Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of TEV-48125 Versus Placebo for the Preventive Treatment of Episodic Migraine

Summary

EudraCT number	2015-004598-34
Trial protocol	DE CZ ES FI DK
Global end of trial date	10 April 2017

Results information

Result version number	v1 (current)
This version publication date	16 June 2018
First version publication date	16 June 2018

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30050

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02629861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc, 001 215-591-3000, Info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc, 001 215-591-3000, Info.era-clinical@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	20 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• to demonstrate the efficacy 2 dose regimens of TEV-48125, as assessed by the decrease in the monthly average number of migraine days during 12-week period after the 1st dose of study drug relative to the baseline period
• to evaluate the safety and tolerability of 2 dose regimens TEV-48125 in the preventive treatment of episodic migraine (EM)

Protection of trial subjects:

This study was conducted in full accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, 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 GCP in the conduct of clinical trials on medicinal products for human use).

Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP, and for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where the study center is located.

Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2016
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	Poland: 20
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Czech Republic: 37

Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Japan: 75
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	United States: 679
Worldwide total number of subjects	875
EEA total number of subjects	69

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)	853
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2995 patients with migraine provided written informed consent. Of the 2995 patients screened, 875 met entry criteria, including diagnostic criteria for episodic migraine (EM) and diary compliance during the run-in period, and were randomized into this study from 123 study centers by 123 investigators.

Period 1

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

Blinding implementation details:

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients were blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients randomized to receive placebo received three 1.5-mL placebo injections on Day 0, and a single 1.5-mL placebo injection on Days 28 and 56.

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 2.25-mL pre-filled syringes identical in appearance to active intervention. Patients were dosed once approximately every 28 days for a total of 3 times. Study drug was administered at the clinical site.

Arm title	Fremanezumab 675 mg/placebo/placebo

Arm description:

Patients who were randomized to receive fremanezumab 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	
Other name	TEV-48125, anti-calcitonin gene-related peptide (anti-CGRP)
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was provided as a sterile, unpreserved, aqueous solution for injection, supplied in a 2.25-mL pre-filled syringe for single-use administration. The initial dose of 675 mg on Day 0 was given as 3 injections. Study drug was administered at the clinical site.

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 2.25-mL pre-filled syringes identical in appearance to active intervention. Patients were dosed with placebo on Days 28 and 56. Study drug was administered at the clinical site.

Arm title	Fremanezumab 225/225/225 mg

Arm description:

Patients who were randomized to receive fremanezumab 225/225/225 mg received 1 active injection (225 mg/1.5 mL) on Days 0, 28 and 56.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	
Other name	TEV-48125, anti-calcitonin gene-related peptide (anti-CGRP)
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Fremanezumab was provided as a sterile, unpreserved, aqueous solution for injection, supplied in a 2.25-mL pre-filled syringe for single-use administration. The initial dose of 275 mg on Day 0 was repeated on Days 28 and 56. Study drug was administered at the clinical site.

Number of subjects in period 1	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg
Started	294	291	290
ITT population	294	291	290
Safety population	294	291	289
Full analysis set	290	288	287
Completed	265	264	262
Not completed	29	27	28
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	5	8	13
Adverse event, non-fatal	7	4	4
Pregnancy	2	1	-
Lost to follow-up	12	9	4
Protocol deviation	2	3	7
not specified	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients randomized to receive placebo received three 1.5-mL placebo injections on Day 0, and a single 1.5-mL placebo injection on Days 28 and 56.	
Reporting group title	Fremanezumab 675 mg/placebo/placebo
Reporting group description:	
Patients who were randomized to receive fremanezumab 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.	
Reporting group title	Fremanezumab 225/225/225 mg
Reporting group description:	
Patients who were randomized to receive fremanezumab 225/225/225 mg received 1 active injection (225 mg/1.5 mL) on Days 0, 28 and 56.	

Reporting group values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg
Number of subjects	294	291	290
Age categorical Units: Subjects			
18-45 years	184	178	163
46-65 years	102	110	120
>65 years	8	3	7
Age continuous Units: years			
arithmetic mean	41.3	41.1	42.9
standard deviation	± 12.04	± 11.41	± 12.67
Gender categorical Units: Subjects			
Female	247	251	244
Male	47	40	46
Race Units: Subjects			
White	225	232	243
Black	40	28	18
Asian	25	27	25
American Indian or Alaskan Native	0	1	3
Native Hawaiian or Other Pacific Islander	0	1	0
Other	4	2	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	267	251	252
Hispanic or Latino	27	39	37
Unknown	0	1	1
Preventive Medication Use During Baseline Period			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device. During randomization, patients were stratified based on sex, country, and baseline preventive migraine			

medication use (yes, no) to ensure balance for the covariates.			
Units: Subjects			
Yes	62	58	62
No	232	233	228
Weight			
Units: kg			
arithmetic mean	75.3	74.2	72.1
standard deviation	± 16.01	± 15.42	± 15.77
Time Since Initial Migraine Diagnosis			
Units: years			
arithmetic mean	19.9	20.0	20.7
standard deviation	± 11.87	± 12.14	± 12.85
Total Number of Headache Days of Any Duration And Any Severity During the 28 Day Baseiine Period			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device.			
Units: days			
arithmetic mean	11.2	11.1	11.0
standard deviation	± 2.45	± 2.42	± 2.49
Number of Migraine Days			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device. Migraine headaches are as defined in The International Classification of Headache Disorders 3rd edition (ICHD-3).			
Units: days			
arithmetic mean	9.1	9.3	8.9
standard deviation	± 2.65	± 2.65	± 2.63
Number of Headache Days of At Least Moderate Severity			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device. Headache severity was subjectively rated by the patient as mild, moderate or severe.			
Units: days			
arithmetic mean	6.9	7.2	6.8
standard deviation	± 3.12	± 3.14	± 2.90
Number of Days of Use of Any Acute Headache Medications			
Eligible patients entered a 28-day run-in/baseline period during which headache information (including information about use of headache medications) was captured daily throughout study participation using the electronic headache diary device.			
Units: days			
arithmetic mean	7.7	7.8	7.7
standard deviation	± 3.60	± 3.74	± 3.37
Migraine Disability Assessment (MIDAS) Total Score			
The MIDAS questionnaire is a 5-item instrument developed to assess headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the previous 3 months. The total score, ie, the sum of the # lost days answered for the first 5 questions, is used for grading of disability, with scores of 0-5 = grade 1 (little or no disability), 6-10 =grade 2 (mild disability), 11-20 = grade 3 (moderate disability), and ≥21 interpreted as grade 4 (severe disability).			
Units: # of lost days			
arithmetic mean	37.3	41.7	38.0
standard deviation	± 27.59	± 32.96	± 33.19

Reporting group values	Total		
Number of subjects	875		

Age categorical Units: Subjects			
18-45 years	525		
46-65 years	332		
>65 years	18		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	742		
Male	133		
Race Units: Subjects			
White	700		
Black	86		
Asian	77		
American Indian or Alaskan Native	4		
Native Hawaiian or Other Pacific Islander	1		
Other	7		
Ethnicity Units: Subjects			
Not Hispanic or Latino	770		
Hispanic or Latino	103		
Unknown	2		
Preventive Medication Use During Baseline Period			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device. During randomization, patients were stratified based on sex, country, and baseline preventive migraine medication use (yes, no) to ensure balance for the covariates.			
Units: Subjects			
Yes	182		
No	693		
Weight Units: kg arithmetic mean standard deviation	- -		
Time Since Initial Migraine Diagnosis Units: years arithmetic mean standard deviation	- -		
Total Number of Headache Days of Any Duration And Any Severity During the 28 Day Baseiine Period			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device.			
Units: days arithmetic mean standard deviation	- -		
Number of Migraine Days			
Eligible patients entered a 28-day run-in/baseline period during which headache information was			

captured daily throughout study participation using the electronic headache diary device. Migraine headaches are as defined in The International Classification of Headache Disorders 3rd edition (ICHD-3).			
Units: days arithmetic mean standard deviation	-		
Number of Headache Days of At Least Moderate Severity			
Eligible patients entered a 28-day run-in/baseline period during which headache information was captured daily throughout study participation using the electronic headache diary device. Headache severity was subjectively rated by the patient as mild, moderate or severe.			
Units: days arithmetic mean standard deviation	-		
Number of Days of Use of Any Acute Headache Medications			
Eligible patients entered a 28-day run-in/baseline period during which headache information (including information about use of headache medications) was captured daily throughout study participation using the electronic headache diary device.			
Units: days arithmetic mean standard deviation	-		
Migraine Disability Assessment (MIDAS) Total Score			
The MIDAS questionnaire is a 5-item instrument developed to assess headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the previous 3 months. The total score, ie, the sum of the # lost days answered for the first 5 questions, is used for grading of disability, with scores of 0-5 = grade 1 (little or no disability), 6-10 =grade 2 (mild disability), 11-20 = grade 3 (moderate disability), and ≥21 interpreted as grade 4 (severe disability).			
Units: # of lost days arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients randomized to receive placebo received three 1.5-mL placebo injections on Day 0, and a single 1.5-mL placebo injection on Days 28 and 56.	
Reporting group title	Fremanezumab 675 mg/placebo/placebo
Reporting group description:	
Patients who were randomized to receive fremanezumab 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.	
Reporting group title	Fremanezumab 225/225/225 mg
Reporting group description:	
Patients who were randomized to receive fremanezumab 225/225/225 mg received 1 active injection (225 mg/1.5 mL) on Days 0, 28 and 56.	

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

End point title	Change from Baseline in the Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Study Drug

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 endorsing criteria for migraine with or without aura
- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache endorsing criteria for probable migraine, a migraine subtype where only 1 migraine criterion is 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 are derived and normalized to 28 days equivalent by the following formula: (# days of efficacy variable over relevant period / # days with assessments recorded in the e-diary over the relevant period) * 28.
The change is calculated as postbaseline value – baseline value.

End point type	Primary

End point timeframe:

Baseline (Days -28 to Day -1), Treatment (Days 1 – Week 12)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	290[1]	288[2]	287[3]	
Units: migraine days				
median (inter-quartile range (Q1-Q3))	-2.7 (-4.7 to -0.5)	-4.0 (-6.4 to -1.9)	-4.2 (-6.2 to -2.0)	

Notes:

[1] - Full analysis set

[2] - Full analysis set

[3] - Full analysis set

Statistical analyses

Statistical analysis title	Primary: Active 675/placebo/placebo to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the primary analysis was conducted using the Wilcoxon rank-sum test as outlined in the SAP.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - 0.05 level of significance

Statistical analysis title	Primary: Active 225/225/225 to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the primary analysis was conducted using the Wilcoxon rank-sum test as outlined in the SAP.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - 0.05 level of significance

Primary: Participants with Adverse Events

End point title	Participants with Adverse Events[6]

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents usual activities. Relationship of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, 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 the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Primary

End point timeframe:

Day 1 to Week 12

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	293[7]	291[8]	290[9]	
Units: participants				
Any AEs	171	193	192	
Severe AEs	11	16	10	
Treatment-related AEs	109	137	138	
Serious adverse events	7	3	3	
Deaths	0	1	0	
Discontinued from study due to AE	5	5	5	

Notes:

[7] - Safety population

[8] - Safety population

[9] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With At Least 50% Reduction In Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Study Drug

End point title	Percentage of Participants With At Least 50% Reduction In Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Study Drug

End point description:

Responder rates were defined as the percentage of total subjects who reached at least a 50% reduction in the monthly average of headache days (as subjectively reported by participants in the study diary) of at least moderate severity relative to the baseline period.
For the overall analysis (Month 1-3), patients who discontinued early were considered nonresponders.

Monthly averages are derived and normalized to 28 days equivalent by the following formula: (# days of efficacy variable over relevant period / # days with assessments recorded in the e-diary over the relevant period) * 28.

The percentage reduction in monthly average is calculated as: ((baseline value - postbaseline value) / baseline value) * 100

End point type	Secondary

End point timeframe:

Baseline (Days -28 to Day -1), Treatment Month 1, Month 2, Month 3, Month 1-3 (Days 1 – Week 12)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	290[10]	288[11]	287[12]	
Units: percentage of subjects				
number (not applicable)				
Month 1 (n=290, 288, 287)	25.2	44.1	47.0	
Month 2 (n=274, 274, 274)	34.8	46.9	48.4	

Month 3 (n=268, 269, 263)	37.2	49.0	51.2	
Overall - Months 1-3 (n=290, 288, 287)	27.9	44.4	47.7	

Notes:

[10] - Full analysis set

[11] - Full analysis set

[12] - Full analysis set

Statistical analyses

Statistical analysis title	Month 1: Active 675/placebo/placebo to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel

Notes:

[13] - 0.05 level of significance

Statistical analysis title	Month 1: Active 225/225/225 to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Cochran-Mantel-Haenszel

Notes:

[14] - 0.05 level of significance

Statistical analysis title	Month 2: Active 675/placebo/placebo to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [15]
Method	Cochran-Mantel-Haenszel

Notes:

[15] - 0.05 level of significance

Statistical analysis title	Month 2: Active 225/225/225 to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo

Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [16]
Method	Cochran-Mantel-Haenszel

Notes:

[16] - 0.05 level of significance

Statistical analysis title	Month 3: Active 675/placebo/placebo to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048 [17]
Method	Cochran-Mantel-Haenszel

Notes:

[17] - 0.05 level of significance

Statistical analysis title	Month 3: Active 225/225/225 to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [18]
Method	Cochran-Mantel-Haenszel

Notes:

[18] - 0.05 level of significance

Statistical analysis title	Overall: Active 675/placebo/placebo to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use. For the overall analysis, patients who discontinued early were considered nonresponders.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel

Notes:

[19] - 0.05 level of significance

Statistical analysis title	Overall: Active 225/225/225 to Placebo

Statistical analysis description:

P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use. For the overall analysis, patients who discontinued early were considered nonresponders.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo

Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel

Notes:

[20] - 0.05 level of significance

Secondary: Change from Baseline in the Monthly Average Number of Days of Use of Any Acute Headache Medicine During the 12 Week Period After the First Dose of Study Drug

End point title	Change from Baseline in the Monthly Average Number of Days of Use of Any Acute Headache Medicine During the 12 Week Period After the First Dose of Study Drug

End point description:

Patients recorded any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day in their electronic headache diary device. Acute migraine-specific medication included triptans or ergots.

Monthly averages are derived and normalized to 28 days equivalent by the following formula: (# days of efficacy variable over relevant period / # days with assessments recorded in the e-diary over the relevant period) * 28.

The change is calculated as postbaseline value – baseline value.

End point type	Secondary

End point timeframe:

Baseline (Days -28 to Day -1), Treatment (Days 1 – Week 12)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	290[21]	288[22]	287[23]	
Units: days				
median (inter-quartile range (Q1-Q3))	-1.7 (-4.0 to 0.0)	-3.0 (-5.6 to -0.8)	-3.2 (-5.2 to -1.2)	

Notes:

[21] - Full analysis set

[22] - Full analysis set

[23] - Full analysis set

Statistical analyses

Statistical analysis title	Active 675/placebo/placebo to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint

Comparison groups	Placebo v Fremanezumab 675 mg/placebo/placebo

Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - 0.05 level of significance

Statistical analysis title	Active 225/225/225 to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - 0.05 level of significance

Secondary: Change from Baseline in the Number of Migraine Days During the 4 Week Period After the First Dose of Study Drug

End point title	Change from Baseline in the Number of Migraine Days During the 4 Week Period After the First Dose of Study Drug

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 endorsing criteria for migraine with or without aura
- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache endorsing criteria for probable migraine, a migraine subtype where only 1 migraine criterion is 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 are derived and normalized to 28 days equivalent by the following formula: (# days of efficacy variable over relevant period / # days with assessments recorded in the e-diary over the relevant period) * 28.

The change is calculated as postbaseline value – baseline value.

End point type	Secondary

End point timeframe:

Baseline (Days -28 to Day -1), Treatment (Days 1 – Week 4)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	290[26]	285[27]	287[28]	
Units: days				
median (inter-quartile range (Q1-Q3))	-2.0 (-4.2 to 0.5)	-4.0 (-6.2 to -1.3)	-4.0 (-6.1 to -1.7)	

Notes:

[26] - Full analysis set

[27] - Full analysis set

[28] - Full analysis set

Statistical analyses

Statistical analysis title	Active 675/placebo/placebo to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - 0.05 level of significance

Statistical analysis title	Active 225/225/225 to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - 0.05 level of significance

Secondary: Change from Baseline in the Monthly Average Number of Migraine Days During the 12 Week Period After the First Dose of Study Medication in Patients Not Receiving Concomitant Preventive Migraine Medications

End point title	Change from Baseline in the Monthly Average Number of Migraine Days During the 12 Week Period After the First Dose of Study Medication in Patients Not Receiving Concomitant Preventive Migraine Medications

End point description:

A subset of patients (specified in the protocol not to exceed 30%) were allowed to use 1 concomitant migraine preventive medication. This outcome only includes those participants who did not take concomitant preventive migraine medication during this study.

A migraine day has been previously defined.

Monthly averages are derived and normalized to 28 days equivalent by the following formula: (# days of efficacy variable over relevant period / # days with assessments recorded in the e-diary over the relevant period) * 28.
The change is calculated as postbaseline value – baseline value.

End point type	Secondary

End point timeframe:

Baseline (Days -28 to Day -1), Treatment (Days 1 – Week 12)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230[31]	230[32]	225[33]	
Units: days				
median (inter-quartile range (Q1-Q3))	-2.9 (-4.9 to -0.6)	-4.0 (-6.3 to -2.0)	-4.2 (-6.2 to -2.0)	

Notes:

[31] - FAS of subjects who did not receive concomitant migraine prevention medication

[32] - FAS of subjects who did not receive concomitant migraine prevention medication

[33] - FAS of subjects who did not receive concomitant migraine prevention medication

Statistical analyses

Statistical analysis title	Active 675/225/225 to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - 0.05 level of significance

Statistical analysis title	Active 225/225/225 to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[35] - 0.05 level of significance

Secondary: Change from Baseline in Migraine-Related Disability Score (MIDAS), As Measured by the Migraine Disability Assessment At 4 Weeks After the Last (3rd) Dose of Study Drug

End point title	Change from Baseline in Migraine-Related Disability Score (MIDAS), As Measured by the Migraine Disability Assessment At 4 Weeks After the Last (3rd) Dose of Study Drug

End point description:

The MIDAS questionnaire is a 5-item instrument developed to assess headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the previous 3 months. The total score, ie, the sum of the # lost days answered for the first 5 questions, is used for grading of disability, with scores of 0-5 lost days = grade 1 (little or no disability), 6-10 lost days =grade 2 (mild disability), 11-20 lost days = grade 3 (moderate disability), and ≥21 lost days interpreted as grade 4 (severe disability). Negative change from baseline scores indicate a reduction (improvement) in headache-related disability.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Treatment Week 12 (4 weeks after the 3rd dose)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	290[36]	288[37]	287[38]	
Units: lost days				
median (inter-quartile range (Q1-Q3))	-12.5 (-29.5 to -2.0)	-18.0 (-39.0 to -6.0)	-19.0 (-36.0 to -7.0)	

Notes:

[36] - Full analysis set

[37] - Full analysis set

[38] - Full analysis set

Statistical analyses

Statistical analysis title	Active 675/placebo/placebo to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for this endpoint.

Comparison groups	Fremanezumab 675 mg/placebo/placebo v Placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 [39]
Method	Wilcoxon (Mann-Whitney)

Notes:

[39] - 0.05 level of significance

Statistical analysis title	Active 225/225/225 to Placebo

Statistical analysis description:

Due to the deviation from the normal distribution assumption of the data, the Wilcoxon rank-sum test was conducted as the primary analysis for each active treatment group and placebo treatment group for

this endpoint.

Comparison groups	Fremanezumab 225/225/225 mg v Placebo
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [40]
Method	Wilcoxon (Mann-Whitney)

Notes:

[40] - 0.05 level of significance

Secondary: Electrocardiogram Finding Shifts From Baseline to Overall

End point title	Electrocardiogram Finding Shifts From Baseline to Overall

End point description:

12-lead ECGs were performed before other assessments (eg, blood draws and administration of questionnaires) and performed in triplicate. The worst postbaseline finding for the patient is summarized. Only patients with both baseline and postbaseline ECGs are included.
The ECG was evaluated by the investigator at the time of recording (signed and dated), and the printout was kept in the source documentation file. When
potentially clinically significant findings were detected by the investigator, a cardiologist at a central diagnostic center was consulted for a definitive interpretation. Any ECG finding that was judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value was considered an adverse event.
NCS = abnormal, not clinically significant
CS = abnormal, clinically significant
Shift format is: baseline finding / worst postbaseline finding

End point type	Secondary

End point timeframe:

Baseline (Day 0), Treatment Week 12 (or early withdrawal)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	293[41]	291[42]	290[43]	
Units: participants				
Normal / Normal	161	169	181	
Normal / NCS	32	41	25	
Normal / CS	0	0	0	
NCS / Normal	27	23	29	
NCS / NCS	58	43	46	
NCS / CS	0	0	0	
CS / Normal	0	0	0	
CS / NCS	0	0	0	
CS / CS	0	0	0	

Notes:

[41] - Safety population of participants with both baseline and posttreatment ECGs

[42] - Safety population of participants with both baseline and posttreatment ECGs

[43] - Safety population of participants with both baseline and posttreatment ECGs

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Vital Signs Potentially Clinically Significant Abnormal Values

End point title	Participants with Vital Signs Potentially Clinically Significant Abnormal Values

End point description:

Vital signs were performed before other assessments (eg, blood draws and administration of questionnaires).
Vital signs with at least one participant showing potentially clinically significant abnormal findings included:
- Pulse Rate Low: <=50 and decrease of >=15 beats per minute
- Systolic Blood Pressure Low: <=90 mmHg and decrease of >=20 mmHg
- Diastolic Blood Pressure High: >=105 mmHg and increase of >=15 mmHg
- Diastolic Blood Pressure Low: <=50 mmHg and decrease of >=15 mmHg
- Respiratory Rate Low: <10 breaths / minute

End point type	Secondary

End point timeframe:

Treatment Days 28, 56 and 84. Changes from previous reading may reflect the baseline reading performed on Day 0.

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	285[44]	285[45]	285[46]	
Units: participants				
Patients with at least 1 abnormality	3	4	5	
Pulse Rate Low	0	1	0	
Systolic Blood Pressure Low	0	2	1	
Diastolic Blood Pressure High	0	1	2	
Diastolic Blood Pressure Low	2	1	0	
Respiratory Rate Low	1	0	2	

Notes:

[44] - Safety population of participants with both baseline and posttreatment values for each vital sign.

[45] - Safety population of participants with both baseline and posttreatment values for each vital sign.

[46] - Safety population of participants with both baseline and posttreatment values for each vital sign.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Serum Chemistry and Hematology Potentially Clinically Significant Abnormal Results

End point title	Participants with Serum Chemistry and Hematology Potentially Clinically Significant Abnormal Results

End point description:

Serum chemistry and hematology laboratory tests with potentially clinically significant abnormal findings included:
- Blood Urea Nitrogen (BUN) High: >=10.71 mmol/L
- Bilirubin High: >=34.2 umol/L
- Alanine Aminotransferase (ALT): >=3*upper limit of normal (ULN)
- Aspartate Aminotransferase (AST): >=3*upper limit of normal (ULN)
- Gamma Glutamyl Transferase (GGT): >=3*upper limit of normal (ULN)

- Hemoglobin: Male: <115 g/L or Female: <=95 g/L
- Hematocrit: Male: <0.37 L/L or Female: <0.32 L/L
- Leukocytes: >=20*10^9/L or <=3*10^9/L
- Eosinophils/Leukocytes: >=10%
- Platelets: >=700*10^9/L or <=75*10^9/L

End point type	Secondary

End point timeframe:

Treatment Days 28, 56 and 84 (or early withdrawal)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	285[47]	285[48]	285[49]	
Units: participants				
Blood Urea Nitrogen (BUN)	1	0	1	
Bilirubin	1	0	1	
Alanine Aminotransferase (ALT)	0	1	0	
Aspartate Aminotransferase (AST)	0	0	1	
Gamma Glutamyl Transferase (GGT)	4	4	8	
Hemoglobin	1	4	2	
Hematocrit	3	6	6	
Leukocytes	4	1	6	
Eosinophils/Leukocytes	7	3	5	
Platelets	1	0	0	

Notes:

[47] - Safety population of participants with at least one postbaseline result for the tests.

[48] - Safety population of participants with at least one postbaseline result for the tests.

[49] - Safety population of participants with at least one postbaseline result for the tests.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Urinalysis Laboratory Tests Potentially Clinically Significant Abnormal Results

End point title	Participants with Urinalysis Laboratory Tests Potentially Clinically Significant Abnormal Results

End point description:

Urinalysis with potentially clinically significant abnormal findings included:
- Blood: >=2 unit increase from baseline
- Urine Glucose (mg/dL): >=2 unit increase from baseline
- Ketones (mg/dL): >=2 unit increase from baseline
- Urine Protein (mg/dL): >=2 unit increase from baseline

End point type	Secondary

End point timeframe:

Treatment Days 28, 56 and 84. Changes from previous reading reflect the baseline reading performed on Day 0.

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	285[50]	285[51]	285[52]	
Units: participants				
Patients with at least 1 abnormality	55	54	49	
Blood	29	30	23	
Urine Glucose	5	8	2	
Ketones	5	7	9	
Urine Protein	25	19	23	

Notes:

[50] - Safety population of participants with at least one postbaseline result for the tests.

[51] - Safety population of participants with at least one postbaseline result for the tests.

[52] - Safety population of participants with at least one postbaseline result for the tests.

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin Time Shifts from Baseline to Endpoint

End point title	Prothrombin Time Shifts from Baseline to Endpoint

End point description:

Shifts in prothrombin time from baseline to endpoint were summarized using patient counts grouped into three categories:
- Low (below normal range)
- Normal (within the normal range of 9.4 to 12.5 seconds)
- High (above normal range)

Shift format is: baseline finding / endpoint finding

End point type	Secondary

End point timeframe:

Baseline (Day 0), Treatment Endpoint (Week 12)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	284[53]	285[54]	284[55]	
Units: participants				
Low / Low	0	0	0	
Low / Normal	0	1	1	
Low / High	0	0	0	
Normal / Low	0	1	0	
Normal / Normal	232	248	250	
Normal / High	12	10	13	
High / Low	0	0	0	
High / Normal	8	15	12	
High / High	8	10	8	

Notes:

[53] - Safety population of participants with both baseline and posttreatment values

[54] - Safety population of participants with both baseline and posttreatment values

[55] - Safety population of participants with both baseline and posttreatment values

Statistical analyses

No statistical analyses for this end point

Secondary: Injection Site Reaction Adverse Events

End point title	Injection Site Reaction Adverse Events

End point description:

Counts of participants who reported treatment-emergent injection site reactions as AEs are summarized. Preferred terms from MedDRA version 18.1 are offered without a threshold applied.

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	293[56]	291[57]	290[58]	
Units: participants				
Patients with at least 1 injection site reaction	106	131	130	
Injection site pain	76	86	87	
Injection site induration	45	57	71	
Injection site erythema	41	55	52	
Injection site haemorrhage	6	9	3	
Injection site pruritus	2	4	4	
Injection site swelling	0	2	3	
Injection site urticaria	2	2	1	
Injection site rash	0	1	3	
Fatigue	0	1	0	
Injection site bruising	1	0	0	
Injection site dermatitis	0	0	1	
Injection site hypersensitivity	0	0	1	
Injection site nodule	0	0	1	
Injection site oedema	0	0	1	
Injection site warmth	0	1	0	

Notes:

[56] - Safety population

[57] - Safety population

[58] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Positive Electronic Columbia Suicide Severity Rating Scale Results After the First Dose of Study Drug

End point title	Participants with Positive Electronic Columbia Suicide Severity Rating Scale Results After the First Dose of Study Drug

End point description:

The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) was used to assess the patient's suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The eC-SSRS Baseline/Screening version was completed by the patient at visit 2, and the eC-SSRS Since Last Visit version was completed by the patient at all other time points.
Any positive findings on the eC-SSRS Since Last Visit version required evaluation by a physician or doctoral-level psychologist.
Findings after the first dose of study drug using the eC-SSRS Since Last Visit version are summarized.

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294[59]	291[60]	289[61]	
Units: participants				
Suicidal Ideation	0	0	2	
Suicidal Behaviour	0	0	0	

Notes:

[59] - Safety

[60] - Safety

[61] - Safety

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 to Week 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients randomized to receive placebo received three 1.5-mL placebo injections Day 0, and a single 1.5-mL placebo injection on Days 28 and 56.	
Reporting group title	Fremanezumab 675 mg/placebo/placebo
Reporting group description:	
Patients who were randomized to receive fremanezumab 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.	
Reporting group title	Fremanezumab 225/225/225 mg
Reporting group description:	
Patients who were randomized to receive fremanezumab 225/225/225 mg received 1 active injection (225 mg/1.5 mL) on Days 0, 28 and 56.	

Serious adverse events	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 294 (2.38%)	3 / 291 (1.03%)	3 / 289 (1.04%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lentigo maligna			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
Road traffic accident			

subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
Fall			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
Tendon injury			
subjects affected / exposed	0 / 294 (0.00%)	1 / 291 (0.34%)	0 / 289 (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
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 294 (0.00%)	0 / 291 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status migrainosus			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
General disorders and administration site conditions			
Death			

subjects affected / exposed	0 / 294 (0.00%)	1 / 291 (0.34%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (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
Gastrointestinal disorders			
Intestinal haemorrhage			
subjects affected / exposed	0 / 294 (0.00%)	1 / 291 (0.34%)	0 / 289 (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			
Menorrhagia			
subjects affected / exposed	0 / 294 (0.00%)	0 / 291 (0.00%)	1 / 289 (0.35%)
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			
Appendicitis			
subjects affected / exposed	0 / 294 (0.00%)	0 / 291 (0.00%)	1 / 289 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 291 (0.00%)	0 / 289 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 225/225/225 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 294 (38.44%)	133 / 291 (45.70%)	132 / 289 (45.67%)

General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	41 / 294 (13.95%)	55 / 291 (18.90%)	52 / 289 (17.99%)
occurrences (all)	88	110	102
Injection site pain			
subjects affected / exposed	76 / 294 (25.85%)	86 / 291 (29.55%)	87 / 289 (30.10%)
occurrences (all)	191	234	245
Injection site induration			
subjects affected / exposed	45 / 294 (15.31%)	57 / 291 (19.59%)	71 / 289 (24.57%)
occurrences (all)	93	126	134
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	15 / 294 (5.10%)	11 / 291 (3.78%)	16 / 289 (5.54%)
occurrences (all)	15	11	17

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	Amendment 1 to the protocol was issued while 3 patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - incorporation of required revisions based on health authority input from the European Medicines Agency, FDA, and Pharmaceuticals and Medical Devices Agency - provision of clarifying language for the inclusion and exclusion criteria - clarification of allowed and disallowed preventive medications - revision of protocol-defined adverse events of special interest and addition of clinical criteria for diagnosing anaphylaxis - update and/or clarification of versions of certain exploratory endpoints, including the EQ-5D (now -5L) and PGIC, respectively

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported