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 Chronic Migraine

Summary

EudraCT number	2015-004549-23
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	15 June 2018
First version publication date	15 June 2018

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30049

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02621931
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., 1 215-591-3000, Info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, 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	19 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 of 2 dose regimens of TEV-48125, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 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 of TEV-48125 in the preventive treatment of chronic migraine (CM)

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 March 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: 28
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Czech Republic: 47
Country: Number of subjects enrolled	Finland: 36
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Japan: 109
Country: Number of subjects enrolled	Russian Federation: 41

Country: Number of subjects enrolled	United States: 796
Worldwide total number of subjects	1130
EEA total number of subjects	125

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)	1106
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 3148 patients with migraine provided written informed consent and were screened for entry into either Study TV48125-CNS-30049 or Study TV48125-CNS-30050. Of the 3148 patients screened, 1130 met the entry criteria, including diagnostic criteria for CM and diary compliance during the run-in period, and were randomized into this study.

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, Data analyst

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 who were randomized to receive placebo received three 1.5-mL placebo injections at Day 0 and a single 1.5-mL placebo injection at 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 active 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	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.

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 675 mg dose on Day 0 was given as 3 injections. Study drug was administered at the clinical site.

Arm title	Fremanezumab 675/225/225 mg

Arm description:

Patients who were randomized to receive fremanezumab 675/225/225 mg received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) 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 675 mg dose on Day 0 was given as 3 injections; doses of 225 mg on Days 28 and 56 were given as a single injection. Study drug was administered at the clinical site.

Number of subjects in period 1	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 675/225/225 mg
Started	375	376	379
Safety and ITT population	375	376	379
Full analysis set (FAS)	371	375	375
Completed	342	349	343
Not completed	33	27	36
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	12	10	11
Adverse event, non-fatal	8	5	7
Pregnancy	2	-	-
non-compliance to study procedures	-	1	2
Lost to follow-up	8	7	10
Protocol deviation	2	2	2
not specified	1	1	3
Lack of efficacy	-	-	1

Baseline characteristics

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

Reporting group values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 675/225/225 mg
Number of subjects	375	376	379
Age categorical Units: Subjects			
18-45 years	229	218	248
46-65 years	143	149	123
>65 years	3	9	8
Age continuous Units: years			
arithmetic mean	41.4	42.0	40.6
standard deviation	± 12.03	± 12.37	± 11.95
Gender categorical Units: Subjects			
Female	330	331	330
Male	45	45	49
Race Units: Subjects			
White	303	293	297
Black	29	33	37
Asian	40	40	41
American Indian or Alaskan Native	0	4	2
Native Hawaiian or Other Pacific Islander	1	2	0
Other	2	4	2
Ethnicity Units: Subjects			
Not Hispanic or Latino	343	352	338
Hispanic or Latino	32	22	41
Unknown	0	1	0
Not reported	0	1	0
Preventive Medication Use During Baseline			
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	77	77	85
No	298	299	294
Weight			
Units: kg			
arithmetic mean	72.6	72.4	72.5
standard deviation	± 15.58	± 15.79	± 16.36
Time Since Initial Migraine			
Units: years			
arithmetic mean	19.9	19.7	20.1
standard deviation	± 12.86	± 12.84	± 11.98
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	20.3	20.4	20.3
standard deviation	± 4.19	± 3.93	± 4.26
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	13.3	13.2	12.8
standard deviation	± 5.82	± 5.47	± 5.80
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	16.4	16.2	16.0
standard deviation	± 5.15	± 4.88	± 5.19
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	13.0	13.1	13.1
standard deviation	± 6.92	± 6.79	± 7.20
Headache Impact Test (HIT-6) Disability Score			
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. HIT-6 measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It also assesses headache severity. Scores range from 36 to 78, where a higher score indicates a greater impact of headache on the daily life of the patient. Scores ≥60 indicate severe impact.			
Units: units on a scale			
arithmetic mean	64.1	64.3	64.6
standard deviation	± 4.80	± 4.74	± 4.42

Reporting group values	Total		
Number of subjects	1130		
Age categorical Units: Subjects			
18-45 years	695		
46-65 years	415		
>65 years	20		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	991		
Male	139		
Race Units: Subjects			
White	893		
Black	99		
Asian	121		
American Indian or Alaskan Native	6		
Native Hawaiian or Other Pacific Islander	3		
Other	8		
Ethnicity Units: Subjects			
Not Hispanic or Latino	1033		
Hispanic or Latino	95		
Unknown	1		
Not reported	1		
Preventive Medication Use During Baseline			
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	239		
No	891		
Weight Units: kg arithmetic mean standard deviation	- -		
Time Since Initial Migraine 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 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 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 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	 -		
Headache Impact Test (HIT-6) Disability Score			
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. HIT-6 measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It also assesses headache severity. Scores range from 36 to 78, where a higher score indicates a greater impact of headache on the daily life of the patient. Scores ≥60 indicate severe impact.			
Units: units on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Patients who were randomized to receive placebo received three 1.5-mL placebo injections at Day 0 and a single 1.5-mL placebo injection at 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 675/225/225 mg

Reporting group description:

Patients who were randomized to receive fremanezumab 675/225/225 mg received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) on Days 28 and 56.

Subject analysis set title	Fremanezumab
Subject analysis set type	Full analysis

Subject analysis set description:

The first dose was 675 mg by subcutaneous injection for both fremanezumab treatment groups; therefore the data from both groups were combined for this comparison during the first 4 weeks of treatment.

Subject analysis set title	Placebo: no concomitant preventive migraine meds
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who were randomized to receive placebo received three 1.5-mL placebo injections at Day 0 and a single 1.5-mL placebo injection at Days 28 and 56. Patients in this sub-group did not receive concomitant preventive migraine medication during the study.

Subject analysis set title	Active 675/placebo/p: no concomitant preventive migraine meds
Subject analysis set type	Sub-group analysis

Subject analysis set 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. Patients in this sub-group did not receive concomitant preventive migraine medication during the study.

Subject analysis set title	Active 675/225/225: no concomitant preventive migraine meds
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who were randomized to receive fremanezumab 675/225/225 mg received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) on Days 28 and 56. Patients in this sub-group did not receive concomitant preventive migraine medication during the study.

Primary: Change from Baseline in the Monthly Average Number of Headache Days of At Least Moderate Severity During the 12-Week Period After the First Dose of Study Drug

End point title	Change from Baseline in the Monthly Average Number of Headache Days of At Least Moderate Severity During the 12-Week Period After the First Dose of Study Drug

End point description:

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) where the patient (using the electronic headache diary device) reports: - a day with headache pain that lasts ≥4 hours with a peak severity of at least moderate severity or - a day when the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration. 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. Full analysis set (FAS) included those in the ITT population who received at least 1 dose of study drug and had at least 10 days of post-baseline efficacy assessments on the primary endpoint.

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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	371[1]	375[2]	375[3]	
Units: headache days				
median (inter-quartile range (Q1-Q3))	-2.5 (-5.6 to 0.0)	-4.2 (-7.7 to -1.7)	-4.5 (-7.8 to -1.7)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

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	Placebo v Fremanezumab 675 mg/placebo/placebo
Number of subjects included in analysis	746
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 675/225/225 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	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	746
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 (AEs)

End point title	Participants with Adverse Events (AEs)[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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	375[7]	376[8]	379[9]	
Units: participants				
Any AEs	240	265	270	
Severe AEs	20	14	15	
Treatment-related AEs	159	186	194	
Serious adverse events	6	3	5	
Deaths	0	1	0	
Discontinued from study due to AE	8	5	7	

Notes:

[7] - Safety population

[8] - Safety population

[9] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 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	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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	371[10]	375[11]	375[12]	
Units: migraine days / month				
least squares mean (standard error)	-3.2 (± 0.35)	-4.9 (± 0.35)	-5.0 (± 0.35)	

Notes:
[10] - FAS
[11] - FAS
[12] - FAS

Statistical analyses

Statistical analysis title	Active 675/placebo/placebo to Placebo
Comparison groups	Placebo v Fremanezumab 675 mg/placebo/placebo
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	-0.97
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:
[13] - 0.05 level of significance

Statistical analysis title	Active 675/225/225 to Placebo
Comparison groups	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-1.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	-1.09
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[14] - 0.05 level of significance

Secondary: Percentage of Participants With At Least 50% Reduction In Monthly Average Number of Headache Days of At Least Moderate Severity

End point title	Percentage of Participants With At Least 50% Reduction In Monthly Average Number of Headache Days of At Least Moderate Severity

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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	370[15]	375[16]	374[17]	
Units: percentage of total participants				
number (not applicable)				
Month 1 (n=370, 375, 374)	21.6	41.3	40.0	
Month 2 (n=355, 365, 361)	24.3	39.7	41.9	
Month 3 (n=342, 350, 345)	26.4	40.5	44.5	
Overall - Months 1-3 (n=370, 375, 374)	18.1	37.6	40.8	

Notes:

[15] - FAS minus one subject who had 0 headache days of >= moderate severity during baseline and treatment

[16] - FAS

[17] - FAS minus one subject who had 0 headache days of >= moderate severity during baseline and treatment

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	Placebo v Fremanezumab 675 mg/placebo/placebo

Number of subjects included in analysis	745
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Cochran-Mantel-Haenszel

Notes:
[18] - 0.05 level of significance

Statistical analysis title	Month 1: Active 675/225/225 to Placebo

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

Comparison groups	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	744
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	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	Placebo v Fremanezumab 675 mg/placebo/placebo
Number of subjects included in analysis	745
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel

Notes:
[20] - 0.05 level of significance

Statistical analysis title	Month 2: Active 675/225/225 to Placebo

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

Comparison groups	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	744
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Cochran-Mantel-Haenszel

Notes:
[21] - 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	Placebo v Fremanezumab 675 mg/placebo/placebo

Number of subjects included in analysis	745
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel

Notes:

[22] - 0.05 level of significance

Statistical analysis title	Month 3: Active 675/225/225 to Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	744
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Cochran-Mantel-Haenszel

Notes:

[23] - 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	Placebo v Fremanezumab 675 mg/placebo/placebo
Number of subjects included in analysis	745
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Cochran-Mantel-Haenszel

Notes:

[24] - 0.05 level of significance

Statistical analysis title	Overall: Active 675/225/225 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	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	744
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Cochran-Mantel-Haenszel

Notes:

[25] - 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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	371[26]	375[27]	375[28]	
Units: days				
median (inter-quartile range (Q1-Q3))	-2.0 (-5.3 to 0.2)	-3.6 (-7.3 to -0.7)	-4.2 (-7.6 to -1.1)	

Notes:

[26] - FAS

[27] - FAS

[28] - FAS

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 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	746
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 675/225/225 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	Placebo v Fremanezumab 675/225/225 mg

Number of subjects included in analysis	746
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 Number of Headache Days of At Least Moderate Severity During the 4 Week Period After the First Dose of Study Drug

End point title	Change from Baseline in the Number of Headache Days of At Least Moderate Severity During the 4 Week Period After the First Dose of Study Drug[31]

End point description:

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) where the patient (using the electronic headache diary device) reports: - a day with headache pain that lasts ≥4 hours with a peak severity of at least moderate severity or - a day when the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration. The change is calculated as postbaseline value – baseline value. Full analysis set (FAS) included those in the ITT population who received at least 1 dose of study drug and had at least 10 days of post-baseline efficacy assessments on the primary endpoint.

End point type	Secondary

End point timeframe:

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

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This warning is a system artifact since there is a statistical analysis that compares the Placebo treatment group to the combined Fremanezumab analysis set.

End point values	Placebo	Fremanezumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	371[32]	750[33]		
Units: days				
least squares mean (standard error)	-2.3 (± 0.33)	-4.6 (± 0.27)		

Notes:

[32] - FAS

[33] - FAS

Statistical analyses

Statistical analysis title	Change in Headache Days Over 4 Weeks
Comparison groups	Placebo v Fremanezumab
Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.95
upper limit	-1.73
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[34] - 0.05 level of significance

Secondary: Change from Baseline in the Monthly Average Number of Headache Days of At Least Moderate Severity 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 Headache Days of At Least Moderate Severity 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. Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of >= moderate severity was defined as a calendar day where the patient (using the electronic headache diary device) reports: - a day with headache pain that lasts ≥4 hours with a peak severity of >= moderate severity or - a day when the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration. 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. Change is 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: no concomitant preventive migraine meds	Active 675/placebo/p: no concomitant preventive migraine meds	Active 675/225/225: no concomitant preventive migraine meds	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	294[35]	298[36]	290[37]	
Units: days				
median (inter-quartile range (Q1-Q3))	-2.4 (-5.3 to 0.0)	-4.4 (-8.0 to -1.7)	-4.6 (-7.8 to -1.5)	

Notes:

[35] - FAS

[36] - FAS

[37] - FAS

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 primary analysis was

conducted using the Wilcoxon rank-sum test as outlined in the SAP.

Comparison groups	Placebo: no concomitant preventive migraine meds v Active 675/placebo/p: no concomitant preventive migraine meds
Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [38]
Method	Wilcoxon (Mann-Whitney)

Notes:

[38] - 0.05 level of significance

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 primary analysis was conducted using the Wilcoxon rank-sum test as outlined in the SAP.

Comparison groups	Placebo: no concomitant preventive migraine meds v Active 675/225/225: no concomitant preventive migraine meds
Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [39]
Method	Wilcoxon (Mann-Whitney)

Notes:

[39] - 0.05 level of significance

Secondary: Change from Baseline in Migraine-Related Disability Score, As Measured by the 6-Item Headache Impact Test (HIT) At Week 12

End point title	Change from Baseline in Migraine-Related Disability Score, As Measured by the 6-Item Headache Impact Test (HIT) At Week 12

End point description:

The HIT-6 was developed by Kosinski et al (2003) as a short form for reliably assessing the adverse headache impact in clinical practice and clinical research settings. The questionnaire measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It also assesses headache severity. Scores range from 36 to 78, where a higher score indicates a greater impact of headache on the daily life of the patient, ie, scores ≤49 represent little or no impact, scores between 50 and 55 represent some impact, scores between 56 and 59 represent substantial impact; and scores ≥60 indicate severe impact. Negative change from baseline values indicate less adverse impact of headache.

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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	371[40]	375[41]	375[42]	
Units: units on a scale				
median (inter-quartile range (Q1-Q3))	-4.0 (-7.0 to 0.0)	-5.0 (-10.0 to -2.0)	-6.0 (-11.0 to -2.0)	

Notes:

[40] - FAS

[41] - FAS

[42] - FAS

Statistical analyses

Statistical analysis title	HIT-6: 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	746
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [43]
Method	Wilcoxon (Mann-Whitney)

Notes:

[43] - 0.05 level of significance

Statistical analysis title	HIT-6: Active 675/225/225 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 675/225/225 mg v Placebo
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	Wilcoxon (Mann-Whitney)

Notes:

[44] - 0.05 level of significance

Secondary: Electrocardiogram (ECG) Findings Shifts From Baseline to Overall

End point title	Electrocardiogram (ECG) Findings 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 endpoint)

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	360[45]	361[46]	362[47]	
Units: participants				
Normal / Normal	215	220	223	
Normal / NCS	54	48	43	
Normal / CS	1	0	0	
NCS / Normal	31	34	34	
NCS / NCS	59	59	62	
NCS / CS	0	0	0	
CS / Normal	0	0	0	
CS / NCS	0	0	0	
CS / CS	0	0	0	

Notes:

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

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

[47] - 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 potentially clinically significant abnormal findings included: - Pulse Rate High: >=120 and increase of >=15 beats per minute - 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 (or endpoint). Changes from previous reading may reflect the baseline reading performed on Day 0.

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	366[48]	373[49]	372[50]	
Units: participants				
Patients with at least 1 abnormality	7	10	14	

Pulse Rate High	0	0	1	
Pulse Rate Low	1	1	0	
Systolic Blood Pressure Low	2	4	6	
Diastolic Blood Pressure High	1	2	3	
Diastolic Blood Pressure Low	0	1	2	
Respiratory Rate Low	3	2	3	

Notes:

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

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

[50] - 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 - Creatinine High: >=177 umol/L - Bilirubin High: >=34.2 umol/L - Alanine Aminotransfrase (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 endpoint).

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	366[51]	373[52]	371[53]	
Units: participants				
BUN	1	1	1	
Creatinine	2	0	0	
Bilirubin	0	2	0	
ALT	2	2	7	
AST	0	3	4	
GGT	7	7	8	
Hemoglobin	2	5	3	
Hematocrit	8	9	7	
Leukocytes	2	9	5	
Eosinophils/Leukocytes	4	5	4	
Platelets	1	2	0	

Notes:

[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.

[53] - 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 (or endpoint). Changes from previous reading reflect the baseline reading performed on Day 0.

End point values	Placebo	Fremanezumab 675 mg/placebo/placebo	Fremanezumab 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365[54]	373[55]	372[56]	
Units: participants				
Patients with at least 1 abnormality	78	57	68	
Blood	33	32	35	
Urine Glucose	7	7	5	
Ketones	7	7	7	
Urine Protein	40	19	34	

Notes:

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

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

[56] - 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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	366[57]	373[58]	370[59]	
Units: participants				
Low / Low	0	0	0	
Low / Normal	2	0	1	
Low / High	0	0	0	
Normal / Low	0	1	2	
Normal / Normal	330	318	327	
Normal / High	13	17	19	
High / Low	0	0	0	
High / Normal	14	19	12	
High / High	7	18	9	

Notes:

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

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

[59] - 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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	375[60]	376[61]	379[62]	
Units: participants				
Patients with at least 1 injection site reaction	151	176	183	
Injection site pain	104	114	99	
Injection site induration	68	74	90	
Injection site erythema	60	80	75	

Injection site haemorrhage	10	7	8	
Injection site pruritus	0	6	8	
Injection site rash	0	4	3	
Injection site bruising	2	1	2	
Injection site swelling	0	2	1	
Injection site dermatitis	0	1	0	
Injection site discomfort	0	1	0	
Injection site haematoma	0	0	1	
Injection site hypoaesthesia	0	0	1	
Injection site inflammation	0	0	1	
Injection site oedema	0	1	0	
Injection site paraesthesia	0	0	1	
Injection site urticaria	2	0	1	
Injection site warmth	2	0	1	

Notes:

[60] - Safety

[61] - Safety

[62] - Safety

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 675/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	375[63]	376[64]	379[65]	
Units: participants				
Participants with positive eC-SSRS responses	1	1	1	
Specific finding: interrupted suicide attempt	1	1	0	
Specific finding: suicidal ideation	0	0	1	

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

Serious adverse events	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 675 mg/placebo/placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 375 (1.60%)	5 / 379 (1.32%)	3 / 376 (0.80%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 375 (0.00%)	0 / 379 (0.00%)	1 / 376 (0.27%)
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 / 375 (0.00%)	0 / 379 (0.00%)	1 / 376 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Accident			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Ulna fracture			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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
Radius fracture			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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
Fall			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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			
Migraine			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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			
Oedema peripheral			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 375 (0.00%)	0 / 379 (0.00%)	1 / 376 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthma			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Dyspnoea			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 375 (0.27%)	0 / 379 (0.00%)	0 / 376 (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
Calculus urinary			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 375 (0.00%)	1 / 379 (0.26%)	0 / 376 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 375 (0.00%)	0 / 379 (0.00%)	1 / 376 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 675/225/225 mg	Fremanezumab 675 mg/placebo/placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 375 (42.67%)	178 / 379 (46.97%)	185 / 376 (49.20%)
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	104 / 375 (27.73%)	99 / 379 (26.12%)	114 / 376 (30.32%)
occurrences (all)	288	271	296
Injection site induration			
subjects affected / exposed	68 / 375 (18.13%)	90 / 379 (23.75%)	74 / 376 (19.68%)
occurrences (all)	130	196	159
Injection site erythema			
subjects affected / exposed	60 / 375 (16.00%)	75 / 379 (19.79%)	80 / 376 (21.28%)
occurrences (all)	129	166	172
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 375 (5.33%) 24	15 / 379 (3.96%) 16	19 / 376 (5.05%) 20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported