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 Episodic Cluster Headache

Summary

EudraCT number	2016-003278-42
Trial protocol	GB SE DE ES IT NL PL FI
Global end of trial date	13 May 2019

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30056

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02945046
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2019
Global end of trial reached?	Yes
Global end of trial date	13 May 2019
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 episodic cluster headache (ECH) 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 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).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 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	Australia: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	169
EEA total number of subjects	80

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)	164
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 169 participants were randomized in a 1:1:1 ratio to placebo, fremanezumab 675 milligrams (mg)/placebo/placebo, or fremanezumab 900/225/225 mg groups.

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

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

Dosage and administration details:

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

Arm title	Fremanezumab 675 mg/Placebo/Placebo

Arm description:

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

Arm type	Experimental
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 matched to fremanezumab was administered per schedule specified in the arm.

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

Dosage and administration details:

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

Arm title	Fremanezumab 900/225/225 mg

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg
Started	59	55	55
Safety analysis set	59	55	55
Full analysis set	57	53	55
Completed	46	42	40
Not completed	13	13	15
Consent withdrawn by subject	3	3	3
Adverse event, non-fatal	1	-	2
Other than specified	5	4	7
Lost to follow-up	1	1	-
Protocol deviation	2	3	2
Lack of efficacy	1	2	1

Baseline characteristics

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

Reporting group values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg
Number of subjects	59	55	55
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	43.1	45.4	43.5
standard deviation	± 10.39	± 11.23	± 11.48
Sex: Female, Male			
Units: participants			
Female	16	17	17
Male	43	38	38
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	0	2
White	54	55	51
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	56	52	49
Unknown or Not Reported	1	0	1

Number of CH Attacks			
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.			
Units: CH attacks			
arithmetic mean	14.8	15.9	14.5
standard deviation	± 10.50	± 9.18	± 7.55

Reporting group values	Total		
Number of subjects	169		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	50		
Male	119		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	160		
More than one race	0		
Unknown or Not Reported	2		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	10		
Not Hispanic or Latino	157		
Unknown or Not Reported	2		
Number of CH Attacks			
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.			
Units: CH attacks			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

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

Primary: Mean Change From Baseline in the Weekly Average Number of Cluster Headache (CH) Attacks During the 4-Week Period After Administration of the First Dose of the IMP

End point title	Mean Change From Baseline in the Weekly Average Number of Cluster Headache (CH) Attacks During the 4-Week Period After Administration of the First Dose of the IMP
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. Least Squares (LS) mean calculated using analysis of covariance (ANCOVA) model with baseline preventive medication use (yes or no), sex, region (United States [US]/Canada or other), and treatment as fixed effects and the baseline number of CH attacks as a covariate. Full analysis set included all randomized participants who received at least 1 dose of IMP and had at least 10 days of postbaseline efficacy assessment in the first 4 weeks on the primary endpoint.	
End point type	Primary
End point timeframe:	
Baseline (Week 0), up to Week 4	

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	53	55	
Units: CH attacks/week				
least squares mean (standard error)	-5.7 (± 1.00)	-5.8 (± 1.02)	-7.6 (± 1.01)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fremanezumab 675 mg/Placebo/Placebo v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9093 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	2.42
Variability estimate	Standard error of the mean
Dispersion value	1.3

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Fremanezumab 900/225/225 mg v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1345 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	1.29

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Percentage of Participants With a ≥50% Reduction From Baseline in the Weekly Average Number of CH Attacks During the 4-Week Period After the First Dose of the IMP

End point title	Percentage of Participants With a ≥50% Reduction From Baseline in the Weekly Average Number of CH Attacks During

	the 4-Week Period After the First Dose of the IMP

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 IMP and had at least 10 days of postbaseline efficacy assessment in the first 4 weeks on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), up to Week 4

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	53	55	
Units: percentage of participants	60	55	75	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Weekly Average Number of CH Attacks During the 12-Week Period After Administration of the First Dose of the IMP

End point title	Mean Change From Baseline in Weekly Average Number of CH Attacks During the 12-Week Period After Administration of the First Dose of the IMP

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. LS mean calculated using mixed model for repeated measures (MMRM) with baseline preventive medication use (yes or no), gender, region (US/Canada or other), treatment, month, and month-by-treatment interaction as fixed effects and baseline number of CH attacks as a covariate. Full analysis set included all randomized participants who received at least 1 dose of IMP and had at least 10 days of postbaseline efficacy assessment in the first 4 weeks on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	53	55	
Units: CH attacks/week				
least squares mean (standard error)	-8.4 (± 0.66)	-8.9 (± 0.68)	-9.6 (± 0.67)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Weekly Average Number of CH Attacks During the 4-Week Period After Administration of the Third Dose of the IMP

End point title	Mean Change From Baseline in Weekly Average Number of CH Attacks During the 4-Week Period After Administration of the Third Dose of the IMP

End point description:

CH attack: a severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes with either or both of following 2 categories: 1) at least 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; -sensation of fullness in ear; -miosis and/or ptosis. 2) a sense of restlessness or agitation. LS mean calculated using MMRM with baseline preventive medication use (yes/no), gender, region (US/Canada or other), treatment, month, and month-by-treatment interaction as fixed effects and baseline number of CH attacks as a covariate. Full analysis set: all randomized participants who received at least 1 dose of IMP and had at least 10 days of postbaseline efficacy assessment in first 4 weeks on primary endpoint. Here, 'overall number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 8 up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	42	40	
Units: CH attacks/week				
least squares mean (standard error)	-10.8 (± 0.75)	-10.8 (± 0.78)	-10.9 (± 0.78)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Weekly Average Number of Days with Use of Cluster-Specific Acute Headache Medications (Triptans and Ergot Compounds) During the 12-Week Period After the First Dose of the IMP

End point title	Mean Change From Baseline in the Weekly Average Number of Days with Use of Cluster-Specific Acute Headache Medications (Triptans and Ergot Compounds) During the 12-Week Period After the First Dose of the IMP

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. LS mean calculated using ANCOVA model with baseline preventive medication use (yes or no), gender, region (US/Canada or other), and treatment as fixed effects and the baseline number of cluster headache attacks as a covariate. 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 IMP and had at least 10 days of postbaseline efficacy assessment in the first 4 weeks on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	53	55	
Units: days of use/week				
least squares mean (standard error)	-1.6 (± 0.36)	-2.4 (± 0.36)	-2.8 (± 0.36)	

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 Episodic Cluster Headache (ECH) During the 12-Week Period After the First Dose of the IMP

End point title	Mean Change From Baseline in the Weekly Average Number of Days Oxygen was Used to Treat Episodic Cluster Headache (ECH) During the 12-Week Period After the First Dose of the IMP

End point description:

LS mean calculated using ANCOVA model with baseline preventive medication use (yes or no), gender, region (US/Canada or other), and treatment as fixed effects and the baseline number of cluster headache attacks as a covariate. Baseline data and the mean change from baseline in the overall weekly average number of days oxygen was used to treat ECH during the 12-week period after administration of the first dose of IMP (based on Week 0 to 12 data) is reported. Full analysis set included all randomized participants who received at least 1 dose of IMP and had at least 10 days of postbaseline efficacy assessment in the first 4 weeks on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week 0), up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	53	55	
Units: days of use/week				
least squares mean (standard error)	-1.1 (± 0.30)	-1.5 (± 0.31)	-1.0 (± 0.30)	

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 "7=much improved" compared with 4 weeks prior. PPSI was defined as the change in pain that corresponds with a minimal rating of "5=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 IMP and had at least 10 days of postbaseline efficacy assessment in the first 4 weeks on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 8, and 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	53	55	
Units: participants				
Baseline|Much worse	10	14	7	
Week 1|Much worse	2	4	1	
Week 4|Much worse	1	1	2	
Week 8|Much worse	1	1	0	
Week 12|Much worse	3	2	2	
Baseline|Moderately worse	3	5	8	
Week 1|Moderately worse	2	2	1	
Week 4|Moderately worse	3	0	1	
Week 8|Moderately worse	3	0	1	
Week 12|Moderately worse	0	0	1	

Baseline|Slightly worse	3	3	3	
Week 1|Slightly worse	5	3	2	
Week 4|Slightly worse	4	2	0	
Week 8|Slightly worse	0	1	1	
Week 12|Slightly worse	2	1	0	
Baseline|Unchanged	37	31	28	
Week 1|Unchanged	19	11	9	
Week 4|Unchanged	8	11	5	
Week 8|Unchanged	13	8	12	
Week 12|Unchanged	16	16	16	
Baseline|Slightly improved	3	0	6	
Week 1|Slightly improved	11	8	14	
Week 4|Slightly improved	9	9	8	
Week 8|Slightly improved	1	6	5	
Week 12|Slightly improved	5	5	4	
Baseline|Moderately improved	1	0	1	
Week 1|Moderately improved	5	3	6	
Week 4|Moderately improved	5	7	8	
Week 8|Moderately improved	7	6	7	
Week 12|Moderately improved	8	7	5	
Baseline|Much improved	0	0	2	
Week 1|Much improved	6	12	12	
Week 4|Much improved	23	19	27	
Week 8|Much improved	20	20	17	
Week 12|Much improved	17	19	24	
Baseline|Missing	0	0	0	
Week 1|Missing	7	10	10	
Week 4|Missing	4	4	4	
Week 8|Missing	12	11	12	
Week 12|Missing	6	3	3	

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 the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. 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 analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants				
Any AEs	28	26	28	
Treatment-related AEs	8	11	13	
Serious AEs	5	0	1	
AEs leading to discontinuation	1	0	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:

Serum chemistry, hematology, urinalysis tests with potentially clinically significant abnormal findings: alanine aminotransferase (ALP), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH) each ≥3*upper limit of normal(ULN); blood urea nitrogen ≥10.71 millimole (mmol)/L; Bilirubin ≥34.2 micromole/liter (umol/L); creatinine ≥177 umol/L; hemoglobin ≤115 grams(g)/L (males) or ≤95 g/L (females); leukocytes ≥20*10^9/L or ≤3*10^9/L; eosinophils ≥10%; hematocrit <0.37 L/L (males) and <0.32 L/L (females); platelets ≥700*10^9/L or ≤75*10^9/L; haemoglobin, urine glucose, ketones, total protein each ≥2 unit(U) increase from baseline. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety analysis set: all randomized participants who received at least 1 dose of the IMP. Here, 'overall number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	54	54	
Units: participants				
With at least 1 serum chemistry abnormality	1	1	0	
With at least 1 hematology abnormality	4	1	4	
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) and prothrombin international normalized ratio (INR). 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). Missing PT and prothrombin INR shift data are also presented. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants				
PT|Low-Low	0	0	0	
Prothrombin INR|Low-Low	0	0	0	
PT|Low-Normal	0	0	0	
Prothrombin INR|Low-Normal	0	0	0	
PT|Low-High	0	0	0	
Prothrombin INR|Low-High	0	0	0	
PT|Normal-Low	0	0	0	
Prothrombin INR|Normal-Low	0	0	0	
PT|Normal-Normal	47	46	44	
Prothrombin INR|Normal-Normal	48	48	47	
PT|Normal-High	2	2	3	
Prothrombin INR|Normal-High	2	2	1	
PT|High-Low	0	0	0	
Prothrombin INR|High-Low	0	0	0	
PT|High-Normal	4	4	4	
Prothrombin INR|High-Normal	3	3	3	
PT|High-High	1	1	2	
Prothrombin INR|High-High	1	0	2	

PT|Missing	5	2	2	
Prothrombin INR|Missing	5	2	2	

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 ≥120 beats per minute (bpm) and increase of 15 bpm; systolic blood pressure ≤90 millimeters of mercury (mmHg) and decrease of 20 mmHg; diastolic blood pressure ≤50 mmHg and decrease of 15 mmHg, or ≥105 mmHg and increase of 15 mmHg. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety analysis set included all randomized participants who received at least 1 dose of the IMP. Here, 'overall number of participants analyzed'=participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	54	54	
Units: participants	3	0	1	

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. Missing ECG shift data are also presented. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants				
Normal / Normal	35	33	23	
Normal / Abnormal NCS	6	1	5	
Normal / Abnormal CS	0	0	0	
Abnormal NCS / Normal	4	9	4	
Abnormal NCS / Abnormal NCS	7	9	18	
Abnormal NCS / Abnormal CS	0	0	0	
Abnormal CS / Normal	0	0	0	
Abnormal CS / Abnormal NCS	0	0	0	
Abnormal CS / Abnormal CS	0	0	0	
Missing	7	3	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Received Concomitant Medications

End point title	Number of Participants Who Received Concomitant Medications

End point description:

Concomitant medications included: agents acting on renin-angiotensin system, all other therapeutic products (for example: homeopathic preparation), allergens, analgesics, anesthetics, anti-parkinson drugs, antianemic preparations, antibacterials for systemic use, antibiotics and chemotherapeutics for dermatological use, antidiarrheals, intestinal antiinflammatory/antiinfective agents, antiemetic, antiepileptics, antifungals for dermatologiocal use, antigout preparations, antihemorrhagics, antihypertensives, antiinflammatory and antirheumatic products, antipruritics, antipsoriatics, antivirals for systemic use, beta blocking agents, cardiac therapy, corticosteroids, cough and cold preparations, diagnostic radiopharmaceuticals, diuretics, thyroid therapy, urologicals, vaccines, psycoleptics, ophthalmologicals, muscle relaxants, drugs used in diabetes etc. Safety analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants	57	52	52	

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, swelling, and pruritus. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants				
Injection site induration	1	3	6	
Injection site pain	4	2	6	
Injection site erythema	2	0	2	
Injection site haemorrhage	0	0	1	
Injection site pruritus	1	0	1	
Injection site swelling	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Hypersensitivity/Anaphylaxis Reactions

End point title	Number of Participants With Hypersensitivity/Anaphylaxis Reactions

End point description:

A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants	0	0	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 analysis set included all randomized participants who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	55	55	
Units: participants	0	1	4	

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 analysis set included all randomized participants who received at least 1 dose of the IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

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

Reporting group title	Fremanezumab 675 mg/Placebo/Placebo

Reporting group description:

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

Reporting group title	Fremanezumab 900/225/225 mg

Reporting group description:

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

Serious adverse events	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 59 (8.47%)	0 / 55 (0.00%)	1 / 55 (1.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 59 (0.00%)	0 / 55 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			

subjects affected / exposed	1 / 59 (1.69%)	0 / 55 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cluster headache			
subjects affected / exposed	2 / 59 (3.39%)	0 / 55 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 59 (1.69%)	0 / 55 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 59 (1.69%)	0 / 55 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 55 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Fremanezumab 675 mg/Placebo/Placebo	Fremanezumab 900/225/225 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 59 (11.86%)	9 / 55 (16.36%)	16 / 55 (29.09%)
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	1 / 59 (1.69%)	3 / 55 (5.45%)	6 / 55 (10.91%)
occurrences (all)	1	7	10
Injection site pain			

subjects affected / exposed	4 / 59 (6.78%)	2 / 55 (3.64%)	6 / 55 (10.91%)
occurrences (all)	6	5	17
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 59 (3.39%)	0 / 55 (0.00%)	3 / 55 (5.45%)
occurrences (all)	2	0	3
Nasopharyngitis			
subjects affected / exposed	1 / 59 (1.69%)	4 / 55 (7.27%)	4 / 55 (7.27%)
occurrences (all)	1	5	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2017	The following major procedural changes (not all inclusive) were made to the protocol: - Clarification was provided based on feedback from participating investigators and regulatory agencies. - Table (Study Procedures and Assessments) was revised.

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.

Study was terminated as a result of a pre-specified futility analysis at the interim of 150 participants completing the efficacy analysis of the study.

Notes: