

**Clinical trial results:****A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study With an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients With Inadequate Response to Prior Preventive Treatments**  
**Summary**

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2017-002441-30                |
| Trial protocol           | DK GB SE BE DE CZ FI NL ES IT |
| Global end of trial date | 29 May 2019                   |

**Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v2 (current)    |
| This version publication date  | 19 March 2020   |
| First version publication date | 19 October 2019 |
| Version creation reason        |                 |

**Trial information****Trial identification**

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | TV48125-CNS-30068 |
|-----------------------|-------------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03308968 |
| 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 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                       | 26 June 2019    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 02 October 2018 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 29 May 2019     |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous injections to adult participants with migraine with documented inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (for example; Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of 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                          | 10 November 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 | Belgium: 50         |
| Country: Number of subjects enrolled | Switzerland: 2      |
| Country: Number of subjects enrolled | Czech Republic: 188 |
| Country: Number of subjects enrolled | Germany: 74         |
| Country: Number of subjects enrolled | Denmark: 34         |
| Country: Number of subjects enrolled | Spain: 78           |
| Country: Number of subjects enrolled | Finland: 85         |
| Country: Number of subjects enrolled | France: 35          |
| Country: Number of subjects enrolled | United Kingdom: 36  |
| Country: Number of subjects enrolled | Italy: 10           |
| Country: Number of subjects enrolled | Netherlands: 23     |
| Country: Number of subjects enrolled | Poland: 66          |
| Country: Number of subjects enrolled | Sweden: 37          |
| Country: Number of subjects enrolled | United States: 120  |
| Worldwide total number of subjects   | 838                 |
| EEA total number of subjects         | 716                 |

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)                      | 807 |
| From 65 to 84 years                       | 31  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 838 participants were randomized in a 1:1:1 ratio to placebo, fremanezumab quarterly, or fremanezumab monthly treatment groups.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Double-Blind Period (12 Weeks)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Investigator, Subject, Carer, Assessor |

### Arms

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

Arm description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

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

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Fremanezumab Quarterly |
|------------------|------------------------|

Arm description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

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

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

Dosage and administration details:

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

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Fremanezumab Monthly |
|------------------|----------------------|

Arm description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

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

Dosage and administration details:

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

| <b>Number of subjects in period 1</b> | Placebo | Fremanezumab Quarterly | Fremanezumab Monthly |
|---------------------------------------|---------|------------------------|----------------------|
| Started                               | 279     | 276                    | 283                  |
| DB Modified ITT (mITT) analysis set   | 278     | 276                    | 283                  |
| Completed                             | 264     | 271                    | 272                  |
| Not completed                         | 15      | 5                      | 11                   |
| Consent withdrawn by subject          | 2       | 2                      | 3                    |
| Non-compliance to study procedures    | 1       | 1                      | -                    |
| Adverse event, non-fatal              | 3       | 1                      | 4                    |
| Other than specified                  | 1       | -                      | 2                    |
| Lost to follow-up                     | 1       | -                      | -                    |
| Protocol deviation                    | 6       | -                      | 2                    |
| Lack of efficacy                      | 1       | 1                      | -                    |

|  |  |
|--|--|
| <b>Period 2</b>  |  |
| Period 2 title   | Open-Label Period (12 Weeks)                 |
| Is this the baseline period?   | No   |
| Allocation method  | Not applicable                               |
| Blinding used  | Not blinded                                  |
| <b>Arms</b>  |  |
| Are arms mutually exclusive?   | Yes  |
| <b>Arm title</b>   | Placebo                                      |
| Arm description:   |  |
| Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.  |  |
| Arm type   | Placebo                                      |
| Investigational medicinal product name   | Fremanezumab                                 |
| Investigational medicinal product code   | TEV-48125                                    |
| Other name   |  |
| Pharmaceutical forms   | Solution for injection in pre-filled syringe |
| Routes of administration   | Subcutaneous use                             |
| Dosage and administration details:   |  |
| Fremanezumab was administered per dose and schedule specified in the arm.  |  |
| <b>Arm title</b>   | Fremanezumab Quarterly                       |
| Arm description:   |  |
| DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.  |  |
| Arm type   | Experimental                                 |
| Investigational medicinal product name   | Fremanezumab                                 |
| Investigational medicinal product code   | TEV-48125                                    |
| Other name   |  |
| Pharmaceutical forms   | Solution for injection in pre-filled syringe |
| Routes of administration   | Subcutaneous use                             |
| Dosage and administration details:   |  |
| Fremanezumab was administered per dose and schedule specified in the arm.  |  |
| <b>Arm title</b>   | Fremanezumab Monthly                         |
| Arm description:   |  |
| DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140. |  |
| Arm type   | Experimental                                 |

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

Dosage and administration details:

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

| <b>Number of subjects in period 2</b> | Placebo | Fremanezumab<br>Quarterly | Fremanezumab<br>Monthly |
|---------------------------------------|---------|---------------------------|-------------------------|
| Started                               | 264     | 271                       | 272                     |
| OL mITT analysis set                  | 263     | 271                       | 272                     |
| Completed                             | 253     | 259                       | 260                     |
| Not completed                         | 11      | 12                        | 12                      |
| Consent withdrawn by subject          | 5       | 5                         | 7                       |
| Non-compliance to study procedures    | -       | -                         | 1                       |
| Adverse event, non-fatal              | 4       | 1                         | 1                       |
| Other than specified                  | 1       | 2                         | 1                       |
| Lost to follow-up                     | -       | 1                         | 1                       |
| Lack of efficacy                      | 1       | 2                         | -                       |
| Protocol deviation                    | -       | 1                         | 1                       |

## Baseline characteristics

### Reporting groups

|  |                        |
|--|------------------------|
| Reporting group title  | Placebo                |
| Reporting group description:   |                        |
| Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.  |                        |
| Reporting group title  | Fremanezumab Quarterly |
| Reporting group description:   |                        |
| DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.  |                        |
| Reporting group title  | Fremanezumab Monthly   |
| Reporting group description:   |                        |
| DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140. |                        |

| Reporting group values | Placebo | Fremanezumab Quarterly | Fremanezumab Monthly |
|------------------------|---------|------------------------|----------------------|
| Number of subjects     | 279     | 276                    | 283                  |
| Age categorical        |         |                        |                      |
| Units: Subjects        |         |                        |                      |

|   |         |         |         |
|---|---------|---------|---------|
| Age Continuous                            |         |         |         |
| Units: years                              |         |         |         |
| arithmetic mean                           | 46.8    | 45.8    | 45.9    |
| standard deviation                        | ± 11.10 | ± 10.97 | ± 11.05 |
| Sex: Female, Male                         |         |         |         |
| Units: Subjects                           |         |         |         |
| Female                                    | 233     | 229     | 238     |
| Male                                      | 46      | 47      | 45      |
| Ethnicity (NIH/OMB)                       |         |         |         |
| Units: Subjects                           |         |         |         |
| Hispanic or Latino                        | 11      | 6       | 7       |
| Not Hispanic or Latino                    | 255     | 260     | 264     |
| Unknown or Not Reported                   | 13      | 10      | 12      |
| Race/Ethnicity, Customized                |         |         |         |
| Units: Subjects                           |         |         |         |
| American Indian or Alaska Native          | 0       | 0       | 1       |
| Asian                                     | 1       | 0       | 3       |
| Native Hawaiian or Other Pacific Islander | 0       | 0       | 0       |
| Black or African American                 | 2       | 2       | 4       |
| White                                     | 262     | 262     | 262     |



|                         |    |    |    |
|-------------------------|----|----|----|
| Other                   | 1  | 2  | 1  |
| Unknown or Not Reported | 13 | 10 | 12 |

|   |  |  |  |
|---|--|--|--|
| Number of Migraine Days During the 28 Day Baseline Period |  |  |  |
|---|--|--|--|

A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine; a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications. 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.

|                    |        |        |        |
|--------------------|--------|--------|--------|
| Units: days        |        |        |        |
| arithmetic mean    | 14.3   | 14.1   | 14.1   |
| standard deviation | ± 6.12 | ± 5.61 | ± 5.58 |

|   |  |  |  |
|---|--|--|--|
| Number of Headache Days of at Least Moderate Severity During the 28 Day Baseline Period |  |  |  |
|---|--|--|--|

Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of at least moderate severity was defined as a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific acute medications (triptans and ergot compounds). 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.

|                    |        |        |        |
|--------------------|--------|--------|--------|
| Units: days        |        |        |        |
| arithmetic mean    | 12.8   | 12.4   | 12.7   |
| standard deviation | ± 5.92 | ± 5.84 | ± 5.82 |

|                               |       |  |  |
|-------------------------------|-------|--|--|
| <b>Reporting group values</b> | Total |  |  |
| Number of subjects            | 838   |  |  |
| Age categorical               |       |  |  |
| Units: Subjects               |       |  |  |

|   |     |  |  |
|---|-----|--|--|
| Age Continuous                            |     |  |  |
| Units: years                              |     |  |  |
| arithmetic mean                           |     |  |  |
| standard deviation                        | -   |  |  |
| Sex: Female, Male                         |     |  |  |
| Units: Subjects                           |     |  |  |
| Female                                    | 700 |  |  |
| Male                                      | 138 |  |  |
| Ethnicity (NIH/OMB)                       |     |  |  |
| Units: Subjects                           |     |  |  |
| Hispanic or Latino                        | 24  |  |  |
| Not Hispanic or Latino                    | 779 |  |  |
| Unknown or Not Reported                   | 35  |  |  |
| Race/Ethnicity, Customized                |     |  |  |
| Units: Subjects                           |     |  |  |
| American Indian or Alaska Native          | 1   |  |  |
| Asian                                     | 4   |  |  |
| Native Hawaiian or Other Pacific Islander | 0   |  |  |
| Black or African American                 | 8   |  |  |
| White                                     | 786 |  |  |
| Other                                     | 4   |  |  |
| Unknown or Not Reported                   | 35  |  |  |

|   |   |  |  |
|---|---|--|--|
| Number of Migraine Days During the 28 Day Baseline Period   |   |  |  |
| A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine; a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications. 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively. |   |  |  |
| Units: days<br>arithmetic mean<br>standard deviation  | - |  |  |
| Number of Headache Days of at Least Moderate Severity During the 28 Day Baseline Period   |   |  |  |
| Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of at least moderate severity was defined as a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific acute medications (triptans and ergot compounds). 'Number of participants analyzed' for this measure were 279, 275, and 283 for Placebo, Fremanezumab Quarterly, and Fremanezumab Monthly arms respectively.                        |   |  |  |
| Units: days<br>arithmetic mean<br>standard deviation  | - |  |  |

## End points

### End points reporting groups

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

Reporting group description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Fremanezumab Quarterly |
|-----------------------|------------------------|

Reporting group description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Fremanezumab Monthly |
|-----------------------|----------------------|

Reporting group description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

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

Reporting group description:

Double-blind (DB) period: Participants with chronic migraine (CM) or episodic migraine (EM) received 3 injections of placebo 1.5 milliliters (mL) subcutaneously (SC) on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. Open-label (OL) period: Participants with CM or EM received fremanezumab (TEV-48125) 225 milligrams (mg) SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Fremanezumab Quarterly |
|-----------------------|------------------------|

Reporting group description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Fremanezumab Monthly |
|-----------------------|----------------------|

Reporting group description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                            |         |
|----------------------------|---------|
| Subject analysis set title | Placebo |
|----------------------------|---------|

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

Subject analysis set description:

DB period: Participants with CM or EM received 3 injections of placebo 1.5 mL SC on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56.

|                            |                        |
|----------------------------|------------------------|
| Subject analysis set title | Fremanezumab Quarterly |
|----------------------------|------------------------|

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

Subject analysis set description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2

months (on Days 28 and 56).

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Fremanezumab Monthly |
| Subject analysis set type  | Safety analysis      |

Subject analysis set description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56).

### **Primary: DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab**

|                 |   |
|-----------------|---|
| End point title | DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab |
|-----------------|---|

End point description:

A migraine day was defined as when at least 1 of the following occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion was missing; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)\*28. Change was calculated as post-baseline value – baseline value. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on primary endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day -28 to Day -1), up to Week 12

| End point values                    | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-------------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                  | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed         | 278             | 276                    | 283                  |  |
| Units: days/month                   |                 |                        |                      |  |
| least squares mean (standard error) | -0.6 (± 0.34)   | -3.7 (± 0.34)          | -4.1 (± 0.34)        |  |

### **Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Analysis was performed using analysis of covariance (ANCOVA) method with treatment, sex, region, special group of treatment failure (yes or no), migraine classification (that is; CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The stratification factors (as randomized) were used in the model.

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Placebo v Fremanezumab Quarterly |
|-------------------|----------------------------------|

|   |                                   |
|---|-----------------------------------|
| Number of subjects included in analysis | 554                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | other                             |
| P-value                                 | < 0.0001                          |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | Least square (LS) mean difference |
| Point estimate                          | -3.1                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -3.84                             |
| upper limit                             | -2.42                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.36                              |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was performed using ANCOVA method with treatment, sex, region, special group of treatment failure (yes or no), migraine classification (that is; CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The stratification factors (as randomized) were used in the model.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Placebo v Fremanezumab Monthly |
| Number of subjects included in analysis | 561                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | < 0.0001                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -3.5                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -4.19                          |
| upper limit                             | -2.78                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.36                           |

**Secondary: DB Period: Percentage of Participants Reaching at Least 50 Percent (%) Reduction From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab**

|                 |  |
|-----------------|--|
| End point title | DB Period: Percentage of Participants Reaching at Least 50 Percent (%) Reduction From Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab |
|-----------------|--|

End point description:

A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion was missing; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was

treated with migraine-specific medications (triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)\*28. DB mITT analysis set included participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on the primary endpoint.

|  |           |
|--|-----------|
| End point type                             | Secondary |
| End point timeframe:                       |           |
| Baseline (Day -28 to Day-1), up to Week 12 |           |

| End point values                  | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed       | 278             | 276                    | 283                  |  |
| Units: percentage of participants |                 |                        |                      |  |
| number (not applicable)           | 9               | 34                     | 34                   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 12-Week Period After the First Dose of Fremanezumab

|                 |   |
|-----------------|---|
| End point title | DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 12-Week Period After the First Dose of Fremanezumab |
|-----------------|---|

End point description:

A headache day of at least moderate severity: a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day demonstrating a headache of any duration that was treated with migraine-specific acute medications. Monthly averages were derived and normalized to 28 days equivalent by the following formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in the e-diary over the relevant period) \* 28. LS mean calculated using ANCOVA model with treatment, gender, region, special group of treatment failure(yes/no), migraine classification (EM/CM), and treatment\*migraine classification as fixed effects and baseline number of headache days of at least moderate severity and years since onset of migraine as covariates. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on primary endpoint.

|   |           |
|---|-----------|
| End point type                              | Secondary |
| End point timeframe:                        |           |
| Baseline (Day -28 to Day -1), up to Week 12 |           |

| End point values                    | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-------------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                  | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed         | 278             | 276                    | 283                  |  |
| Units: days/month                   |                 |                        |                      |  |
| least squares mean (standard error) | -0.6 (± 0.33)   | -3.9 (± 0.34)          | -4.2 (± 0.34)        |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab

|                 |  |
|-----------------|--|
| End point title | DB Period: Change From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab |
|-----------------|--|

#### End point description:

A migraine day was defined as when at least 1 of following occurred: A calendar day demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with/without aura; at least 4 consecutive hours of a headache meeting criteria for probable migraine; a headache of any duration that was treated with migraine-specific drugs. Monthly averages were derived and normalized to 28 days equivalent by: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)\*28. LS mean calculated using ANCOVA model with treatment, gender, region, special group of treatment failure(yes/no), migraine classification(EM/CM), and treatment\*migraine classification as fixed effects, and baseline number of migraine days, years since onset of migraines as covariates. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on

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

#### End point timeframe:

Baseline (Day -28 to Day -1), up to Week 4

| End point values                    | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-------------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                  | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed         | 278             | 276                    | 283                  |  |
| Units: days/month                   |                 |                        |                      |  |
| least squares mean (standard error) | -0.6 (± 0.35)   | -4.1 (± 0.35)          | -4.1 (± 0.35)        |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Percentage of Participants Reaching at Least 50% Reduction From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab

|                 |  |
|-----------------|--|
| End point title | DB Period: Percentage of Participants Reaching at Least 50% Reduction From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period After the First Dose of Fremanezumab |
|-----------------|--|

#### End point description:

A migraine day was defined as when at least 1 of the following situations occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with

or without aura; a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion was missing; a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds). Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in e-diary over relevant period)\*28. DB mITT analysis set included participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on the primary endpoint.

|   |           |
|---|-----------|
| End point type                            | Secondary |
| End point timeframe:                      |           |
| Baseline (Day -28 to Day-1), up to Week 4 |           |

| End point values                  | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed       | 278             | 276                    | 283                  |  |
| Units: percentage of participants |                 |                        |                      |  |
| number (not applicable)           | 10              | 38                     | 36                   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: DB Period: Change From Baseline in Monthly Average Number of Days of Use of Any Acute Headache Medications During the 12-Week Period After the First Dose of Fremanezumab

|                 |   |
|-----------------|---|
| End point title | DB Period: Change From Baseline in Monthly Average Number of Days of Use of Any Acute Headache Medications During the 12-Week Period After the First Dose of Fremanezumab |
|-----------------|---|

End point description:

Baseline data and the mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week period after administration of the first dose of study drug (based on Week 0 to 12 data) is reported. Least Squares (LS) mean calculated using analysis of covariance (ANCOVA) model with treatment, gender, region, special group of treatment failure (yes/no), migraine classification (EM/CM), and treatment\*migraine classification as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. DB mITT analysis set included participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on the primary endpoint.

|   |           |
|---|-----------|
| End point type                              | Secondary |
| End point timeframe:                        |           |
| Baseline (Day -28 to Day -1), up to Week 12 |           |

| End point values                    | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-------------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                  | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed         | 278             | 276                    | 283                  |  |
| Units: days/month                   |                 |                        |                      |  |
| least squares mean (standard error) | -0.6 (± 0.32)   | -3.7 (± 0.32)          | -3.9 (± 0.32)        |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 4-Week Period After the First Dose of Fremanezumab

|                 |  |
|-----------------|--|
| End point title | DB Period: Change From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 4-Week Period After the First Dose of Fremanezumab |
|-----------------|--|

#### End point description:

A headache day of at least moderate severity: a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity or; a calendar day demonstrating a headache of any duration that was treated with migraine-specific acute medications. Monthly averages were derived and normalized to 28 days equivalent by following formula: (number of days of efficacy variable over relevant period/number of days with assessments recorded in the e-diary over the relevant period) \* 28. LS mean calculated using ANCOVA model with treatment, gender, region, special group of treatment failure (yes/no), migraine classification (EM/CM), and treatment\*migraine classification as fixed effects, and baseline number of headache days of at least moderate severity and years since onset of migraines as covariates. DB mITT analysis set: participants who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessment on primary endpoint.

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

#### End point timeframe:

Baseline (Day -28 to Day -1), up to Week 4

| End point values                    | Placebo            | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-------------------------------------|--------------------|------------------------|----------------------|--|
| Subject group type                  | Reporting group    | Reporting group        | Reporting group      |  |
| Number of subjects analysed         | 278                | 276                    | 283                  |  |
| Units: days/month                   |                    |                        |                      |  |
| least squares mean (standard error) | -0.5 ( $\pm$ 0.34) | -4.2 ( $\pm$ 0.35)     | -4.5 ( $\pm$ 0.34)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Number of Participants With Adverse Events (AEs) and Who Did Not Complete the Study Due to AEs

|                 |   |
|-----------------|---|
| End point title | DB Period: Number of Participants With Adverse Events (AEs) and Who Did Not Complete the Study Due to AEs |
|-----------------|---|

#### End point description:

An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severe AE was defined as inability to carry out usual activities. Treatment-related AEs were defined as AEs with possible, probable, definite, or missing relationship to study drug. Serious AEs were defined as death, a life-threatening AE, 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 participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period.

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| Baseline (Day 0) up to Week 12 |           |

| End point values                     | Placebo              | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|--------------------------------------|----------------------|------------------------|----------------------|--|
| Subject group type                   | Subject analysis set | Subject analysis set   | Subject analysis set |  |
| Number of subjects analysed          | 277                  | 276                    | 285                  |  |
| Units: participants                  |                      |                        |                      |  |
| Any AEs                              | 134                  | 151                    | 129                  |  |
| AEs leading to withdrawal from study | 3                    | 1                      | 4                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: OL Period: Number of Participants With AEs and Who Did Not Complete the Study Due to AEs

|                 |  |
|-----------------|--|
| End point title | OL Period: Number of Participants With AEs and Who Did Not Complete the Study Due to AEs |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severe AE was defined as inability to carry out usual activities. Treatment-related AEs were defined as AEs with possible, probable, definite, or missing relationship to study drug. Serious AEs were defined as death, a life-threatening AE, 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 participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Week 12 up to Week 24 |           |

| End point values                     | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|--------------------------------------|-----------------|------------------------|----------------------|--|
| Subject group type                   | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed          | 262             | 271                    | 274                  |  |
| Units: participants                  |                 |                        |                      |  |
| Any AEs                              | 137             | 149                    | 155                  |  |
| AEs leading to withdrawal from study | 4               | 1                      | 2                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results

|  |  |
|--|--|
| End point title  | DB Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results |
| End point description:<br>Criteria for potentially clinically significant abnormal serum chemistry values included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and lactate dehydrogenase (LDH) (units/liter [U/L]): greater than or equal to ( $\geq$ ) 3*upper limit of normal (ULN); Blood Urea Nitrogen (BUN): $\geq 10.71$ millimoles/liter (mmol/L); creatinine: $\geq 177$ micromoles/liter ( $\mu\text{mol/L}$ ); bilirubin (total): $\geq 34.2$ $\mu\text{mol/L}$ ; and uric acid: $\geq 625$ $\mu\text{mol/L}$ (men), and $\geq 506$ $\mu\text{mol/L}$ (women). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline up to Week 12   |  |

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 272             | 268                    | 280                  |  |
| Units: participants         | 1               | 3                      | 4                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results

|  |  |
|--|--|
| End point title  | OL Period: Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results |
| End point description:<br>Criteria for potentially clinically significant abnormal serum chemistry values included: ALT, AST, ALP, GGT, and LDH (U/L): $\geq 3$ *ULN; BUN: $\geq 10.71$ mmol/L; creatinine: $\geq 177$ $\mu\text{mol/L}$ ; bilirubin (total): $\geq 34.2$ $\mu\text{mol/L}$ ; and uric acid: $\geq 625$ $\mu\text{mol/L}$ (men), and $\geq 506$ $\mu\text{mol/L}$ (women). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. |  |
| End point type   | Secondary  |

End point timeframe:  
Week 12 up to Week 24

| End point values            | Placebo         | Fremanezumab<br>Quarterly | Fremanezumab<br>Monthly |  |
|-----------------------------|-----------------|---------------------------|-------------------------|--|
| Subject group type          | Reporting group | Reporting group           | Reporting group         |  |
| Number of subjects analysed | 259             | 268                       | 273                     |  |
| Units: participants         | 2               | 3                         | 2                       |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

|                 |   |
|-----------------|---|
| End point title | DB Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results |
|-----------------|---|

End point description:

Criteria for potentially clinically significant abnormal hematology values included: hemoglobin: less than (<) 115 grams/liter (g/L) (in men) or less than or equal to ( $\leq$ ) 95 g/L (in women), hematocrit: <0.37 L/L (in men) or <0.32 L/L (in women), leukocytes:  $\geq 20 \times 10^9/L$  or  $\leq 3 \times 10^9/L$ , eosinophils:  $\geq 10\%$ , platelets:  $\geq 700 \times 10^9/L$  or  $\leq 75 \times 10^9/L$ , and absolute neutrophil count (ANC):  $\leq 1 \times 10^9/L$ . A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to Week 12

| End point values            | Placebo         | Fremanezumab<br>Quarterly | Fremanezumab<br>Monthly |  |
|-----------------------------|-----------------|---------------------------|-------------------------|--|
| Subject group type          | Reporting group | Reporting group           | Reporting group         |  |
| Number of subjects analysed | 271             | 268                       | 278                     |  |
| Units: participants         | 11              | 12                        | 3                       |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

|                 |   |
|-----------------|---|
| End point title | OL Period: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results |
|-----------------|---|

End point description:

Criteria for potentially clinically significant abnormal hematology values included: hemoglobin: <115 g/L (in men) or ≤95 g/L (in women), hematocrit: <0.37 L/L (in men) or <0.32 L/L (in women), leukocytes: ≥20\*10<sup>9</sup>/L or ≤3\*10<sup>9</sup>/L, eosinophils: >=10%, platelets: ≥700\*10<sup>9</sup>/L or ≤75\*10<sup>9</sup>/L, and ANC: ≤1\*10<sup>9</sup>/L. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Week 12 up to Week 24

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 258             | 268                    | 273                  |  |
| Units: participants         | 7               | 10                     | 4                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results

|                 |  |
|-----------------|--|
| End point title | DB Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results |
|-----------------|--|

End point description:

Criteria for potentially clinically significant abnormal coagulation values included: prothrombin international normalized ratio (INR): greater than (>) 1.5. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to Week 12

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 269             | 267                    | 277                  |  |
| Units: participants         | 2               | 4                      | 4                    |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results**

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|                 |  |
|-----------------|--|
| End point title | OL Period: Number of Participants With Potentially Clinically Significant Abnormal Coagulation Laboratory Test Results |
|-----------------|--|

End point description:

Criteria for potentially clinically significant abnormal coagulation values included: prothrombin INR: >1.5. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Week 12 up to Week 24

---

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 257             | 270                    | 272                  |  |
| Units: participants         | 3               | 1                      | 3                    |  |

---

**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: DB Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results**

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|                 |  |
|-----------------|--|
| End point title | DB Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results |
|-----------------|--|

End point description:

Criteria for potentially clinically significant abnormal urinalysis values included: urine glucose (milligrams/deciliter [mg/dL]):  $\geq 2$  unit increase from baseline, ketones (mg/dL):  $\geq 2$  unit increase from baseline, urine total protein (mg/dL):  $\geq 2$  unit increase from baseline, and haemoglobin  $\geq 2$  unit increase from baseline. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period.

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

End point timeframe:

Baseline up to Week 12

---

| End point values            | Placebo              | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|----------------------|------------------------|----------------------|--|
| Subject group type          | Subject analysis set | Subject analysis set   | Subject analysis set |  |
| Number of subjects analysed | 277                  | 276                    | 285                  |  |
| Units: participants         | 0                    | 0                      | 0                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: OL Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results

|  |  |
|--|--|
| End point title  | OL Period: Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results |
| End point description:<br>Criteria for potentially clinically significant abnormal urinalysis values included: urine glucose (mg/dL): $\geq 2$ unit increase from baseline, ketones (mg/dL): $\geq 2$ unit increase from baseline, urine total protein (mg/dL): $\geq 2$ unit increase from baseline, and haemoglobin $\geq 2$ unit increase from baseline. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Week 12 up to Week 24  |  |

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 262             | 271                    | 274                  |  |
| Units: participants         | 0               | 0                      | 0                    |  |

### Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | DB Period: Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values |
| End point description:<br>Criteria for potentially clinically significant abnormal vital signs values 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 celsius and change of $\geq 1.1$ degrees celsius. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. B safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome |   |

measure.

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

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 277             | 276                    | 283                  |  |
| Units: participants         | 9               | 8                      | 8                    |  |

### Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | OL Period: Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values |
|-----------------|---|

End point description:

Criteria for potentially clinically significant abnormal vital signs values included: pulse rate:  $\leq 50$  bpm and decrease of  $\geq 15$  bpm, or  $\geq 120$  bpm and increase of  $\geq 15$  bpm; systolic blood pressure:  $\leq 90$  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 celsius and change of  $\geq 1.1$  degrees celsius. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Week 12 up to Week 24 |           |

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 261             | 270                    | 273                  |  |
| Units: participants         | 10              | 14                     | 8                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Number of Participants With Shift From Baseline to Week 12



## in Electrocardiogram (ECG) Parameters

|                 |   |
|-----------------|---|
| End point title | DB Period: Number of Participants With Shift From Baseline to Week 12 in Electrocardiogram (ECG) Parameters |
|-----------------|---|

End point description:

ECG parameters included: heart rate, PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - Week 12 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. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. Here, 'Overall number of participants analyzed' = participants with both baseline and Week 12 ECG findings.

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

End point timeframe:

Baseline, Week 12

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 258             | 271                    | 270                  |  |
| Units: participants         |                 |                        |                      |  |
| Normal - Normal             | 199             | 218                    | 212                  |  |
| Normal - Abnormal NCS       | 21              | 14                     | 15                   |  |
| Normal - Abnormal CS        | 0               | 0                      | 0                    |  |
| Abnormal NCS - Normal       | 10              | 19                     | 12                   |  |
| Abnormal NCS - Abnormal NCS | 28              | 20                     | 31                   |  |
| 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                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: OL Period: Number of Participants With Shift From Baseline to Week 24 in ECG Parameters

|                 |   |
|-----------------|---|
| End point title | OL Period: Number of Participants With Shift From Baseline to Week 24 in ECG Parameters |
|-----------------|---|

End point description:

ECG parameters included: heart rate, PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - Week 24 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. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period. Here, 'Overall number of participants analyzed' = participants with both baseline and Week 24 ECG findings.

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

End point timeframe:

Baseline, Week 24

| <b>End point values</b>     | Placebo         | Fremanezumab<br>Quarterly | Fremanezumab<br>Monthly |  |
|-----------------------------|-----------------|---------------------------|-------------------------|--|
| Subject group type          | Reporting group | Reporting group           | Reporting group         |  |
| Number of subjects analysed | 245             | 256                       | 260                     |  |
| Units: participants         |                 |                           |                         |  |
| Normal - Normal             | 193             | 214                       | 203                     |  |
| Normal - Abnormal NCS       | 15              | 5                         | 15                      |  |
| Normal - Abnormal CS        | 0               | 0                         | 1                       |  |
| Abnormal NCS - Normal       | 13              | 20                        | 16                      |  |
| Abnormal NCS - Abnormal NCS | 24              | 17                        | 25                      |  |
| 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                       |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DB Period: Number of Participants Who Received Concomitant Medications for Adverse Events

|                 |   |
|-----------------|---|
| End point title | DB Period: Number of Participants Who Received Concomitant Medications for Adverse Events |
|-----------------|---|

End point description:

Concomitant medications included: agents acting on the renin-angiotensin system, all other therapeutic products (for example: homeopathic preparation), allergens, analgesics, anesthetics, anti-parkinson drugs, antianemic preparations, antibacterials for systemic use, antibiotics and chemotherapeutics for dermatological use, antidiarrheals, intestinal antiinflammatory/antiinfective agents, antifungals for dermatological use, antigout preparations, antihemorrhagics, antihistamines for systemic use, antihypertensives, antiinflammatory and antirheumatic products, antipruritics, antipsoriatics, antivirals for systemic use, blood substitutes and perfusion solutions, cardiac therapy, corticosteroids, cough and cold preparations, diagnostic radiopharmaceuticals, diuretics, vaccines, ophthalmologicals, muscle relaxants, drugs used in diabetes etc. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period.

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

End point timeframe:

Baseline up to Week 12

| <b>End point values</b>     | Placebo              | Fremanezumab<br>Quarterly | Fremanezumab<br>Monthly |  |
|-----------------------------|----------------------|---------------------------|-------------------------|--|
| Subject group type          | Subject analysis set | Subject analysis set      | Subject analysis set    |  |
| Number of subjects analysed | 277                  | 276                       | 285                     |  |
| Units: participants         | 274                  | 269                       | 280                     |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OL Period: Number of Participants Who Received Concomitant Medications for Adverse Events

|                 |   |
|-----------------|---|
| End point title | OL Period: Number of Participants Who Received Concomitant Medications for Adverse Events |
|-----------------|---|

End point description:

Concomitant medications included: agents acting on the renin-angiotensin system, all other therapeutic products (for example: homeopathic preparation), allergens, analgesics, anesthetics, anti-parkinson drugs, antianemic preparations, antibacterials for systemic use, antibiotics and chemotherapeutics for dermatological use, antidiarrheals, intestinal antiinflammatory/antiinfective agents, antifungals for dermatological use, antigout preparations, antihemorrhagics, antihistamines for systemic use, antihypertensives, antiinflammatory and antirheumatic products, antipruritics, antipsoriatics, antivirals for systemic use, blood substitutes and perfusion solutions, cardiac therapy, corticosteroids, cough and cold preparations, diagnostic radiopharmaceuticals, diuretics, vaccines, ophthalmologicals, muscle relaxants, drugs used in diabetes etc. OL safety analysis set included all participants who received at least 1 dose of study drug during the OL treatment period.

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

End point timeframe:

Week 12 up to Week 24

| End point values            | Placebo         | Fremanezumab Quarterly | Fremanezumab Monthly |  |
|-----------------------------|-----------------|------------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group        | Reporting group      |  |
| Number of subjects analysed | 262             | 271                    | 274                  |  |
| Units: participants         | 262             | 266                    | 270                  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 0) up to follow-up visit (Week 46)

Adverse event reporting additional description:

Safety analysis set: all participants who received at least 1 dose of study drug. AE data were summarized collectively for both periods. 2 participants (1 with CM and 1 with EM) randomized to placebo but received Fremanezumab monthly dosing during double-blind treatment period. They were analyzed in the treatment arm per actual treatment received.

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

### Dictionary used

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

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

### Reporting groups

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

Reporting group description:

DB period: Participants with CM or EM received 3 injections of placebo 1.5 mL SC on Day 0 and single injection of placebo 1.5 mL SC on Days 28 and 56. OL period: Participants with CM or EM received fremanezumab (TEV-48125) 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Fremanezumab Monthly |
|-----------------------|----------------------|

Reporting group description:

DB period: Participants with CM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). Participants with EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL) on Day 0 followed by monthly SC administration of fremanezumab 225 mg (1 injection of fremanezumab 225 mg/1.5 mL) for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Fremanezumab Quarterly |
|-----------------------|------------------------|

Reporting group description:

DB period: Participants with CM or EM received fremanezumab 675 mg SC (3 injections of fremanezumab 225 mg/1.5 mL) on Day 0 followed by monthly SC administration of placebo 1.5 mL for 2 months (on Days 28 and 56). OL period: Participants with CM or EM received fremanezumab 225 mg SC (1 injection of fremanezumab 225 mg/1.5 mL) at Days 84, 112, and 140.

| Serious adverse events  | Placebo          | Fremanezumab Monthly | Fremanezumab Quarterly |
|---|------------------|----------------------|------------------------|
| Total subjects affected by serious adverse events                   |                  |                      |                        |
| subjects affected / exposed   | 13 / 277 (4.69%) | 11 / 285 (3.86%)     | 10 / 276 (3.62%)       |
| number of deaths (all causes)                                       | 0                | 0                    | 0                      |
| number of deaths resulting from adverse events                      |                  |                      |                        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                      |                        |
| Angiomyxoma   |                  |                      |                        |
| subjects affected / exposed   | 0 / 277 (0.00%)  | 1 / 285 (0.35%)      | 0 / 276 (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                  |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| Breast cancer                                   |  |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%)  | 0 / 285 (0.00%) | 0 / 276 (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           |
| Thyroid adenoma                                 |  |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%)  | 0 / 285 (0.00%) | 0 / 276 (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           |
| Uterine leiomyoma                               | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |
| subjects affected / exposed <sup>[1]</sup>      | 1 / 231 (0.43%)  | 0 / 240 (0.00%) | 0 / 229 (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           |
| Vulval cancer                                   | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |
| subjects affected / exposed <sup>[2]</sup>      | 1 / 231 (0.43%)  | 0 / 240 (0.00%) | 0 / 229 (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           |
| Immune system disorders                         |  |                 |                 |
| Anaphylactic reaction                           |  |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%)  | 1 / 285 (0.35%) | 0 / 276 (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           |
| Reproductive system and breast disorders        |  |                 |                 |
| Dysmenorrhoea                                   | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |
| subjects affected / exposed <sup>[3]</sup>      | 0 / 231 (0.00%)  | 0 / 240 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Endometriosis                                   | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |
| subjects affected / exposed <sup>[4]</sup>      | 0 / 231 (0.00%)  | 1 / 240 (0.42%) | 0 / 229 (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           |
| Menometrorrhagia                                | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| subjects affected / exposed <sup>[5]</sup>      | 0 / 231 (0.00%)  | 1 / 240 (0.42%) | 0 / 229 (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           |
| Menorrhagia                                     | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |
| subjects affected / exposed <sup>[6]</sup>      | 0 / 231 (0.00%)  | 0 / 240 (0.00%) | 1 / 229 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Metrorrhagia                                    | Additional description: This is a gender-specific AE. Only female participants were at risk. |                 |                 |
| subjects affected / exposed <sup>[7]</sup>      | 1 / 231 (0.43%)  | 0 / 240 (0.00%) | 0 / 229 (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 |  |                 |                 |
| Vocal cord thickening                           |  |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%)  | 1 / 285 (0.35%) | 0 / 276 (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           |
| Investigations                                  |  |                 |                 |
| Blood pressure increased                        |  |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%)  | 0 / 285 (0.00%) | 0 / 276 (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           |
| International normalised ratio abnormal         |  |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%)  | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |  |                 |                 |
| Clavicle fracture                               |  |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%)  | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Foot fracture                                   |  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory fume inhalation disorder            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 1 / 285 (0.35%) | 0 / 276 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thoracic vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Congenital diaphragmatic hernia                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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                               |                 |                 |                 |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 1 / 285 (0.35%) | 0 / 276 (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           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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                        |                 |                 |                 |
| Hypoaesthesia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intracranial aneurysm                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Migraine  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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           |
| Multiple sclerosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 1 / 285 (0.35%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Optic neuritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 1 / 285 (0.35%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Retinal tear                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 1 / 285 (0.35%) | 0 / 276 (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           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Anal polyp                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrooesophageal reflux disease                |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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 acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 1 / 285 (0.35%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 2 / 285 (0.70%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal colic                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Dengue fever                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 277 (0.00%) | 0 / 285 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 277 (0.36%) | 0 / 285 (0.00%) | 0 / 276 (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           |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a gender-specific AE. Only female participants were at risk.

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

| Non-serious adverse events                            | Placebo           | Fremanezumab Monthly | Fremanezumab Quarterly |
|---|-------------------|----------------------|------------------------|
| Total subjects affected by non-serious adverse events |                   |                      |                        |
| subjects affected / exposed                           | 88 / 277 (31.77%) | 81 / 285 (28.42%)    | 90 / 276 (32.61%)      |
| Nervous system disorders                              |                   |                      |                        |

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| Migraine<br>subjects affected / exposed<br>occurrences (all)                          | 21 / 277 (7.58%)<br>26  | 12 / 285 (4.21%)<br>14  | 14 / 276 (5.07%)<br>15  |
| General disorders and administration<br>site conditions                               |                         |                         |                         |
| Injection site erythema<br>subjects affected / exposed<br>occurrences (all)           | 24 / 277 (8.66%)<br>53  | 32 / 285 (11.23%)<br>80 | 31 / 276 (11.23%)<br>66 |
| Injection site induration<br>subjects affected / exposed<br>occurrences (all)         | 16 / 277 (5.78%)<br>52  | 18 / 285 (6.32%)<br>65  | 19 / 276 (6.88%)<br>41  |
| Injection site pain<br>subjects affected / exposed<br>occurrences (all)               | 10 / 277 (3.61%)<br>20  | 14 / 285 (4.91%)<br>42  | 15 / 276 (5.43%)<br>42  |
| Infections and infestations   |                         |                         |                         |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 32 / 277 (11.55%)<br>37 | 25 / 285 (8.77%)<br>30  | 30 / 276 (10.87%)<br>41 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 10 / 277 (3.61%)<br>10  | 16 / 285 (5.61%)<br>17  | 8 / 276 (2.90%)<br>11   |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported