



Clinical trial results:

A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache Summary

EudraCT number	2016-003172-43
Trial protocol	SE GB DE ES IT NL PL FI
Global end of trial date	11 June 2019

Results information

Result version number	v1 (current)
This version publication date	08 May 2020
First version publication date	08 May 2020

Trial information

Trial identification

Sponsor protocol code	TV48125-CNS-30058
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03107052
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	02 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2019
Global end of trial reached?	Yes
Global end of trial date	11 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term safety of fremanezumab in adult participants with cluster headache (CH).

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 (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).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 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	Canada: 4
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Israel: 43
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United States: 106
Worldwide total number of subjects	275
EEA total number of subjects	122

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)	261
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 275 participants with episodic cluster headache (ECH) or chronic cluster headache (CCH) were enrolled in this study.

Pre-assignment

Screening details:

Participants were assigned to receive treatments in fremanezumab 225 milligrams (mg) monthly, fremanezumab 675/225 mg monthly, or fremanezumab 675 mg quarterly groups; based on their randomization in the pivotal studies TV48125-CNS-30056 (NCT02945046) and TV48125-CNS-30057 (NCT02964338).

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	Fremanezumab 225 mg Monthly

Arm description:

Participants with ECH or CCH who received fremanezumab at 900 mg intravenous (IV) infusion at Week 0 and fremanezumab at 225 mg subcutaneous (SC) injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056 or TV48125-CNS-30057, and participants with CCH who received fremanezumab at 675 mg SC injection at Week 0 and fremanezumab at 225 mg SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab at 225 mg SC injection monthly (approximately every 4 weeks, administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 milliliter {mL}] at Week 0 and 36; and 2 placebo SC injections at Weeks 0, 12, 24, and 36 for blinding in participants rolled over from Study TV48125-CNS-30056; fremanezumab at 225 mg as a single SC injection [225 mg/1.5 mL] at Week 0, 12, 24, and 36; 2 SC injections of placebo at Week 0 for blinding in participants rolled over from Study TV48125-CNS-30057) through Week 36 in this study.

Arm type	Experimental
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.

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.

Arm title	Fremanezumab 675/225 mg Monthly
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Arm description:

Participants with CCH who received placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab 675 mg SC injection as loading dose (administered as 3 SC injections of fremanezumab

at 225 mg [225 mg/1.5 mL] at Week 0) followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg SC injection (administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 12, 24, and 36) through Week 36.

Arm type	Experimental
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 675 mg Quarterly
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Arm description:

Participants with ECH who received fremanezumab at 675 mg SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study; or placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056; received fremanezumab at 675 mg SC injection quarterly (approximately every 12 weeks, administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 0 and 36; and single placebo SC injection at Weeks 4, 8, 16, 20, 28, and 32 for blinding) through Week 36.

Arm type	Experimental
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.

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.

Number of subjects in period 1	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly
Started	145	60	70
Completed	26	14	29
Not completed	119	46	41
Consent withdrawn by subject	9	5	8
Adverse event, non-fatal	6	1	2
Other than specified	4	2	-
Lost to follow-up	4	-	1
Study terminated due to futility	67	31	23
Protocol deviation	6	-	3
Lack of efficacy	23	7	4

Baseline characteristics

Reporting groups

Reporting group title	Fremanezumab 225 mg Monthly
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Reporting group description:

Participants with ECH or CCH who received fremanezumab at 900 mg intravenous (IV) infusion at Week 0 and fremanezumab at 225 mg subcutaneous (SC) injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056 or TV48125-CNS-30057, and participants with CCH who received fremanezumab at 675 mg SC injection at Week 0 and fremanezumab at 225 mg SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab at 225 mg SC injection monthly (approximately every 4 weeks, administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 milliliter {mL}] at Week 0 and 36; and 2 placebo SC injections at Weeks 0, 12, 24, and 36 for blinding in participants rolled over from Study TV48125-CNS-30056; fremanezumab at 225 mg as a single SC injection [225 mg/1.5 mL] at Week 0, 12, 24, and 36; 2 SC injections of placebo at Week 0 for blinding in participants rolled over from Study TV48125-CNS-30057) through Week 36 in this study.

Reporting group title	Fremanezumab 675/225 mg Monthly
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Reporting group description:

Participants with CCH who received placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab 675 mg SC injection as loading dose (administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Week 0) followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg SC injection (administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 12, 24, and 36) through Week 36.

Reporting group title	Fremanezumab 675 mg Quarterly
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Reporting group description:

Participants with ECH who received fremanezumab at 675 mg SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study; or placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056; received fremanezumab at 675 mg SC injection quarterly (approximately every 12 weeks, administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 0 and 36; and single placebo SC injection at Weeks 4, 8, 16, 20, 28, and 32 for blinding) through Week 36.

Reporting group values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly
Number of subjects	145	60	70
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	45.2	46.1	43.2
standard deviation	± 12.25	± 11.14	± 11.40
Sex: Female, Male			
Units: participants			
Female	51	20	25
Male	94	40	45
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	3	2
White	136	56	68

More than one race	0	0	0
Unknown or Not Reported	0	1	0

Reporting group values	Total		
Number of subjects	275		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
Sex: Female, Male Units: participants			
Female	96		
Male	179		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	14		
White	260		
More than one race	0		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	Fremanezumab 225 mg Monthly
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Reporting group description:

Participants with ECH or CCH who received fremanezumab at 900 mg intravenous (IV) infusion at Week 0 and fremanezumab at 225 mg subcutaneous (SC) injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056 or TV48125-CNS-30057, and participants with CCH who received fremanezumab at 675 mg SC injection at Week 0 and fremanezumab at 225 mg SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab at 225 mg SC injection monthly (approximately every 4 weeks, administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 milliliter {mL}] at Week 0 and 36; and 2 placebo SC injections at Weeks 0, 12, 24, and 36 for blinding in participants rolled over from Study TV48125-CNS-30056; fremanezumab at 225 mg as a single SC injection [225 mg/1.5 mL] at Week 0, 12, 24, and 36; 2 SC injections of placebo at Week 0 for blinding in participants rolled over from Study TV48125-CNS-30057) through Week 36 in this study.

Reporting group title	Fremanezumab 675/225 mg Monthly
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Reporting group description:

Participants with CCH who received placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab 675 mg SC injection as loading dose (administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Week 0) followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg SC injection (administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 12, 24, and 36) through Week 36.

Reporting group title	Fremanezumab 675 mg Quarterly
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Reporting group description:

Participants with ECH who received fremanezumab at 675 mg SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study; or placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056; received fremanezumab at 675 mg SC injection quarterly (approximately every 12 weeks, administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 0 and 36; and single placebo SC injection at Weeks 4, 8, 16, 20, 28, and 32 for blinding) through Week 36.

Subject analysis set title	Fremanezumab 675 mg Quarterly
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants with ECH who received fremanezumab at 675 mg SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study; or placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056; received fremanezumab at 675 mg SC injection quarterly (approximately every 12 weeks, administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 0 and 36; and single placebo SC injection at Weeks 4, 8, 16, 20, 28, and 32 for blinding) through Week 36.

Primary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs) ^{[1][2]}
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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. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Baseline up to follow-up (Week 68)

Notes:

[1] - 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: Safety analyses were descriptive in nature.

[2] - 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: The endpoint is reporting statistics for specified arms only.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	144	60	71	
Units: participants				
Any AEs	87	31	42	
Treatment-related AEs	26	6	10	
Serious AEs	8	2	1	
AEs leading to discontinuation	6	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Potentially Clinically Significant Abnormal Laboratory Results: Serum Chemistry

End point title	Number of Participants with Potentially Clinically Significant Abnormal Laboratory Results: Serum Chemistry ^[3]
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End point description:

Serum chemistry tests with potentially clinically significant abnormal findings included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH) each $\geq 3 \times$ upper limit of normal (ULN); Blood urea nitrogen (BUN) ≥ 10.71 millimole (mmol)/L; Bilirubin (Total) ≥ 34.2 micromole/liter (umol/L); and Creatinine ≥ 177 umol/L. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' signifies participants with a laboratory result.

End point type	Primary
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End point timeframe:

Baseline up to end of treatment (Week 40)

Notes:

[3] - 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: Safety analyses were descriptive in nature.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	55	67	
Units: participants	2	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Potentially Clinically Significant Abnormal Laboratory Results: Hematology

End point title	Number of Participants with Potentially Clinically Significant Abnormal Laboratory Results: Hematology ^[4]
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End point description:

Hematology tests with potentially clinically significant abnormal findings included: hemoglobin less than or equal to (\leq) 115 grams (g)/L (males) or ≤ 95 g/L (females), leukocytes count $\geq 20 \times 10^9/L$ or $\leq 3 \times 10^9/L$, eosinophils $\geq 10\%$, hematocrit < 0.37 L/L (males) and < 0.32 L/L (females), platelets count $\geq 700 \times 10^9/L$ or $\leq 75 \times 10^9/L$, absolute neutrophil count (ANC) $\leq 1 \times 10^9/L$. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' signifies participants with a laboratory result.

End point type	Primary
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End point timeframe:

Baseline up to end of treatment (Week 40)

Notes:

[4] - 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: Safety analyses were descriptive in nature.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	55	67	
Units: participants	6	3	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Potentially Clinically Significant Abnormal Laboratory Results: Urinalysis

End point title	Number of Participants with Potentially Clinically Significant Abnormal Laboratory Results: Urinalysis ^[5]
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End point description:

Urinalysis laboratory tests with potentially clinically significant abnormal findings included: haemoglobin, urine glucose, ketones, urine 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. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' signifies participants with a laboratory result.

End point type	Primary
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End point timeframe:

Baseline up to end of treatment (Week 40)

Notes:

[5] - 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: Safety analyses were descriptive in nature.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	55	67	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Shift From Baseline to Endpoint (Last Assessment) in Coagulation Laboratory Test Results

End point title	Number of Participants With Shift From Baseline to Endpoint (Last Assessment) in Coagulation Laboratory Test Results ^[6] ^[7]
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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. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Baseline up to end of treatment (Week 40)

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: Safety analyses were descriptive in nature.

[7] - 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: The endpoint is reporting statistics for specified arms only.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	144	60	71	
Units: participants				
Prothrombin INR Low-Low	0	0	0	
PT Low-Low	0	0	0	
Prothrombin INR Low-Normal	0	0	0	
PT Low-Normal	0	0	0	
Prothrombin INR Low-High	0	0	0	
PT Low-High	0	0	0	
Prothrombin INR Normal-Low	1	0	0	
PT Normal-Low	1	0	0	
Prothrombin INR Normal-Normal	103	42	61	
PT Normal-Normal	99	39	59	
Prothrombin INR Normal-High	6	4	1	
PT Normal-High	6	5	1	
Prothrombin INR High-Low	0	0	0	

PT High-Low	0	0	0	
Prothrombin INR High-Normal	7	4	3	
PT High-Normal	11	4	5	
Prothrombin INR High-High	4	2	0	
PT High-High	4	4	0	
Prothrombin INR Missing	23	8	6	
PT Missing	23	8	6	

Statistical analyses

No statistical analyses for this end point

Primary: 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 ^[8]
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End point description:

Potentially clinically significant abnormal vital signs findings included: Pulse rate ≥ 120 beats per minute (bpm) and increase from baseline of ≥ 15 bpm, or ≤ 50 bpm and decrease from baseline of ≥ 15 bpm; Systolic blood pressure ≤ 90 millimeters of mercury (mmHg) and decrease from baseline of ≥ 20 mmHg, or ≥ 180 mmHg and increase from baseline of ≥ 20 mmHg; Diastolic blood pressure ≤ 50 mmHg and decrease from baseline of ≥ 15 mmHg, or ≥ 105 mmHg and increase from baseline of ≥ 15 mmHg; Temperature > 38.3 degrees celsius ($^{\circ}\text{C}$). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug. Here, 'Overall number of participants analyzed' signifies participants with a vital sign result.

End point type	Primary
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End point timeframe:

Baseline up to follow-up (Week 68)

Notes:

[8] - 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: Safety analyses were descriptive in nature.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	57	68	
Units: participants	6	4	2	

Statistical analyses

No statistical analyses for this end point

Primary: 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 ^{[9][10]}
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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. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Baseline up to follow-up (Week 68)

Notes:

[9] - 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: Safety analyses were descriptive in nature.

[10] - 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: The endpoint is reporting statistics for specified arms only.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	144	60	71	
Units: participants				
Normal / Normal	76	30	46	
Normal / Abnormal NCS	16	6	4	
Normal / Abnormal CS	1	0	0	
Abnormal NCS / Normal	15	7	4	
Abnormal NCS / Abnormal NCS	23	12	12	
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	13	5	5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Physical Examination Findings

End point title	Number of Participants With Abnormal Physical Examination Findings ^[11]
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End point description:

A complete physical examination included the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Baseline refers to the baseline values from the pivotal studies. ITT analysis set included all participants who were enrolled in this study for long-term safety evaluation, regardless if they received study treatment or not.

End point type	Primary
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End point timeframe:

Baseline up to follow-up (Week 68)

Notes:

[11] - 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: Safety analyses were descriptive in nature.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	60	70	
Units: participants	22	8	7	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Injection Site Reactions

End point title	Number of Participants With Injection Site Reactions ^{[12][13]}
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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, rash, warmth, and pruritus. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Baseline up to Week 36

Notes:

[12] - 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: Safety analyses were descriptive in nature.

[13] - 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: The endpoint is reporting statistics for specified arms only.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	144	60	71	
Units: participants				
Injection site induration	13	4	5	
Injection site pain	6	1	3	
Injection site erythema	7	1	1	
Injection site haemorrhage	2	0	0	
Injection site pruritus	2	0	0	
Injection site bruising	0	1	0	
Injection site rash	0	0	1	
Injection site warmth	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Hypersensitivity/Anaphylaxis Reactions

End point title	Number of Participants With Hypersensitivity/Anaphylaxis Reactions ^{[14][15]}
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End point description:

A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Baseline refers to the baseline values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Baseline up to Week 36

Notes:

[14] - 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: Safety analyses were descriptive in nature.

[15] - 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: The endpoint is reporting statistics for specified arms only.

End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	144	60	71	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Received Concomitant Medications

End point title	Number of Participants Who Received Concomitant
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End point description:

Concomitant medications included: agents acting on the renin-angiotensin system, all other therapeutic products (homeopathic), analgesics, anesthetics, anti-parkinson drugs, antibacterials, antibiotics and chemotherapeutics for dermatological use, antidiarrheals, intestinal antiinflammatory/antiinfective agents, antiemetic, antiepileptics, antifungals for dermatological use, antihemorrhagics, antihistamines for systemic use, antihypertensives, antiinflammatory and antirheumatic products, antimycotics for systemic use, antipruritics, antipsoriatics, antivirals for systemic use, blood substitutes and perfusion solutions, cardiac therapy, corticosteroids, cough and cold preparations, diagnostic radiopharmaceuticals, diuretics, thyroid therapy, urologicals, vaccines, psycholeptics, psychoanaleptics, muscle relaxants, drugs used in diabetes. Baseline refers to values from the pivotal studies. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Primary			
End point timeframe:				
Baseline up to follow-up (Week 68)				
Notes:				
[16] - 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: Safety analyses were descriptive in nature.				
[17] - 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: The endpoint is reporting statistics for specified arms only.				
End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	144	60	71	
Units: participants	140	56	68	

Statistical analyses

No statistical analyses for this end point

Primary: 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) ^[18]			
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. Baseline refers to the baseline values from the pivotal studies. ITT analysis set included all participants who were enrolled in this study for long-term safety evaluation, regardless if they received study treatment or not.				
End point type	Primary			
End point timeframe:				
Baseline up to follow-up (Week 68)				
Notes:				
[18] - 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: Safety analyses were descriptive in nature.				
End point values	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	60	70	
Units: participants	7	1	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 68

Adverse event reporting additional description:

Safety population included all participants who received at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Fremanezumab 225 mg Monthly
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Reporting group description:

Participants with ECH or CCH who received fremanezumab at 900 mg IV infusion at Week 0 and fremanezumab at 225 mg SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056 or TV48125-CNS-30057, and participants with CCH who received fremanezumab at 675 mg SC injection at Week 0 and fremanezumab at 225 mg SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab at 225 mg SC injection monthly (approximately every 4 weeks, administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 mL] at Week 0 and 36; and 2 placebo SC injections at Weeks 0, 12, 24, and 36 for blinding in participants rolled over from Study TV48125-CNS-30056; fremanezumab at 225 mg as a single SC injection [225 mg/1.5 mL] at Week 0, 12, 24, and 36; 2 SC injections of placebo at Week 0 for blinding in participants rolled over from Study TV48125-CNS-30057) through Week 36 in this study.

Reporting group title	Fremanezumab 675/225 mg Monthly
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Reporting group description:

Participants with CCH who received placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30057; received fremanezumab 675 mg SC injection as loading dose (administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Week 0) followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg SC injection (administered as single SC injection of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 12, 24, and 36) through Week 36.

Reporting group title	Fremanezumab 675 mg Quarterly
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Reporting group description:

Participants with ECH who received fremanezumab at 675 mg SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study; or placebo IV infusion and SC injection at Week 0 and placebo SC injection at Weeks 4 and 8, respectively in the pivotal study TV48125-CNS-30056; received fremanezumab at 675 mg SC injection quarterly (approximately every 12 weeks, administered as 3 SC injections of fremanezumab at 225 mg [225 mg/1.5 mL] at Weeks 0 and 36; and single placebo SC injection at Weeks 4, 8, 16, 20, 28, and 32 for blinding) through Week 36.

Serious adverse events	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 144 (5.56%)	2 / 60 (3.33%)	1 / 71 (1.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Intentional overdose			

subjects affected / exposed	1 / 144 (0.69%)	0 / 60 (0.00%)	0 / 71 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 144 (0.69%)	0 / 60 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 144 (0.69%)	0 / 60 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 144 (0.69%)	0 / 60 (0.00%)	0 / 71 (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			
Carotid artery stenosis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 60 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cluster headache			
subjects affected / exposed	3 / 144 (2.08%)	0 / 60 (0.00%)	0 / 71 (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
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 144 (0.00%)	0 / 60 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 144 (0.69%)	0 / 60 (0.00%)	0 / 71 (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
Cholelithiasis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 60 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 144 (0.00%)	1 / 60 (1.67%)	0 / 71 (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			
Rotator cuff syndrome			
subjects affected / exposed	0 / 144 (0.00%)	1 / 60 (1.67%)	0 / 71 (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			
Influenza			
subjects affected / exposed	0 / 144 (0.00%)	1 / 60 (1.67%)	0 / 71 (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	Fremanezumab 225 mg Monthly	Fremanezumab 675/225 mg Monthly	Fremanezumab 675 mg Quarterly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 144 (21.53%)	11 / 60 (18.33%)	14 / 71 (19.72%)
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	13 / 144 (9.03%)	4 / 60 (6.67%)	5 / 71 (7.04%)
occurrences (all)	44	13	10
Oedema peripheral			

subjects affected / exposed occurrences (all)	0 / 144 (0.00%) 0	3 / 60 (5.00%) 3	0 / 71 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	2 / 144 (1.39%) 3	3 / 60 (5.00%) 4	0 / 71 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	16 / 144 (11.11%) 18 4 / 144 (2.78%) 4	5 / 60 (8.33%) 8 3 / 60 (5.00%) 4	7 / 71 (9.86%) 8 2 / 71 (2.82%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2018	The following major procedural changes (not all-inclusive) were made to the protocol: <ul style="list-style-type: none">- Provided clarification on concomitant preventive medications allowed in the treatment arm of this long-term safety study.- Extended the duration of the study by 6 months because the study recruitment rate into Studies TV48125-CNS-30056 and TV48125-CNS-30057 was lower than initially expected.- Clarified that pharmacogenomics samples were taken only during the pivotal studies and were not collected in Study TV48125-CNS-30058.
28 August 2018	The following major procedural changes (not all-inclusive) were made to the protocol: <ul style="list-style-type: none">- Described the way in which participants who participated in the double-blind study for CCH (Study TV48125-CNS-30057) would continue to participate only in the ADA and safety arm of the long-term safety study (Study TV48125-CNS-30058), since the CCH study was terminated.- Updated standardized text.

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.

The study was terminated after the ECH study (TV48125-CNS-30056) was terminated due to a pre specified futility analyses.

Notes: