baseline, urine total protein (mg/dL): ≥2 unit increase from baseline, and haemoglobin ≥2 unit increase from baseline. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	262	271	274	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values

End point title	DB Period: Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values

End point description:

Criteria for potentially clinically significant abnormal vital signs values included: pulse rate: ≤50 beats/minute (bpm) and decrease of ≥15 bpm, or ≥120 bpm and increase of ≥15 bpm; systolic blood pressure: ≤90 millimeters of mercury (mmHg) and decrease of ≥20 mmHg, or ≥180 mmHg and increase of ≥20 mmHg; diastolic blood pressure: ≤50 mmHg and decrease of ≥15 mmHg or ≥105 mmHg and increase of ≥15 mmHg; respiratory rate: <10 breaths/minute; and body temperature ≥38.3 degrees celsius and change of ≥1.1 degrees celsius. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. B safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome

measure.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	276	283	
Units: participants	9	8	8	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values

End point title	OL Period: Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values

End point description:

Criteria for potentially clinically significant abnormal vital signs values included: pulse rate: ≤50 bpm and decrease of ≥15 bpm, or ≥120 bpm and increase of ≥15 bpm; systolic blood pressure: ≤90 mmHg and decrease of ≥20 mmHg, or ≥180 mmHg and increase of ≥20 mmHg; diastolic blood pressure: ≤50 mmHg and decrease of ≥15 mmHg or ≥105 mmHg and increase of ≥15 mmHg; respiratory rate: <10 breaths/minute; and body temperature ≥38.3 degrees celsius and change of ≥1.1 degrees celsius. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	261	270	273	
Units: participants	10	14	8	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants With Shift From Baseline to Week 12

in Electrocardiogram (ECG) Parameters

End point title	DB Period: Number of Participants With Shift From Baseline to Week 12 in Electrocardiogram (ECG) Parameters

End point description:

ECG parameters included: heart rate, PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - Week 12 value. Abnormal NCS indicated an abnormal but not clinically significant finding. Abnormal CS indicated an abnormal and clinically significant finding. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' = participants with both baseline and Week 12 ECG findings.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	258	271	270	
Units: participants				
Normal - Normal	199	218	212	
Normal - Abnormal NCS	21	14	15	
Normal - Abnormal CS	0	0	0	
Abnormal NCS - Normal	10	19	12	
Abnormal NCS - Abnormal NCS	28	20	31	
Abnormal NCS - Abnormal CS	0	0	0	
Abnormal CS - Normal	0	0	0	
Abnormal CS - Abnormal NCS	0	0	0	
Abnormal CS - Abnormal CS	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants With Shift From Baseline to Week 24 in ECG Parameters

End point title	OL Period: Number of Participants With Shift From Baseline to Week 24 in ECG Parameters

End point description:

ECG parameters included: heart rate, PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - Week 24 value. Abnormal NCS indicated an abnormal but not clinically significant finding. Abnormal CS indicated an abnormal and clinically significant finding. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' = participants with both baseline and Week 24 ECG findings.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	245	256	260	
Units: participants				
Normal - Normal	193	214	203	
Normal - Abnormal NCS	15	5	15	
Normal - Abnormal CS	0	0	1	
Abnormal NCS - Normal	13	20	16	
Abnormal NCS - Abnormal NCS	24	17	25	
Abnormal NCS - Abnormal CS	0	0	0	
Abnormal CS - Normal	0	0	0	
Abnormal CS - Abnormal NCS	0	0	0	
Abnormal CS - Abnormal CS	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Participants Who Received Concomitant Medications for Adverse Events

End point title	DB Period: Number of Participants Who Received Concomitant Medications for Adverse Events

End point description:

Concomitant medications included: agents acting on the renin-angiotensin system, all other therapeutic products (for example: homeopathic preparation), allergens, analgesics, anesthetics, anti-parkinson drugs, antianemic preparations, antibacterials for systemic use, antibiotics and chemotherapeutics for dermatological use, antidiarrheals, intestinal antiinflammatory/antiinfective agents, antifungals for dermatologiocal use, antigout preparations, antihemorrhagics, antihistamines for systemic use, antihypertensives, antiinflammatory and antirheumatic products, antipruritics, antipsoriatics, antivirals for systemic use, blood substitutes and perfusion solutions, cardiac therapy, corticosteroids, cough and cold preparations, diagnostic radiopharmaceuticals, diuretics, vaccines, ophthalmologicals, muscle relaxants, drugs used in diabetes etc. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	277	276	285	
Units: participants	274	269	280	

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Number of Participants Who Received Concomitant Medications for Adverse Events

End point title	OL Period: Number of Participants Who Received Concomitant Medications for Adverse Events

End point description:

Concomitant medications included: agents acting on the renin-angiotensin system, all other therapeutic products (for example: homeopathic preparation), allergens, analgesics, anesthetics, anti-parkinson drugs, antianemic preparations, antibacterials for systemic use, antibiotics and chemotherapeutics for dermatological use, antidiarrheals, intestinal antiinflammatory/antiinfective agents, antifungals for dermatologiocal use, antigout preparations, antihemorrhagics, antihistamines for systemic use, antihypertensives, antiinflammatory and antirheumatic products, antipruritics, antipsoriatics, antivirals for systemic use, blood substitutes and perfusion solutions, cardiac therapy, corticosteroids, cough and cold preparations, diagnostic radiopharmaceuticals, diuretics, vaccines, ophthalmologicals, muscle relaxants, drugs used in diabetes etc. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Week 12 up to Week 24

End point values	Placebo	Fremanezumab Quarterly	Fremanezumab Monthly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	262	271	274	
Units: participants	262	266	270	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 0) up to follow-up visit (Week 46)

Adverse event reporting additional description:

Safety analysis set: all participants who received at least 1 dose of study drug. AE data were summarized collectively for both periods. 2 participants (1 with CM and 1 with EM) randomized to placebo but received Fremanezumab monthly dosing during double-blind treatment period. They were analyzed in the treatment arm per actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

DB period: Participants with CM or EM received 3 injections of placebo 1.5 mL SC on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. OL period: Participants with CM or EM received fremanezumab (TEV-48125) 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Fremanezumab Monthly

Reporting group description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Reporting group title	Fremanezumab Quarterly

Reporting group description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

Serious adverse events	Placebo	Fremanezumab Monthly	Fremanezumab Quarterly
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 277 (4.69%)	11 / 285 (3.86%)	10 / 276 (3.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyxoma			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (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

Breast cancer			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Thyroid adenoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Uterine leiomyoma	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[1]	1 / 231 (0.43%)	0 / 240 (0.00%)	0 / 229 (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
Vulval cancer	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[2]	1 / 231 (0.43%)	0 / 240 (0.00%)	0 / 229 (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 reaction			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (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
Reproductive system and breast disorders			
Dysmenorrhoea	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[3]	0 / 231 (0.00%)	0 / 240 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[4]	0 / 231 (0.00%)	1 / 240 (0.42%)	0 / 229 (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
Menometrorrhagia	Additional description: This is a gender-specific AE. Only female participants were at risk.		

subjects affected / exposed[5]	0 / 231 (0.00%)	1 / 240 (0.42%)	0 / 229 (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
Menorrhagia	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[6]	0 / 231 (0.00%)	0 / 240 (0.00%)	1 / 229 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[7]	1 / 231 (0.43%)	0 / 240 (0.00%)	0 / 229 (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
Respiratory, thoracic and mediastinal disorders			
Vocal cord thickening			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (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
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
International normalised ratio abnormal			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			

subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (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
Rib fracture			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Congenital, familial and genetic disorders			
Congenital diaphragmatic hernia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (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
Palpitations			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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

Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Multiple sclerosis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal tear			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	0 / 276 (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
Gastrointestinal disorders			
Anal polyp			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 285 (0.35%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 277 (0.00%)	2 / 285 (0.70%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Dengue fever			

subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Diverticulitis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 285 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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
Sinusitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 285 (0.00%)	0 / 276 (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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

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

Non-serious adverse events	Placebo	Fremanezumab Monthly	Fremanezumab Quarterly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 277 (31.77%)	81 / 285 (28.42%)	90 / 276 (32.61%)
Nervous system disorders			

Migraine			
subjects affected / exposed	21 / 277 (7.58%)	12 / 285 (4.21%)	14 / 276 (5.07%)
occurrences (all)	26	14	15
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	24 / 277 (8.66%)	32 / 285 (11.23%)	31 / 276 (11.23%)
occurrences (all)	53	80	66
Injection site induration			
subjects affected / exposed	16 / 277 (5.78%)	18 / 285 (6.32%)	19 / 276 (6.88%)
occurrences (all)	52	65	41
Injection site pain			
subjects affected / exposed	10 / 277 (3.61%)	14 / 285 (4.91%)	15 / 276 (5.43%)
occurrences (all)	20	42	42
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	32 / 277 (11.55%)	25 / 285 (8.77%)	30 / 276 (10.87%)
occurrences (all)	37	30	41
Upper respiratory tract infection			
subjects affected / exposed	10 / 277 (3.61%)	16 / 285 (5.61%)	8 / 276 (2.90%)
occurrences (all)	10	17	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported