

**Clinical trial results:****A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of Fremanezumab (TEV-48125) for the Preventive Treatment of Migraine****Summary**

EudraCT number	2015-004550-18
Trial protocol	DE CZ ES FI DK
Global end of trial date	07 December 2018

Results information

Result version number	v1 (current)
This version publication date	30 August 2019
First version publication date	30 August 2019

Trial information**Trial identification**

Sponsor protocol code	TV48125-CNS-30051
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02638103
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	07 December 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 December 2018
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 evaluate the long-term safety and tolerability of subcutaneous (SC) fremanezumab (TEV-48125) in the preventive treatment of migraine.

Protection of trial subjects:

This study was conducted in full accordance with the International Council for 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; EU Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 48
Country: Number of subjects enrolled	Czech Republic: 79
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Finland: 42
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Japan: 176
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Russian Federation: 59
Country: Number of subjects enrolled	United States: 1390
Worldwide total number of subjects	1890
EEA total number of subjects	184

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	1831
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with chronic or episodic migraine (CM or EM) who completed the pivotal efficacy studies of fremanezumab (TV48125-CNS-30049 [NCT02621931] and TV48125-CNS-30050 [NCT02629861]) and agreed to participate in this study; and new participants meeting eligibility criteria (not rolling over from pivotal studies), were enrolled in this study.

Pre-assignment

Screening details:

A total of 1890 participants were enrolled, including 917 participants with CM rolled over from Study TV48125-CNS-30049, 661 participants with EM rolled over from Study TV48125-CNS-30050, and 312 newly enrolled participants (193 with CM and 119 with EM).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants

Arm description:

Participants with CM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab (TEV-48125) 675 milligrams (mg) subcutaneously (SC) as loading dose (3 injections of fremanezumab 225 mg/1.5 milliliters [mL] on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

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 as per the 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 as per the dose and schedule specified in the arm.

Arm title	TEV-48125 225 mg Monthly: Active Rollover Participants
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Arm description:

Participants with CM who were randomized to the active treatment group (Fremanezumab 675/225 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg

(1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the active treatment group (Fremanezumab 225 mg) in the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

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 as per the 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 as per the dose and schedule specified in the arm.

Arm title	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants
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Arm description:

Participants with CM or EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

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 as per the 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 as per the dose and schedule specified in the arm.

Arm title	TEV-48125 675 mg Quarterly: Active Rollover Participants
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Arm description:

Participants with CM or EM who were randomized to the active treatment group (Fremanezumab 675 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Arm type	Experimental
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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 as per the 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 as per the schedule specified in the arm.

Number of subjects in period 1	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants
	Started	419	526
Safety analysis set	418	526	419
Full analysis set (FAS)	416	520	419
Completed	313	408	335
Not completed	106	118	85
Consent withdrawn by subject	43	53	30
Adverse event, non-fatal	13	12	19
Pregnancy	2	3	-
Other than specified	5	4	2
Lost to follow-up	26	33	20
Protocol deviation	1	2	1
Non-compliance to Study Procedures	2	1	1
Lack of efficacy	14	10	12

Number of subjects in period 1	TEV-48125 675 mg Quarterly: Active Rollover Participants
Started	525
Safety analysis set	525
Full analysis set (FAS)	523
Completed	383
Not completed	142
Consent withdrawn by subject	61
Adverse event, non-fatal	12
Pregnancy	1

Other than specified	4
Lost to follow-up	37
Protocol deviation	4
Non-compliance to Study Procedures	1
Lack of efficacy	22

Baseline characteristics

Reporting groups

Reporting group title	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants
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Reporting group description:

Participants with CM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab (TEV-48125) 675 milligrams (mg) subcutaneously (SC) as loading dose (3 injections of fremanezumab 225 mg/1.5 milliliters [mL] on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 225 mg Monthly: Active Rollover Participants
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Reporting group description:

Participants with CM who were randomized to the active treatment group (Fremanezumab 675/225 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the active treatment group (Fremanezumab 225 mg) in the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants
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Reporting group description:

Participants with CM or EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 675 mg Quarterly: Active Rollover Participants
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Reporting group description:

Participants with CM or EM who were randomized to the active treatment group (Fremanezumab 675 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants
Number of subjects	419	526	420
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	44.1 ± 12.09	42.9 ± 11.97	44.0 ± 11.67
Sex: Female, Male Units: Subjects			
Female	365	454	369
Male	54	72	51

Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	29	45	34
Not Hispanic or Latino	387	481	386
Unknown or Not Reported	3	0	0
Race/Ethnicity, Customized			
Units: Subjects			
White	351	424	343
Black	32	38	38
Asian	29	62	36
American Indian or Alaskan Native	1	2	0
Native Hawaiian or other Pacific Islander	1	0	0
Other	5	0	3
Number of Migraine Days			
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 (for CM participants) or at least 2 consecutive hours (for EM participants) of a headache meeting criteria for migraine with or without aura; a calendar day demonstrating at least 4 consecutive hours (for CM participants) or at least 2 consecutive hours (for EM participants) of a headache meeting criteria for probable migraine; a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications.			
Units: days			
arithmetic mean	13.9	13.1	13.6
standard deviation	± 5.99	± 5.49	± 5.86
Number of Headache Days of Any Severity			
Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of any severity for both CM and EM participants was defined as a calendar day (00:00 to 23:59) where the participant (using the electronic headache diary device) reports: a day with headache pain that lasts at least 4 hours with a peak severity of any severity or; a day when the participant used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration.			
Units: days			
arithmetic mean	13.6	12.7	13.2
standard deviation	± 6.68	± 6.20	± 6.32
Reporting group values	TEV-48125 675 mg Quarterly: Active Rollover Participants	Total	
Number of subjects	525	1890	
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	43.2	-	
standard deviation	± 11.73		
Sex: Female, Male			
Units: Subjects			
Female	457	1645	
Male	68	245	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	38	146	
Not Hispanic or Latino	484	1738	
Unknown or Not Reported	3	6	

Race/Ethnicity, Customized			
Units: Subjects			
White	412	1530	
Black	40	148	
Asian	64	191	
American Indian or Alaskan Native	3	6	
Native Hawaiian or other Pacific Islander	2	3	
Other	4	12	
Number of Migraine Days			
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 (for CM participants) or at least 2 consecutive hours (for EM participants) of a headache meeting criteria for migraine with or without aura; a calendar day demonstrating at least 4 consecutive hours (for CM participants) or at least 2 consecutive hours (for EM participants) of a headache meeting criteria for probable migraine; a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications.			
Units: days			
arithmetic mean	13.2		
standard deviation	± 5.26	-	
Number of Headache Days of Any Severity			
Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of any severity for both CM and EM participants was defined as a calendar day (00:00 to 23:59) where the participant (using the electronic headache diary device) reports: a day with headache pain that lasts at least 4 hours with a peak severity of any severity or; a day when the participant used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration.			
Units: days			
arithmetic mean	12.9		
standard deviation	± 6.02	-	

End points

End points reporting groups

Reporting group title	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants
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Reporting group description:

Participants with CM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab (TEV-48125) 675 milligrams (mg) subcutaneously (SC) as loading dose (3 injections of fremanezumab 225 mg/1.5 milliliters [mL] on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 225 mg Monthly: Active Rollover Participants
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Reporting group description:

Participants with CM who were randomized to the active treatment group (Fremanezumab 675/225 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the active treatment group (Fremanezumab 225 mg) in the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants
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Reporting group description:

Participants with CM or EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 675 mg Quarterly: Active Rollover Participants
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Reporting group description:

Participants with CM or EM who were randomized to the active treatment group (Fremanezumab 675 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 225 mg Monthly: New/Placebo Rollover CM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with CM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 225 mg Monthly: Active Rollover CM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with CM who were randomized to the active treatment group (Fremanezumab 675/225 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 675mg Quarterly:New/Placebo Rollover CM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with CM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 675 mg Quarterly: Active Rollover CM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with CM who were randomized to the active treatment group (Fremanezumab 675 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 225 mg Monthly: New/Placebo Rollover EM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 225 mg Monthly: Active Rollover EM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with EM who were randomized to the active treatment group (Fremanezumab 225 mg) in the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 675mg Quarterly:New/Placebo Rollover EM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Subject analysis set title	TEV-48125 675 mg Quarterly: Active Rollover EM Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with EM who were randomized to the active treatment group (Fremanezumab 675 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Primary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs) ^[1]
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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. Safety population included all participants who received at least 1 dose of fremanezumab.

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to follow-up visit (Day 533)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	418	526	419	525
Units: participants				
Any AEs	365	456	365	426
Severe AEs	47	51	45	50
Treatment-related AEs	263	288	242	270
Serious AEs	27	29	36	23
AEs leading to discontinuation from study	18	18	22	18

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Shift From Baseline to Endpoint in Electrocardiogram (ECG) Parameters

End point title	Number of Participants With Shift From Baseline to Endpoint in Electrocardiogram (ECG) Parameters ^[2]
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End point description:

ECG parameters included: PR interval, QRS interval, QT interval corrected using the Fridericia formula (QTcF), QT interval corrected using the Bazett's formula (QTcB) and RR interval. Shifts represented as Baseline - endpoint value (last observed post-baseline value). Abnormal NCS indicated an abnormal but not clinically significant finding. Abnormal CS indicated an abnormal and clinically significant finding. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received at least 1 dose of fremanezumab. Here, 'Overall number of participants analyzed' = participants with both baseline and endpoint electrocardiogram findings.

End point type	Primary
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End point timeframe:

Baseline (Day 0), endpoint (Day 336)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	386	492	391	489
Units: participants				
Normal - Normal	239	295	230	296
Normal - Abnormal NCS	45	64	49	67

Normal - Abnormal CS	0	0	0	1
Abnormal NCS - Normal	42	53	43	60
Abnormal NCS - Abnormal NCS	60	79	69	65
Abnormal NCS - Abnormal CS	0	1	0	0
Abnormal CS - Normal	0	0	0	0
Abnormal CS - Abnormal NCS	0	0	0	0
Abnormal CS - Abnormal CS	0	0	0	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Shift From Baseline to Endpoint in Coagulation Laboratory Test Results ^[3]
End point description:	
Coagulation parameters included: prothrombin time (PT) (seconds), prothrombin international normalized ratio (INR), activated partial thromboplastin time (aPTT) (seconds). Shifts represented as Baseline - endpoint value (last observed post-baseline value). Shifts from baseline to endpoint were summarized using participant counts grouped into three categories: - Low (below normal range) - Normal (within the normal range of 9.4 to 12.5 seconds) - High (above normal range). A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received at least 1 dose of fremanezumab. Here, 'Overall number of participants analyzed' = participants with both baseline and endpoint coagulation laboratory test results. 'n' = participants evaluable for specified categories.	
End point type	Primary
End point timeframe:	
Baseline (Day 0), endpoint (Day 336)	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	407	516	410	513
Units: participants				
PT: Low-Low (n=407,516,410,513)	0	0	0	0
PT: Low-Normal (n=407,516,410,513)	0	0	0	0
PT: Low-High (n=407,516,410,513)	0	0	0	0
PT: Normal-Low (n=407,516,410,513)	0	0	0	0
PT: Normal-Normal (n=407,516,410,513)	0	0	0	0
PT: Normal-High (n=407,516,410,513)	0	0	0	0
PT: High-Low (n=407,516,410,513)	0	0	0	0
PT: High-Normal (n=407,516,410,513)	0	0	0	0
PT: High-High (n=407,516,410,513)	0	0	0	0
Prothrombin INR: Low-Low (n=406,516,410,513)	0	1	4	1

Prothrombin INR: Low-Normal (n=406,516,410,513)	11	11	11	9
Prothrombin INR: Low-High (n=406,516,410,513)	0	0	0	0
Prothrombin INR: Normal-Low (n=406,516,410,513)	12	15	9	4
Prothrombin INR: Normal-Normal (n=406,516,410,513)	366	468	372	473
Prothrombin INR: Normal-High (n=406,516,410,513)	6	5	4	4
Prothrombin INR: High-Low (n=406,516,410,513)	0	0	0	1
Prothrombin INR: High-Normal (n=406,516,410,513)	7	11	6	13
Prothrombin INR: High-High (n=406,516,410,513)	4	5	4	6
aPTT: Low-Low (n=406,516,410,513)	2	2	1	0
aPTT: Low-Normal (n=406,516,410,513)	4	1	7	7
aPTT: Low-High (n=406,516,410,513)	0	1	0	0
aPTT: Normal-Low (n=406,516,410,513)	3	11	7	10
aPTT: Normal-Normal (n=406,516,410,513)	341	423	234	414
aPTT: Normal-High (n=406,516,410,513)	14	18	19	22
aPTT: High-Low (n=406,516,410,513)	0	0	0	1
aPTT: High-Normal (n=406,516,410,513)	26	43	26	37
aPTT: High-High (n=406,516,410,513)	16	17	16	22

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Injection Site Reactions

End point title	Number of Participants With Injection Site Reactions ^[4]
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End point description:

Number of participants who reported treatment-emergent injection site reactions are summarized. Preferred terms from MedDRA version 18.1 were offered without a threshold applied. Injection site reactions included injection site induration, pain, erythema, haemorrhage, pruritus, swelling, bruising, rash, urticaria, warmth, dermatitis, haematoma, inflammation, discolouration, discomfort, hypersensitivity, hypoaesthesia, irritation, oedema, papule, paraesthesia, vesicles and pallor. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received at least 1 dose of fremanezumab.

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to follow-up visit (Day 533)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	418	526	419	525
Units: participants				
Injection site induration	167	174	144	134
Injection site pain	149	156	135	140
Injection site erythema	130	144	99	124
Injection site haemorrhage	34	38	21	38
Injection site pruritus	31	43	17	24
Injection site swelling	7	10	6	8
Injection site bruising	2	2	4	3
Injection site rash	4	2	5	2
Injection site urticaria	4	2	3	2
Injection site warmth	3	2	1	1
Injection site dermatitis	0	1	0	1
Injection site haematoma	1	0	0	1
Injection site inflammation	0	1	1	0
Injection site discolouration	0	1	0	0
Injection site discomfort	0	0	0	1
Injection site hypersensitivity	1	0	0	0
Injection site hypoaesthesia	1	1	0	0
Injection site irritation	0	0	0	1
Injection site oedema	1	1	1	0
Injection site papule	1	0	0	0
Injection site paraesthesia	0	0	1	0
Injection site vesicles	0	1	1	0
Injection site pallor	0	0	0	1

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Suicidal Ideation and Suicidal Behavior as Assessed by the Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) ^[5]
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End point description:

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

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to follow-up visit (Day 533)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	418	526	419	525
Units: participants				
Suicidal ideation	2	0	2	1
Suicidal attempt	0	0	1	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Potentially Clinically Significant Abnormal Serum Chemistry Results ^[6]
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End point description:

Potentially clinically significant abnormal serum chemistry findings included: Blood Urea Nitrogen (BUN): greater than or equal to (\geq) 10.71 millimoles/liter (mmol/L), creatinine: \geq 177 micromoles/liter (μ mol/L), bilirubin: \geq 34.2 μ mol/L, Alanine Aminotransferase (ALT) (units/liter [U/L]): \geq 3*upper limit of normal (ULN) Aspartate Aminotransferase (AST) (U/L): \geq 3*ULN, and Gamma Glutamyl Transferase (GGT) (U/L): \geq 3*ULN. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received at least 1 dose of fremanezumab. Here, 'Overall number of participants analysed'=participants with both baseline and post-baseline serum chemistry values.

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to end of treatment (EOT) visit (Day 336)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	408	518	412	513
Units: participants	27	26	11	23

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Potentially Clinically Significant Abnormal Hematology Results

End point title	Number of Participants With Potentially Clinically Significant Abnormal Hematology Results ^[7]
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End point description:

Potentially clinically significant abnormal hematology findings included: hemoglobin: less than (<) 115 grams/liter (g/L) (in males) or <=95 g/L (in females), hematocrit: <0.37 L/L (in males) or <0.32 L/L (in females), leukocytes: >=20*10⁹/L or <=3*10⁹/L, eosinophils/leukocytes: >=10%, and platelets: >=700*10⁹/L or <=75*10⁹/L. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received at least 1 dose of fremanezumab. Here, 'Overall number of participants analysed'=participants with both baseline and post-baseline hematology parameter values.

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to end of treatment (EOT) visit (Day 336)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	408	518	412	513
Units: participants	34	39	27	40

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Potentially Clinically Significant Abnormal Urinalysis Laboratory Tests Results ^[8]
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End point description:

Potentially clinically significant abnormal urinalysis findings included: blood: >=2 unit increase from baseline, urine glucose (milligrams/decilitre [mg/dL]): >=2 unit increase from baseline, ketones (mg/dL): >=2 unit increase from baseline, urine protein (mg/dL): >=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. Safety population included all participants who received at least 1 dose of fremanezumab. Here, 'Overall number of participants analysed'=participants with both baseline and post-baseline urinalysis values.

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to (EOT visit (Day 336)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	408	517	412	513
Units: participants	128	170	120	146

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values ^[9]
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End point description:

Potentially clinically significant abnormal vital signs findings included: pulse rate: ≤ 50 beats/minute (bpm) and decrease of ≥ 15 bpm, or ≥ 120 bpm and increase of ≥ 15 bpm; systolic blood pressure: ≤ 90 millimeters of mercury (mmHg) and decrease of ≥ 20 mmHg, or ≥ 180 mmHg and increase of ≥ 20 mmHg; diastolic blood pressure: ≥ 105 mmHg and increase of ≥ 15 mmHg, or ≤ 50 mmHg and decrease of ≥ 15 mmHg; respiratory rate: < 10 breaths/minute; and body temperature ≥ 38.3 degrees centigrade and change of ≥ 1.1 degrees centigrade. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. Safety population included all participants who received at least 1 dose of fremanezumab. Here, 'Overall number of participants analysed'=participants with both baseline and post-baseline vital signs values.

End point type	Primary
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End point timeframe:

Baseline (Day 0) up to EOT visit (Day 336)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety analyses were descriptive in nature.

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415	520	414	519
Units: participants	20	33	24	40

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period at Month 12

End point title	Change From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period at Month 12
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End point description:

A migraine day: when at least 1 of following situations occurred: A calendar day(0:00 to 23:59) demonstrating ≥ 4 consecutive hours (hrs) (for CM participants) or ≥ 2 consecutive hrs (for EM participants) of a headache meeting criteria for migraine with or without aura; or of a headache meeting criteria for probable migraine; and a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications. 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. Full analysis set (FAS):all participants who received at least 1 dose of fremanezumab, had at least 10 days of efficacy assessments by e-diary after first injection. Data for this endpoint was collected and reported separately for CM and EM participants.'Overall number of participants analysed'=participants evaluable for this endpoint.

End point type	Other pre-specified
End point timeframe:	
Baseline (Day -28 to Day -1), Month 12	

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover CM Participants	TEV-48125 225 mg Monthly: Active Rollover CM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover CM Participants	TEV-48125 675 mg Quarterly: Active Rollover CM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	192	233	194	230
Units: days/month				
arithmetic mean (standard deviation)	-7.8 (\pm 6.98)	-8.2 (\pm 6.14)	-7.6 (\pm 6.87)	-7.0 (\pm 6.54)

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover EM Participants	TEV-48125 225 mg Monthly: Active Rollover EM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover EM Participants	TEV-48125 675 mg Quarterly: Active Rollover EM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	124	173	138	173
Units: days/month				
arithmetic mean (standard deviation)	-4.5 (\pm 4.20)	-5.5 (\pm 4.01)	-5.5 (\pm 3.65)	-5.0 (\pm 3.78)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Monthly Average Number of Headache Days of Any Severity During the 4-Week Period at Month 12

End point title	Change From Baseline in Monthly Average Number of Headache Days of Any Severity During the 4-Week Period at Month 12
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End point description:

Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of any severity for both CM and EM participants was defined as a calendar day (00:00 to 23:59) where participant reports: a day with headache pain that lasts ≥ 4 hours with a peak severity of any severity or; a day when participant used acute migraine-specific medication to treat a headache of any severity

or duration. 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. FAS: all participants who received at least 1 dose of fremanezumab, and had at least 10 days of efficacy assessments by electronic diary after first injection. Data for this endpoint was collected and reported separately for CM and EM participants. 'Overall number of participants analysed'=participants evaluable for this endpoint.

End point type	Other pre-specified
End point timeframe:	
Baseline (Day -28 to Day -1), Month 12	

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover CM Participants	TEV-48125 225 mg Monthly: Active Rollover CM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover CM Participants	TEV-48125 675 mg Quarterly: Active Rollover CM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	192	233	194	230
Units: days/month				
arithmetic mean (standard deviation)	-7.7 (± 6.79)	-7.9 (± 6.01)	-7.2 (± 6.48)	-7.1 (± 6.88)

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover EM Participants	TEV-48125 225 mg Monthly: Active Rollover EM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover EM Participants	TEV-48125 675 mg Quarterly: Active Rollover EM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	124	173	138	173
Units: days/month				
arithmetic mean (standard deviation)	-4.4 (± 4.25)	-5.0 (± 3.90)	-5.0 (± 3.63)	-4.8 (± 3.74)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With At Least 50% Reduction From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period

End point title	Percentage of Participants With At Least 50% Reduction From Baseline in Monthly Average Number of Migraine Days During the 4-Week Period
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End point description:

A migraine day: when at least 1 of following situations occurred: A calendar day (0:00 to 23:59) demonstrating ≥ 4 consecutive hours (hrs) (for CM participants) or ≥ 2 consecutive hrs (for EM participants) of a headache meeting criteria for migraine with or without aura; or of a headache meeting criteria for probable migraine; and a calendar day demonstrating a headache of any duration that was treated with migraine-specific medications. 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. FAS: all participants who received at least 1 dose of fremanezumab, had at least 10 days of efficacy assessments by e-diary after first injection. Data for this endpoint was collected and reported separately for CM and EM participants. 'Overall number of

participants analysed'=participants evaluable for this endpoint.

End point type	Other pre-specified
End point timeframe:	
Baseline (Day -28 to Day -1), Month 12	

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover CM Participants	TEV-48125 225 mg Monthly: Active Rollover CM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover CM Participants	TEV-48125 675 mg Quarterly: Active Rollover CM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	195	240	197	237
Units: percentage of participants				
number (not applicable)	54	59	52	54

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover EM Participants	TEV-48125 225 mg Monthly: Active Rollover EM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover EM Participants	TEV-48125 675 mg Quarterly: Active Rollover EM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	125	174	139	174
Units: percentage of participants				
number (not applicable)	58	75	68	64

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With At Least 50% Reduction From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 4-Week Period

End point title	Percentage of Participants With At Least 50% Reduction From Baseline in Monthly Average Number of Headache Days of at Least Moderate Severity During the 4-Week Period
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End point description:

Headaches were subjectively rated by participants as mild, moderate or severe. A headache day of any severity for both CM and EM participants was defined as a calendar day (00:00 to 23:59) where participant reports: a day with headache pain that lasts ≥ 4 hours with a peak severity of any severity or; a day when participant used acute migraine-specific medication to treat a headache of any severity or duration. 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. FAS: all participants who received at least 1 dose of fremanezumab, and had at least 10 days of efficacy assessments by electronic diary after first injection. Data for this endpoint was collected and reported separately for CM and EM participants. 'Overall number of participants analysed'=participants evaluable for this endpoint.

End point type	Other pre-specified
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End point timeframe:

Baseline (Day -28 to Day -1), Month 12

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover CM Participants	TEV-48125 225 mg Monthly: Active Rollover CM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover CM Participants	TEV-48125 675 mg Quarterly: Active Rollover CM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	193	240	197	237
Units: percentage of participants				
number (not applicable)	56	62	54	54

End point values	TEV-48125 225 mg Monthly: New/Placebo Rollover EM Participants	TEV-48125 225 mg Monthly: Active Rollover EM Participants	TEV-48125 675mg Quarterly:New/Placebo Rollover EM Participants	TEV-48125 675 mg Quarterly: Active Rollover EM Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	124	174	138	174
Units: percentage of participants				
number (not applicable)	58	72	67	68

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 (Day 533)

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants
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Reporting group description:

Participants with CM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 225 mg Monthly: Active Rollover Participants
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Reporting group description:

Participants with CM who were randomized to the active treatment group (Fremanezumab 675/225 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC as loading dose (3 injections of fremanezumab 225 mg/1.5 mL on Day 0) followed by 11 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308). Participants with EM who were randomized to the active treatment group (Fremanezumab 225 mg) in the pivotal efficacy study, received 12 monthly SC doses of fremanezumab at 225 mg (1 injection of fremanezumab 225 mg/1.5 mL and 2 injections of placebo 1.5 mL on Days 0, 84, 168, and 252; and 1 injection of fremanezumab 225 mg/1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 675 mg Quarterly: Active Rollover Participants
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Reporting group description:

Participants with CM or EM who were randomized to the active treatment group (Fremanezumab 675 mg) in the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Reporting group title	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants
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Reporting group description:

Participants with CM or EM who were randomized to the placebo treatment group or participants who did not rollover from the pivotal efficacy study, received fremanezumab 675 mg SC once every 3 months for 12 months for a total of 4 doses (3 injections of fremanezumab 225 mg/1.5 mL on Days 0, 84, 168, and 252; and 1 injection of placebo 1.5 mL on Days 28, 56, 112, 140, 196, 224, 280, and 308).

Serious adverse events	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Total subjects affected by serious adverse events			

subjects affected / exposed	27 / 418 (6.46%)	29 / 526 (5.51%)	23 / 525 (4.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 418 (0.00%)	2 / 526 (0.38%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign breast neoplasm			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage III			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
High grade B-cell lymphoma Burkitt-like lymphoma			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			

subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phyllodes tumour			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Prostate cancer			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Thyroid cancer			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Hypertension			

subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Surgical and medical procedures			
Salpingo-oophorectomy			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Foetal death			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Premature baby			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Premature separation of placenta			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Ovarian cyst			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Ovarian cyst ruptured			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian mass			

subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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 haemorrhage			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Asthma			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Bronchospasm			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Pneumothorax			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Pulmonary embolism			

subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Pulmonary mass			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder with mixed disturbance of emotion and conduct			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Suicide attempt			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ammonia increased			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			

subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Fall			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Procedural pain			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular arteriovenous malformation			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital cyst			

subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital cystic disease of liver			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hereditary haemochromatosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Central nervous system lesion			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Cerebrovascular accident			

subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cluster headache			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Hypoaesthesia			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
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	0 / 418 (0.00%)	3 / 526 (0.57%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			

subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineurial cyst			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Primary progressive multiple sclerosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Sciatica			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Status migrainosus			
subjects affected / exposed	2 / 418 (0.48%)	1 / 526 (0.19%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Ear and labyrinth disorders			

Sudden hearing loss			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Retinal detachment			
subjects affected / exposed	1 / 418 (0.24%)	1 / 526 (0.19%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 418 (0.48%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Barrett's oesophagus			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Gastric ulcer			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ileal stenosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Hepatic cirrhosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Hepatitis alcoholic			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fibromyalgia			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 418 (0.24%)	1 / 526 (0.19%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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

Spinal column stenosis			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Spinal pain			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Synovial cyst			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Vertebral osteophyte			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	1 / 525 (0.19%)
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			
Abdominal abscess			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Appendicitis			
subjects affected / exposed	2 / 418 (0.48%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Petrositis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 526 (0.19%)	0 / 525 (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
Pneumonia			
subjects affected / exposed	1 / 418 (0.24%)	1 / 526 (0.19%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 418 (0.00%)	0 / 526 (0.00%)	0 / 525 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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
Hypoglycaemia			
subjects affected / exposed	1 / 418 (0.24%)	0 / 526 (0.00%)	0 / 525 (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

Serious adverse events	TEV-48125 675 mg Quarterly: New/Placebo Rollover Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 419 (8.59%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 419 (0.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Benign breast neoplasm			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer stage III			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
High grade B-cell lymphoma Burkitt-like lymphoma			

subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Phyllodes tumour			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superficial spreading melanoma stage unspecified			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic shock			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Salpingo-oophorectomy			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Foetal death			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premature baby			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premature separation of placenta			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic ovarian cyst			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst ruptured			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian mass			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine haemorrhage			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal oedema			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung consolidation			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Adjustment disorder with mixed disturbance of emotion and conduct			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			

subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Ammonia increased			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular arteriovenous malformation			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital cyst			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital cystic disease of liver			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hereditary haemochromatosis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Central nervous system lesion			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cluster headache			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Migraine			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			

subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nerve compression			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinson's disease			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parkinsonism			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perineurial cyst			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Primary progressive multiple sclerosis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Status migrainosus			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient global amnesia			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal tear			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Barrett's oesophagus			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileal stenosis			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			

subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cirrhosis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis alcoholic			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fibromyalgia			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal chest pain				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteochondrosis				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periarthritis				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Synovial cyst				
subjects affected / exposed	0 / 419 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebral osteophyte				

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis aseptic			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Petrositis			

subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	1 / 419 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 419 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 419 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	TEV-48125 225 mg Monthly: New/Placebo Rollover Participants	TEV-48125 225 mg Monthly: Active Rollover Participants	TEV-48125 675 mg Quarterly: Active Rollover Participants
Total subjects affected by non-serious adverse events			
subjects affected / exposed	300 / 418 (71.77%)	367 / 526 (69.77%)	329 / 525 (62.67%)
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	130 / 418 (31.10%) 430	144 / 526 (27.38%) 446	124 / 525 (23.62%) 386
Injection site haemorrhage subjects affected / exposed occurrences (all)	34 / 418 (8.13%) 43	38 / 526 (7.22%) 66	38 / 525 (7.24%) 62
Injection site induration subjects affected / exposed occurrences (all)	167 / 418 (39.95%) 717	174 / 526 (33.08%) 753	134 / 525 (25.52%) 666
Injection site pain subjects affected / exposed occurrences (all)	149 / 418 (35.65%) 980	156 / 526 (29.66%) 982	140 / 525 (26.67%) 811
Injection site pruritus subjects affected / exposed occurrences (all)	31 / 418 (7.42%) 101	43 / 526 (8.17%) 107	24 / 525 (4.57%) 64
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	24 / 418 (5.74%) 25	15 / 526 (2.85%) 16	24 / 525 (4.57%) 26
Influenza subjects affected / exposed occurrences (all)	14 / 418 (3.35%) 18	27 / 526 (5.13%) 29	25 / 525 (4.76%) 28
Nasopharyngitis subjects affected / exposed occurrences (all)	43 / 418 (10.29%) 61	69 / 526 (13.12%) 107	68 / 525 (12.95%) 108
Sinusitis subjects affected / exposed occurrences (all)	30 / 418 (7.18%) 40	27 / 526 (5.13%) 28	31 / 525 (5.90%) 38
Upper respiratory tract infection subjects affected / exposed occurrences (all)	55 / 418 (13.16%) 65	62 / 526 (11.79%) 76	63 / 525 (12.00%) 78
Urinary tract infection subjects affected / exposed occurrences (all)	25 / 418 (5.98%) 38	27 / 526 (5.13%) 43	33 / 525 (6.29%) 37

Non-serious adverse events	TEV-48125 675 mg Quarterly: New/Placebo		
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		Rollover Participants	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	284 / 419 (67.78%)		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	99 / 419 (23.63%)		
occurrences (all)	284		
Injection site haemorrhage			
subjects affected / exposed	21 / 419 (5.01%)		
occurrences (all)	38		
Injection site induration			
subjects affected / exposed	144 / 419 (34.37%)		
occurrences (all)	543		
Injection site pain			
subjects affected / exposed	135 / 419 (32.22%)		
occurrences (all)	981		
Injection site pruritus			
subjects affected / exposed	17 / 419 (4.06%)		
occurrences (all)	64		
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 419 (4.77%)		
occurrences (all)	22		
Influenza			
subjects affected / exposed	8 / 419 (1.91%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	37 / 419 (8.83%)		
occurrences (all)	58		
Sinusitis			
subjects affected / exposed	28 / 419 (6.68%)		
occurrences (all)	35		
Upper respiratory tract infection			
subjects affected / exposed	73 / 419 (17.42%)		
occurrences (all)	97		
Urinary tract infection			

subjects affected / exposed	26 / 419 (6.21%)		
occurrences (all)	29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	The following major procedural changes (not all-inclusive) were made to the protocol: - Incorporation of required revisions based on health authority input from the European Medicines Agency, Food and Drug Administration, and Pharmaceuticals and Medical Devices Agency; - Provision of clarifying language for the inclusion and exclusion criteria; - Clarification of allowed and disallowed preventive medications; - Revision of protocol-defined adverse events of special interest and to add clinical criteria for diagnosing anaphylaxis; - Update and/or clarification of versions of certain exploratory endpoints, including the EuroQol-5 Dimension (EQ-5D) (now EuroQol-5 Dimension, 5 response level version [EQ-5D-5L]) and Patient Global Impression of Change (PGIC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported