# 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 |

### 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 |

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 |

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 |

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 |
|---|---|

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 |
|---|---|

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<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 45.2 | 46.1 | 43.2 |
| standard deviation | ± 12.25 | ± 11.14 | ± 11.40 |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 51 | 20 | 25 |
| Male | 94 | 40 | 45 |
| Race (NIH/OMB)<br>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<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 96 | | |
| Male | 179 | | |
| Race (NIH/OMB)<br>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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|
| Subject analysis set type | Safety analysis |

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 ≥3*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 |
|---|---|

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] |
|---|---|

End point description:

Hematology tests with potentially clinically significant abnormal findings included: hemoglobin less than or equal to (≤)115 grams (g)/L (males) or ≤95 g/L (females), leukocytes count ≥20*10^9/L or ≤3*10^9/L, eosinophils ≥10%, hematocrit <0.37 L/L (males) and <0.32 L/L (females), platelets count ≥700*10^9/L or ≤75*10^9/L, absolute neutrophil count (ANC) ≤1*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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 (°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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 dermatologiocal 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, psycoleptics, psycoanaleptics, 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Fremanezumab 225 mg Monthly |

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 |

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 |

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 | 0 / 144 (0.00%) | 3 / 60 (5.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 144 (1.39%) | 3 / 60 (5.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 16 / 144 (11.11%) | 5 / 60 (8.33%) | 7 / 71 (9.86%) |
| occurrences (all) | 18 | 8 | 8 |
| Sinusitis | | | |
| subjects affected / exposed | 4 / 144 (2.78%) | 3 / 60 (5.00%) | 2 / 71 (2.82%) |
| occurrences (all) | 4 | 4 | 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:<br>- Provided clarification on concomitant preventive medications allowed in the treatment arm of this long-term safety study.<br>- 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.<br>- 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:<br>- 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.<br>- 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: