



## Clinical trial results:

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

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

#### **Results information**

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

#### **Trial information**

##### **Trial identification**

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | TV48125-CNS-30057 |
|-----------------------|-------------------|

##### **Additional study identifiers**

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

Notes:

##### **Sponsors**

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

Notes:

##### **Paediatric regulatory details**

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

Notes:

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## Results analysis stage

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

Notes:

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## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

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## Population of trial subjects

### Subjects enrolled per country

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

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 245 |
| From 65 to 84 years                       | 14  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

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

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

Dosage and administration details:

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

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Fremanezumab 675/225/225 mg |
|------------------|-----------------------------|

Arm description:

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

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

Dosage and administration details:

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

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Fremanezumab 900/225/225 mg |
|------------------|-----------------------------|

Arm description:

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

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

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

Dosage and administration details:

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

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

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Fremanezumab 675/225/225 mg |
|-----------------------|-----------------------------|

Reporting group description:

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

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Fremanezumab 900/225/225 mg |
|-----------------------|-----------------------------|

Reporting group description:

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

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

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

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

## End points

### End points reporting groups

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

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

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

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

## Statistical analyses



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

Notes:

[1] - Threshold for significance at 0.05 level.

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

Notes:

[2] - Threshold for significance at 0.05 level.

### **Secondary: Percentage of Participants With a $\geq 50\%$ Reduction from Baseline in the Monthly Average Number of CH Attacks Up to Week 12**

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

## Statistical analyses

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

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

## End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

## End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 1, 4, 8, and 12

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events (AEs)

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

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the Investigator on a scale of mild, moderate and severe, with severe as an AE that prevents usual activities. Relationship of AE to treatment was determined by the Investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent the previously listed serious outcomes. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

|                        |           |
|------------------------|-----------|
| End point type         | Secondary |
| End point timeframe:   |           |
| Baseline up to Week 12 |           |

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                        |           |
|------------------------|-----------|
| End point type         | Secondary |
| End point timeframe:   |           |
| Baseline up to Week 12 |           |

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Coagulation parameters included: prothrombin time (PT) (seconds), prothrombin international normalized ratio (INR), activated partial thromboplastin time (aPTT) (seconds). Shifts represented as Baseline - endpoint value (last observed post-baseline value). Shifts from baseline to endpoint were summarized using participant counts grouped into three categories: - Low (below normal range) - Normal (within the normal range of 9.4 to 12.5 seconds) - High (above normal range). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Week 12

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

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

## Statistical analyses

No statistical analyses for this end point

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

|   |  |
|---|--|
| End point title   | Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values |
| End point description:<br>Potentially clinically significant abnormal vital signs findings included: pulse rate $\leq 50$ beats/minute (bpm) and decrease of $\geq 15$ bpm, or $\geq 120$ bpm and increase of $\geq 15$ bpm; systolic blood pressure $\leq 90$ millimeters of mercury (mmHg) and decrease of $\geq 20$ mmHg, or $\geq 180$ mmHg and increase of $\geq 20$ mmHg; diastolic blood pressure $\leq 50$ mmHg and decrease of $\geq 15$ mmHg, or $\geq 105$ mmHg and increase of $\geq 15$ mmHg; respiratory rate $< 10$ breaths/minute; and body temperature $\geq 38.3$ degrees centigrade and change of $\geq 1.1$ degrees centigrade. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline up to Week 12  |  |

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

## Statistical analyses

No statistical analyses for this end point

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

|   |   |
|---|---|
| End point title   | Number of Participants With Shift From Baseline to Endpoint (Last Assessment) in Electrocardiogram (ECG) Parameters |
| End point description:<br>ECG parameters included: heart rate, PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - endpoint value (last observed post-baseline value). Abnormal NCS indicated an abnormal but not clinically significant finding. Abnormal CS indicated an abnormal and clinically significant finding. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all randomized participants who received at least 1 dose of study drug. |   |
| End point type  | Secondary   |



End point timeframe:

Baseline to Week 12

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Injection Site Reactions

|                 |  |
|-----------------|--|
| End point title | Number of Participants with Injection Site Reactions |
|-----------------|--|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Week 12

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Week 12

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 12

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Fremanezumab 900/225/225 mg |
|-----------------------|-----------------------------|

Reporting group description:

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

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Fremanezumab 675/225/225 mg |
|-----------------------|-----------------------------|

Reporting group description:

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

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

Notes: