Clinical trial results:
A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 Versus Placebo for the Prevention of Chronic Cluster Headache

Summary

EudraCT number	2016-003171-21
Trial protocol	GB SE DE ES IT NL PL FI
Global end of trial date	18 July 2018

Results information

Result version number	v1 (current)
This version publication date	03 August 2019
First version publication date	03 August 2019

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30057

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02964338
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	41 Moores Road, Frazer, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 18884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 18884838279, info.eraclinical@teva.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2018
Global end of trial reached?	Yes
Global end of trial date	18 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy of fremanezumab in the prevention of chronic cluster headache (CCH) in adult participants.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 103
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	259
EEA total number of subjects	118

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)	245
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with a history of CCH were enrolled. Eligible participants entered baseline cluster headache (CH) attack information into an electronic diary device daily for greater than or equal to (≥)4 weeks during the Baseline Period.

Pre-assignment

Screening details:

A total of 259 participants were randomly assigned with stratification based on sex, country, and baseline concomitant preventive medication use (yes/no) to either placebo, fremanezumab 675/225/225 milligrams (mg), or fremanezumab 900/225/225 mg treatment groups in a 1:1:1 ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo via an approximately 1-hour intravenous infusion and as 3 subcutaneous injections at Week 0 followed by placebo administered as single subcutaneous injections at Weeks 4 and 8.

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

Dosage and administration details:

Placebo matching to fremanezumab will be administered as per the schedule specified in the respective arms.

Arm title	Fremanezumab 675/225/225 mg

Arm description:

Participants received placebo via an approximately 1-hour intravenous infusion and fremanezumab at 675 mg as 3 subcutaneous injections (225 mg/1.5 milliliters [mL]) at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	
Other name	TEV-48125
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Fremanezumab will be administered as per the dose and schedule specified in the respective arms.

Arm title	Fremanezumab 900/225/225 mg

Arm description:

Participants received fremanezumab at 900 mg via an approximately 1-hour intravenous infusion and

placebo administered as 3 subcutaneous injections at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	
Other name	TEV-48125
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Fremanezumab will be administered as per the dose and schedule specified in the respective arms.

Number of subjects in period 1	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg
Started	84	88	87
Intent-to-Treat (ITT) Analysis Set	84	88	87
Safety Analysis Set	83	88	87
Full Analysis Set	81	86	87
Completed	67	64	68
Not completed	17	24	19
Consent withdrawn by subject	1	3	1
Adverse event, non-fatal	2	1	1
Non-compliant with e-diary	-	1	-
Did not meet criteria	1	-	-
Sponsor terminated study for futility	12	15	14
Lost to follow-up	1	-	3
Lack of efficacy	-	3	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo via an approximately 1-hour intravenous infusion and as 3 subcutaneous injections at Week 0 followed by placebo administered as single subcutaneous injections at Weeks 4 and 8.	
Reporting group title	Fremanezumab 675/225/225 mg
Reporting group description:	
Participants received placebo via an approximately 1-hour intravenous infusion and fremanezumab at 675 mg as 3 subcutaneous injections (225 mg/1.5 milliliters [mL]) at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.	
Reporting group title	Fremanezumab 900/225/225 mg
Reporting group description:	
Participants received fremanezumab at 900 mg via an approximately 1-hour intravenous infusion and placebo administered as 3 subcutaneous injections at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.	

Reporting group values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg
Number of subjects	84	88	87
Age categorical Units: Subjects			
Adults (18-64 years)	81	83	81
From 65-84 years	3	5	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	46.3	45.3	43.8
standard deviation	± 11.29	± 11.40	± 12.92
Sex: Female, Male Units: Subjects			
Female	35	36	36
Male	49	52	51
Race Units: Subjects			
White	79	83	79
Black or African American	4	4	8
Asian	0	1	0
American Indian or Alaska native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Middle Eastern	1	0	0
Ethnicity Units: Subjects			
Not Hispanic or Latino	77	78	83
Hispanic or Latino	5	9	4
Missing Ethnicity	2	1	0

Number of CH Attacks During the Baseline Period			
CH attack defined as a severe/very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (min) with either or both of following 2 categories: 1) ≥1 of following symptoms/signs, ipsilateral to headache: -conjunctival injection and/or lacrimation; -nasal congestion and/or rhinorrhea; -eyelid edema; -forehead and facial sweating; -forehead and facial flushing; -fullness in ear sensation; -miosis and/or ptosis. 2) sense of restlessness or agitation. Baseline period (≥4 weeks [wk]) defined as date informed consent was signed up to day before first dose of study drug.			
Units: CH attacks			
arithmetic mean	38.0	33.9	44.0
standard deviation	± 33.88	± 27.37	± 43.78

Reporting group values	Total		
Number of subjects	259		
Age categorical			
Units: Subjects			
Adults (18-64 years)	245		
From 65-84 years	14		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	107		
Male	152		
Race			
Units: Subjects			
White	241		
Black or African American	16		
Asian	1		
American Indian or Alaska native	0		
Native Hawaiian or other Pacific Islander	0		
Middle Eastern	1		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	238		
Hispanic or Latino	18		
Missing Ethnicity	3		
Number of CH Attacks During the Baseline Period			
CH attack defined as a severe/very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (min) with either or both of following 2 categories: 1) ≥1 of following symptoms/signs, ipsilateral to headache: -conjunctival injection and/or lacrimation; -nasal congestion and/or rhinorrhea; -eyelid edema; -forehead and facial sweating; -forehead and facial flushing; -fullness in ear sensation; -miosis and/or ptosis. 2) sense of restlessness or agitation. Baseline period (≥4 weeks [wk]) defined as date informed consent was signed up to day before first dose of study drug.			
Units: CH attacks			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo via an approximately 1-hour intravenous infusion and as 3 subcutaneous injections at Week 0 followed by placebo administered as single subcutaneous injections at Weeks 4 and 8.	

Reporting group title	Fremanezumab 675/225/225 mg
Reporting group description:	
Participants received placebo via an approximately 1-hour intravenous infusion and fremanezumab at 675 mg as 3 subcutaneous injections (225 mg/1.5 milliliters [mL]) at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.	

Reporting group title	Fremanezumab 900/225/225 mg
Reporting group description:	
Participants received fremanezumab at 900 mg via an approximately 1-hour intravenous infusion and placebo administered as 3 subcutaneous injections at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.	

Primary: Mean Change From Baseline in the Overall Monthly Average Number of CH Attacks Up to Week 12

End point title	Mean Change From Baseline in the Overall Monthly Average Number of CH Attacks Up to Week 12
End point description:	
CH: severe/very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180min with either/both of following 2 categories: 1) ≥1 of following symptoms/signs, ipsilateral to headache: -conjunctival injection and/or lacrimation; -nasal congestion and/or rhinorrhea; -eyelid edema; -forehead and facial sweating; -forehead and facial flushing; -fullness in ear sensation; -miosis and/or ptosis. 2) sense of restlessness or agitation. Least Squares mean calculated by analysis of covariance (ANCOVA) model with baseline preventive medication use (yes/no), sex, region (United States/Canada/other) and treatment as fixed effects & baseline number of CH attacks as a covariate. Change from baseline in overall monthly average number of CH attacks during 12-wk period after first dose of study drug (based on Wk0-12 data) is reported. Full analysis set: randomized participants, received ≥1 dose of study drug, had at least 10days of postbaseline efficacy assessments by Wk12 assessment.	
End point type	Primary
End point timeframe:	
Baseline Period (from at least Week -4 to Week 0), Up to Week 12	

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	86	87	
Units: CH attacks				
least squares mean (standard error)	-12.2 (± 2.32)	-8.7 (± 2.26)	-15.5 (± 2.24)	

Statistical analyses

Statistical analysis title	Placebo versus Fremanezumab 675/225/225 mg
Comparison groups	Placebo v Fremanezumab 675/225/225 mg
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2741 [1]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	9.82

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Placebo versus Fremanezumab 900/225/225 mg
Comparison groups	Placebo v Fremanezumab 900/225/225 mg
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3047 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.59
upper limit	3.01

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Percentage of Participants With a ≥50% Reduction from Baseline in the Monthly Average Number of CH Attacks Up to Week 12

End point title	Percentage of Participants With a ≥50% Reduction from Baseline in the Monthly Average Number of CH Attacks Up to Week 12

End point description:

A CH attack was defined as a severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes with either or both of the following 2 categories: 1) at least 1 of the following symptoms or signs, ipsilateral to the headache: -conjunctival injection and/or lacrimation; -nasal congestion and/or rhinorrhea; -eyelid edema; -forehead and facial sweating; -forehead and facial flushing; -sensation of fullness in the ear; -miosis and/or ptosis. 2) a sense of restlessness or agitation. Full analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessments by the Week 12 assessment.

End point type	Secondary

End point timeframe:

Baseline Period (from at least Week -4 to Week 0) up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	86	87	
Units: percentage of participants	40	40	45	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Monthly Average Number of CH Attacks at Week 4 and Week 12

End point title	Mean Change From Baseline in the Monthly Average Number of CH Attacks at Week 4 and Week 12

End point description:

CH attack defined as a severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 min with either or both of following 2 categories: 1) ≥1 of following symptoms or signs, ipsilateral to the headache: -conjunctival injection and/or lacrimation; -nasal congestion and/or rhinorrhea; -eyelid edema; -forehead and facial sweating; -forehead and facial flushing; -fullness in ear sensation; -miosis and/or ptosis. 2) a sense of restlessness or agitation. Mean change from baseline in monthly average number of CH attacks during 4-wk period after administration of first dose of study drug (based on Wk 0-4 data) and during 4-week period after administration of third dose of study drug (based on Wk 8-12 data) is reported. Full analysis set: all randomized participants who received ≥1 dose of study drug and had ≥10 days of postbaseline efficacy assessments by the Wk 12 assessment. Here, 'N' signifies participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline Period (from at least Week -4 to Week 0), Week 4 and Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	86	87	
Units: CH attacks				
arithmetic mean (standard deviation)				
Change at Week 4 (n=81, 86, 87)	-10.4 (± 17.22)	-7.7 (± 19.53)	-15.0 (± 24.17)	
Change at Week 12 (n=67, 62, 72)	-12.6 (± 25.72)	-3.1 (± 34.42)	-17.9 (± 25.98)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Overall Weekly Average Number of Days with Use of Cluster-Specific Acute Headache Medications (Triptans and Ergot Compounds) Up to Week 12

End point title	Mean Change From Baseline in the Overall Weekly Average Number of Days with Use of Cluster-Specific Acute Headache Medications (Triptans and Ergot Compounds) Up to Week 12

End point description:

A maximum of 2 concomitant preventive medications for CH were allowed during the study. Participants must have been on a stable dose and regimen of the concomitant medication for at least 2 weeks before screening and throughout the study. Baseline data and the mean change from baseline in the overall weekly average number of days with the use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12-week period after administration of the first dose of study drug (based on Week 0 to 12 data) is reported. Full analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessments by the Week 12 assessment.

End point type	Secondary

End point timeframe:

Baseline Period (from at least Week -4 to Week 0), Up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	86	87	
Units: days				
arithmetic mean (standard deviation)				
Baseline	2.4 (± 2.42)	2.4 (± 2.18)	2.2 (± 2.27)	
Change at Week 12	-0.7 (± 1.34)	-0.8 (± 1.57)	-0.8 (± 1.20)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Weekly Average Number of Days Oxygen was Used to Treat CCH Up to Week 12

End point title	Mean Change From Baseline in the Weekly Average Number of Days Oxygen was Used to Treat CCH Up to Week 12

End point description:

Baseline data and the mean change from baseline in the overall weekly average number of days oxygen was used to treat CCH during the 12-week period after administration of the first dose of study drug (based on Week 0 to 12 data) is reported. Full analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessments by the Week 12 assessment.

End point type	Secondary

End point timeframe:

Baseline Period (from at least Week -4 to Week 0), Up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	86	87	
Units: days				
arithmetic mean (standard deviation)				
Baseline	2.2 (± 2.59)	1.9 (± 2.53)	1.9 (± 2.59)	
Change at Week 12	-0.5 (± 1.35)	-0.5 (± 1.35)	-0.5 (± 1.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Perceived Improvement of CH-Associated Pain From Baseline as Measured by the Patient-Perceived Satisfactory Improvement (PPSI) Scale at Weeks 1, 4, 8, and 12

End point title	Number of Participants who Perceived Improvement of CH-Associated Pain From Baseline as Measured by the Patient-Perceived Satisfactory Improvement (PPSI) Scale at Weeks 1, 4, 8, and 12

End point description:

The PPSI assessment was developed to measure pain intensity and was adjusted for CH symptoms improvement. Participants marked the level of CH-associated pain and indicated if pain is "1=much worse," "2=moderately worse," "3=slightly worse," "4=unchanged," "5=slightly improved," "6=moderately improved," or "much improved" compared with 4 weeks prior. PPSI was defined as the change in pain that corresponds with a minimal rating of "7=slightly improved." Data at Week 1 was recorded on Day 7 in the electronic diary device at home. Week 12 data also included assessment at the early withdrawal visit for participants who discontinued the study early. Full analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessments by the Week 12 assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 4, 8, and 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	86	87	
Units: participants				
Much worse, Baseline	3	1	1	
Moderately worse, Baseline	1	4	4	
Slightly worse, Baseline	1	5	4	
Unchanged, Baseline	69	72	75	
Slightly improved, Baseline	5	3	3	
Moderately improved, Baseline	1	1	0	

Much improved, Baseline	1	0	0	
Missing, Baseline	0	0	0	
Much worse, Week 1	0	3	3	
Moderately worse, Week 1	0	2	1	
Slightly worse, Week 1	0	2	5	
Unchanged, Week 1	35	31	26	
Slightly improved, Week 1	23	20	32	
Moderately improved, Week 1	5	4	8	
Much improved, Week 1	6	13	8	
Missing, Week 1	12	11	4	
Much worse, Week 4	0	1	0	
Moderately worse, Week 4	1	2	3	
Slightly worse, Week 4	1	2	2	
Unchanged, Week 4	24	24	25	
Slightly improved, Week 4	30	17	25	
Moderately improved, Week 4	5	9	12	
Much improved, Week 4	12	18	11	
Missing, Week 4	8	13	9	
Much worse, Week 8	3	2	0	
Moderately worse, Week 8	1	3	3	
Slightly worse, Week 8	3	4	5	
Unchanged, Week 8	27	18	24	
Slightly improved, Week 8	18	12	13	
Moderately improved, Week 8	10	13	14	
Much improved, Week 8	4	12	15	
Missing, Week 8	15	22	13	
Much worse, Week 12	0	2	1	
Moderately worse, Week 12	3	5	3	
Slightly worse, Week 12	4	6	6	
Unchanged, Week 12	29	27	31	
Slightly improved, Week 12	21	18	15	
Moderately improved, Week 12	8	11	11	
Much improved, Week 12	13	14	12	
Missing, Week 12	3	3	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during 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 as an AE that 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 participant and required medical intervention to prevent the previously listed serious outcomes. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants				
Any AE	43	51	49	
Severe AE	3	1	3	
Treatment-related AE	17	23	28	
Serious AE	2	2	3	
AE leading to discontinuation	2	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Potentially Clinically Significant Laboratory (Serum Chemistry, Hematology, and Urinalysis) Abnormal Results

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

End point description:

Laboratory tests with potentially clinically significant abnormal findings included: Alanine Aminotransferase (units/liter [U/L]) ≥3*upper limit of normal (ULN); Aspartate Aminotransferase (U/L) ≥3*ULN; Bilirubin (Total) ≥34.2 micromoles/liter (umol/L); Blood Urea Nitrogen ≥10.71millimole/L; Creatinine ≥177 umol/L; Gamma Glutamyl Transferase (U/L) ≥3*ULN; hemoglobin less than (<)115grams (g)/L (males) or less than or equal to (≤)95g/L (females); leukocytes ≥20*10^9/L or ≤3*10^9/L; Eosinophils/Leukocytes ≥10%; Hematocrit <0.37L/L (males) and <0.32L/L (females); platelets ≥700*10^9/L or ≤75*10^9/L; blood ≥2 U increase from baseline; urine glucose (milligrams/decilitre [mg/dL]) ≥2 U increase from baseline; ketones (mg/dL) ≥2 U increase from baseline; urine protein (mg/dL) ≥2 U increase from baseline. Summary of other non-serious AEs and all serious AEs, regardless of causality located in Reported AE section. Safety population: randomized participants and received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants				

With at least 1 serum chemistry abnormality	1	2	0	
With at least 1 hematology abnormality	2	1	3	
With at least 1 urinalysis abnormality	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shift From Baseline to Endpoint in Coagulation Laboratory Test Results

End point title	Number of Participants With Shift From Baseline to Endpoint in Coagulation Laboratory Test Results

End point description:

Coagulation parameters included: prothrombin time (PT) (seconds), prothrombin international normalized ratio (INR), activated partial thromboplastin time (aPTT) (seconds). Shifts represented as Baseline - endpoint value (last observed post-baseline value). Shifts from baseline to endpoint were summarized using participant 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). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants				
PT: Low-Low	0	0	0	
PT: Low-Normal	0	0	0	
PT: Low-High	0	0	0	
PT: Normal-Low	0	0	0	
PT: Normal-Normal	68	69	62	
PT: Normal-High	3	2	5	
PT: High-Low	0	0	0	
PT: High-Normal	5	8	11	
PT: High-High	5	4	3	
PT: Missing	2	5	6	
Prothrombin INR: Low-Low	0	0	0	
Prothrombin INR: Low-Normal	0	0	0	
Prothrombin INR: Low-High	0	0	0	
Prothrombin INR: Normal-Low	0	0	0	
Prothrombin INR: Normal-Normal	70	71	69	
Prothrombin INR: Normal-High	4	2	5	
Prothrombin INR: High-Low	0	0	0	
Prothrombin INR: High-Normal	5	7	6	

Prothrombin INR: High-High	2	3	1	
Prothrombin INR: Missing	2	5	6	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Potentially clinically significant abnormal vital signs findings included: pulse rate ≤50 beats/minute (bpm) and decrease of ≥15 bpm, or ≥120 bpm and increase of ≥15 bpm; systolic blood pressure ≤90 millimeters of mercury (mmHg) and decrease of ≥20 mmHg, or ≥180 mmHg and increase of ≥20 mmHg; diastolic blood pressure ≤50 mmHg and decrease of ≥15 mmHg, or ≥105 mmHg and increase of ≥15 mmHg; respiratory rate <10 breaths/minute; and body temperature ≥38.3 degrees centigrade and change of ≥1.1 degrees centigrade. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants	3	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shift From Baseline to Endpoint (Last Assessment) in Electrocardiogram (ECG) Parameters

End point title	Number of Participants With Shift From Baseline to Endpoint (Last Assessment) in Electrocardiogram (ECG) Parameters

End point description:

ECG parameters included: heart rate, PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - endpoint value (last observed post-baseline value). Abnormal NCS indicated an abnormal but not clinically significant finding. Abnormal CS indicated an abnormal and clinically significant finding. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants				
Normal / Normal	47	46	45	
Normal / NCS	8	11	14	
Normal / CS	0	0	0	
NCS / Normal	10	7	8	
NCS / NCS	15	20	12	
NCS / CS	0	0	0	
CS / Normal	0	0	0	
CS / NCS	0	0	0	
CS / CS	0	0	0	
Missing	3	4	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Injection Site Reactions

End point title	Number of Participants with Injection Site Reactions

End point description:

Number of participants who reported treatment-emergent injection site reactions are summarized. Preferred terms from Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 were offered without a threshold applied. Injection site reactions included injection site erythema, induration, pain, haemorrhage, bruising, hypersensitivity, swelling, rash, and flushing. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants				
Injection site erythema	3	7	5	
Injection site induration	3	6	6	
Injection site pain	6	5	2	

Injection site haemorrhage	0	0	2	
Injection site bruising	0	0	1	
Injection site hypersensitivity	0	1	0	
Injection site swelling	2	0	0	
Injection site rash	1	0	0	
Injection site flushing	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Suicidal Ideation and Suicidal Behavior as Assessed by the Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

End point title	Number of Participants with Suicidal Ideation and Suicidal Behavior as Assessed by the Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

End point description:

eC-SSRS is a questionnaire to assess suicidal ideation and suicidal behavior. Suicidal behavior was defined as a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Suicidal ideation was defined as a "yes" answer to any one of 5 suicidal ideation questions: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent, any self-injurious behavior with no suicidal intent. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675/225/225 mg	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	88	87	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 12	
Adverse event reporting additional description:	
Safety population included all randomized participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo via an approximately 1-hour intravenous infusion and as 3 subcutaneous injections at Week 0 followed by placebo administered as single subcutaneous injections at Weeks 4 and 8.	
Reporting group title	Fremanezumab 900/225/225 mg
Reporting group description:	
Participants received fremanezumab at 900 mg via an approximately 1-hour intravenous infusion and placebo administered as 3 subcutaneous injections at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.	
Reporting group title	Fremanezumab 675/225/225 mg
Reporting group description:	
Participants received placebo via an approximately 1-hour intravenous infusion and fremanezumab at 675 mg as 3 subcutaneous injections (225 mg/1.5 mL) at Week 0 followed by fremanezumab at 225 mg administered as single subcutaneous injections (225 mg/1.5 mL) at Weeks 4 and 8.	

Serious adverse events	Placebo	Fremanezumab 900/225/225 mg	Fremanezumab 675/225/225 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 83 (2.41%)	3 / 87 (3.45%)	2 / 88 (2.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
General disorders and administration site conditions			
Infusion site necrosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 87 (1.15%)	0 / 88 (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

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 83 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 83 (1.20%)	0 / 87 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 87 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Pelvic abscess			
subjects affected / exposed	0 / 83 (0.00%)	1 / 87 (1.15%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Fremanezumab 900/225/225 mg	Fremanezumab 675/225/225 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 83 (21.69%)	19 / 87 (21.84%)	22 / 88 (25.00%)
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	3 / 83 (3.61%)	5 / 87 (5.75%)	7 / 88 (7.95%)
occurrences (all)	4	6	15
Injection site induration			
subjects affected / exposed	3 / 83 (3.61%)	6 / 87 (6.90%)	6 / 88 (6.82%)
occurrences (all)	8	12	12
Injection site pain			
subjects affected / exposed	6 / 83 (7.23%)	2 / 87 (2.30%)	5 / 88 (5.68%)
occurrences (all)	11	2	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 83 (4.82%)	3 / 87 (3.45%)	5 / 88 (5.68%)
occurrences (all)	4	4	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 83 (7.23%)	8 / 87 (9.20%)	6 / 88 (6.82%)
occurrences (all)	7	9	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2017	The primary reason for this amendment was to provide clarification based on feedback from participating Investigators and regulatory agencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Futility analysis revealed that the primary endpoint is unlikely to be met. There were no safety concerns observed with fremanezumab treatment in the trial.

Notes: