Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Followed by an Open-Label Extension to Evaluate the Efficacy and Safety of Fremanezumab for Preventive Treatment of Migraine in Patients with Major Depressive Disorder

Summary

EudraCT number	2019-001989-15
Trial protocol	DE CZ FR FI GR ES IT
Global end of trial date	31 August 2022

Results information

Result version number	v1 (current)
This version publication date	15 September 2023
First version publication date	15 September 2023

Trial information

Trial identification

Sponsor protocol code	TV48125-MH-40142

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04041284
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., MedInfo@tevaeu.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., MedInfo@tevaeu.com

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	31 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2022
Global end of trial reached?	Yes
Global end of trial date	31 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of monthly subcutaneous (SC) fremanezumab in adult participants with migraine and major depressive disorder (MDD).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 August 2019
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	Czechia: 62
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Greece: 50
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	Ukraine: 24
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	353
EEA total number of subjects	224

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	342
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 540 participants screened, 353 participants were enrolled/randomized. One participant was randomized to Placebo and received placebo in the double-blind (DB) period but was summarized in the Fremanezumab treatment group in all safety summaries due to an error in recording treatment.

Period 1

Period 1 title	DB Phase (12 Weeks)
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	Placebo

Arm description:

Participants received placebo matched to fremanezumab SC during the 12-week DB period and then continued into the open-label (OL) extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.

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

Dosage and administration details:

Placebo was administered per schedule specified in the arm description.

Arm title	Fremanezumab

Arm description:

Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period and then continued into the OL extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125, LBR-101, PF-04427429, RN307
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Fremanezumab
Started	178	175
DB modified intent-to-treat (mITT) set	178	175
Completed	166	164
Not completed	12	11
Consent withdrawn by subject	6	4
Adverse event, non-fatal	-	3
Protocol deviation	3	3
Other than specified	1	-
Lost to follow-up	1	-
Lack of efficacy	1	1

Period 2

Period 2 title	OL Phase (12 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to fremanezumab subcutaneously (SC) during the 12-week double blind (DB) period and then continued into the open-label (OL) extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.

Arm type	Placebo
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125, LBR-101, PF-04427429, RN307
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Arm title	Fremanezumab

Arm description:

Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period and then continued into the OL extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.

Arm type	Experimental
Investigational medicinal product name	Fremanezumab
Investigational medicinal product code	TEV-48125, LBR-101, PF-04427429, RN307
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Number of subjects in period 2	Placebo	Fremanezumab
Started	166	164
OL mITT analysis set	165	161
Completed	154	155
Not completed	12	9
Consent withdrawn by subject	5	5
Protocol deviation	-	1
Pregnancy	1	1
Other than specified	6	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to fremanezumab SC during the 12-week DB period and then continued into the open-label (OL) extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	
Reporting group title	Fremanezumab
Reporting group description:	
Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period and then continued into the OL extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	

Reporting group values	Placebo	Fremanezumab	Total
Number of subjects	178	175	353
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	42.3	43.5	
standard deviation	± 12.64	± 11.94	-
Sex: Female, Male Units: participants			
Female	156	154	310
Male	22	21	43
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	4	8
White	172	170	342
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	5	11
Not Hispanic or Latino	171	170	341
Unknown or Not Reported	1	0	1
Number of migraine days			
A migraine day was defined as when at least 1 of following occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura; demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine (where only 1 migraine criterion was missing); demonstrating a headache of any duration that was treated with migraine-specific medications; and a calendar day that was immediately consecutive of any day fulfilling the 3 criteria above, where participants report headache of any duration.			
Units: days			
arithmetic mean	14.4	15.1	

standard deviation	± 6.15	± 6.41	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to fremanezumab SC during the 12-week DB period and then continued into the open-label (OL) extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	
Reporting group title	Fremanezumab
Reporting group description:	
Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period and then continued into the OL extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to fremanezumab subcutaneously (SC) during the 12-week double blind (DB) period and then continued into the open-label (OL) extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	
Reporting group title	Fremanezumab
Reporting group description:	
Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period and then continued into the OL extension period in which all participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	
Subject analysis set title	Double-blind Phase: Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received placebo matched to fremanezumab SC during the 12-week DB period.	
Subject analysis set title	Double-blind Phase: Fremanezumab
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period.	
Subject analysis set title	Double-blind Phase: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo matched to fremanezumab SC during the 12-week DB period.	
Subject analysis set title	Double-blind Phase: Fremanezumab
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period.	
Subject analysis set title	Open-label Phase: Placebo/Fremanezumab Dose 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	
Subject analysis set title	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.	

Primary: Change from Baseline in Monthly Average Number of Migraine Days During the 12-Week DB Treatment Phase After the First Dose of Study Drug

End point title	Change from Baseline in Monthly Average Number of Migraine Days During the 12-Week DB Treatment Phase After the First Dose of Study Drug

End point description:

A migraine day was defined as when at least 1 of following occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of headache meeting criteria for migraine with or without aura; at least 4 consecutive hours of headache meeting criteria for probable migraine (1 migraine criterion missing); a headache of any duration that was treated with migraine-specific medications; and a calendar day that was immediately consecutive of any day fulfilling 3 criteria above, where participants report headache of any duration. Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over 12-week/number of days with assessments recorded in e-diary for 12-week)*28. Least square (LS) mean was calculated using analysis of covariance (ANCOVA). DB mITT analysis set: all randomized participants who received at least 1 dose of study drug and had at least 10 days of postrandomization efficacy assessment on primary endpoint.

End point type	Primary

End point timeframe:

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

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	175		
Units: days				
least squares mean (standard error)	-2.9 (± 0.49)	-5.1 (± 0.50)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Phase: Fremanezumab v Double-blind Phase: Placebo
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	-1.21
Variability estimate	Standard error of the mean
Dispersion value	0.5

Secondary: Number of Participants With ≥50% Reduction in Monthly Average Number of Migraine Days During the 12 Weeks After the First Dose of Study Drug

End point title	Number of Participants With ≥50% Reduction in Monthly Average Number of Migraine Days During the 12 Weeks After the First Dose of Study Drug

End point description:

A migraine day was defined as when at least 1 of following occurred: A calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of headache meeting criteria for migraine with or without aura; at least 4 consecutive hours of headache meeting criteria for probable migraine (1 migraine criterion missing); a headache of any duration that was treated with migraine-specific medications; and a calendar day that was immediately consecutive of any day fulfilling 3 criteria above, where participants report headache of any duration. Monthly averages were derived and normalized to 28 days equivalent by formula: (number of days of efficacy variable over 12-week/number of days with assessments recorded in e-diary for 12-week)*28. DB mITT analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postrandomization efficacy assessment on the primary endpoint.

End point type	Secondary

End point timeframe:

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

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	175		
Units: participants	24	57		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.89
upper limit	5.62

Secondary: Change from Baseline in Hamilton Depression Rating Scale-17 (HAM-D 17) Items Total Score at Week 8

End point title	Change from Baseline in Hamilton Depression Rating Scale-17

	(HAM-D 17) Items Total Score at Week 8

End point description:

HAM-D 17 is a list of 17 items used to determine participant's level of depression. HAM-D total score comprises a sum of 17 individual item scores. 8 items scored in a range of 0 (none/absent) to 2 (severe symptom) include: Insomnia (early, middle, late), somatic symptoms (gastrointestinal and general), genital symptoms, loss of weight, and insight. The following 9 items are scored in a range of 0 (none/absent) to 4 (severe symptom): Agitation, depressed mood, feelings of guilt, suicide, work and activities, retardation, anxiety (psychic and somatic), and hypochondriasis. HAM-D17 total score is calculated as the sum of 17 individual symptom scores; total score can range from 0 to 52. Higher scores indicate more severe depression. LS mean was calculated using mixed-effects model for repeated measures (MMRM). DB mITT analysis set: all randomized participants who received at least 1 dose of study drug and had at least 10 days of postrandomization efficacy assessment on primary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	175		
Units: units on a scale				
least squares mean (standard error)	-4.6 (± 0.54)	-6.0 (± 0.55)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0205
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.61

Secondary: Change from Baseline in Migraine-Specific Quality of Life (MSQoL) Questionnaire Role Function-Restrictive and Role Function-Preventive Domain Scores at Week 12

End point title	Change from Baseline in Migraine-Specific Quality of Life

	(MSQoL) Questionnaire Role Function-Restrictive and Role Function-Preventive Domain Scores at Week 12

End point description:

MSQoL v2.1 is a 14-item questionnaire. Each item is scored on a 6-point scale: 1=none of the time to 6=all of the time. MSQoL measures the degree to which performance of normal activities is limited by migraine (Role Function-Restrictive domain comprising 7 items; score range 7 to 42), the degree to which performance of normal activities is prevented by migraine (Role Function-Preventive domain comprising 4 items; score range 4 to 24), and emotional effects of migraine (Emotional Function domain comprising 3 items; score range 3 to 18). Total raw scores for each domain is the sum of final item value for all of the items in that domain. Total raw score for each domain are transformed to a 0-100 scale with higher scores indicating a better health-related quality of life. LS mean was calculated using MMRM. DB mITT analysis set: all randomized participants who received at least 1 dose of study drug and had at least 10 days of postrandomization efficacy assessment on primary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	175		
Units: units on a scale				
least squares mean (standard error)				
Restrictive score	15.9 (± 2.00)	27.2 (± 2.04)		
Preventive score	12.3 (± 1.95)	22.2 (± 2.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restrictive score: Fremanezumab versus placebo

Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.91
upper limit	15.59
Variability estimate	Standard error of the mean
Dispersion value	2.21

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Preventive score: Fremanezumab versus placebo	
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.73
upper limit	14.08
Variability estimate	Standard error of the mean
Dispersion value	2.12

Secondary: Change From Baseline in Clinical Global Impression – Severity (CGI-S) Scale Score at Weeks 4, 8, and 12

End point title	Change From Baseline in Clinical Global Impression – Severity (CGI-S) Scale Score at Weeks 4, 8, and 12
End point description: The CGI-S is a short questionnaire filled out by the investigator that rates a participant's mental health from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). DB mITT analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postrandomization efficacy assessment on the primary endpoint.	
End point type	Secondary
End point timeframe: Baseline, Weeks 4, 8, and 12	

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	175		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4	-0.4 (± 0.10)	-0.6 (± 0.10)		
Change at Week 8	-0.6 (± 0.10)	-0.1 (± 0.10)		
Change at Week 12	-0.8 (± 0.10)	-1.1 (± 0.10)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change at Week 4: Fremanezumab versus Placebo	
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0915
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change at Week 8: Fremanezumab versus Placebo	
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change at Week 12: Fremanezumab versus Placebo	
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Change From Baseline in 6-Item Headache Impact Test (HIT-6) Disability Score at Week 12

End point title	Change From Baseline in 6-Item Headache Impact Test (HIT-6) Disability Score at Week 12

End point description:

Migraine related disability was assessed using the HIT-6. The questionnaire measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It also assesses headache severity. Each question was answered on the scale ranging with the following response options: 6 points (never), 8 points (rarely), 10 points (sometimes), 11 points (very often), and 13 points (always). The total score was obtained from summation of the 6 question points. The HIT-6 total score ranges between 36 and 78, with higher scores reflecting greater impact. DB mITT analysis set included all randomized participants who received at least 1 dose of study drug and had at least 10 days of postrandomization efficacy assessment on the primary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	175		
Units: units on a scale				
least squares mean (standard error)	-5.2 (± 0.71)	-8.8 (± 0.73)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Phase: Placebo v Double-blind Phase: Fremanezumab
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.15
upper limit	-1.96
Variability estimate	Standard error of the mean
Dispersion value	0.81

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious AEs (SAEs) 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. AEs were considered TEAEs if onset occurred on or after the first dose date. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who received at least 1 of dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	165	165
Units: participants	48	70	31	29

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Potentially Clinically Significant Abnormal Vital Signs Values

End point description:

Criteria for potentially clinically significant vital signs values: Pulse: ≥120 beats per minute (bpm) and increase from baseline of ≥15 bpm or ≤50 bpm and decrease from baseline of ≥15 bpm; Systolic blood pressure (SBP): ≥180 millimeters of mercury (mmHg) and increase from baseline of ≥20 mmHg or ≤90 mmHg and decrease from baseline of ≥20 mmHg; Diastolic blood pressure (DBP): ≥105 mmHg and increase from baseline of ≥15 mmHg or ≤50 mmHg and decrease from baseline of ≥15 mmHg; Respiratory rate: <10 breaths per minute; and Body temperature: ≥38.3 degrees celsius (ºC) and change from baseline of ≥1.1ºC. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who received at least 1 of dose of study drug during the OL treatment period. Here, 'overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	174	173	162	164
Units: participants	0	5	2	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Abnormal Physical Examination Findings

End point title	Number of Participants With Clinically Significant Abnormal

	Physical Examination Findings

End point description:

Physical examination included height, weight, general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Clinical significance was per investigator's discretion. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who received at least 1 of dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	165	165
Units: participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Drug Hypersensitivity and Seasonal Allergy

End point title	Number of Participants With Drug Hypersensitivity and Seasonal Allergy

End point description:

DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who received at least 1 of dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	165	165
Units: participants				
Drug hypersensitivity	0	1	0	0
Seasonal allergy	1	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Used Concomitant Medication

End point title	Number of Participants who Used Concomitant Medication

End point description:

Concomitant medications included agents acting on the renin-angiotensin system, analgesics, antibacterials for systemic use, antihistamines for systemic use, anti-inflammatory and antirheumatic products, beta-blocking agents, drugs for acid related disorder, lipid modifying agents, mineral supplement, other gynecologicals, psychoanaleptics, psycholeptics, sex hormones and modulators of the genital system, thyroid therapy, vaccines, and vitamins. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who received at least 1 of dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	165	165
Units: participants	173	173	160	163

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Used Concomitant Medication for Migraine/Headache

End point title	Number of Participants who Used Concomitant Medication for Migraine/Headache

End point description:

Concomitant medications for migraine/headache included analgesics, antiepileptics, muscle relaxants, anti-inflammatory and antirheumatic products, agents acting on the renin-angiotensin system, anesthetics, antianemic preparations, antibacterials for systemic use, antihistamines for systemic use, beta-blocking agents, lipid modifying agents, mineral supplement, other gynecologicals, psychoanaleptics, psycholeptics, sex hormones and modulators of the genital system, thyroid therapy, vaccines, vitamins etc. DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who

received at least 1 of dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	165	165
Units: participants	170	169	156	160

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Did Not Complete the Study Due to AE

End point title	Number of Participants who Did Not Complete the Study Due to AE

End point description:

DB safety analysis set included all randomized participants who received at least 1 dose of study drug during the DB treatment period. OL safety analysis set included all participants who received at least 1 of dose of study drug during the OL treatment period.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	165	165
Units: participants	0	3	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Any Suicidal Ideation or Suicidal

Behavior According to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants Reporting Any Suicidal Ideation or Suicidal Behavior According to the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

C-SSRS included responses for Suicidal Ideation/Behavior: 1 = Wish to be dead; 2 = Non-specific active suicidal thoughts; 3 = Active suicidal ideation with any methods without intent to act; 4 = Active suicidal ideation with some intent to act, without specific plan; 5 = Active suicidal ideation with specific plan and intent; 6 = Preparatory acts; 7 = Aborted attempt; 8 = Interrupted attempt; 9 = Non-fatal suicide attempt; and 10 = Completed suicide. Number of participants with any suicidal ideation/behavior are reported. Any Suicidal ideation/Behavior events reported as TEAEs are included in AE module. DB safety analysis set: all randomized participants who received at least 1 dose of study drug during DB treatment period. 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint of the respective phase of study. '99999' = data not applicable since no participants were evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, and 24

End point values	Double-blind Phase: Placebo	Double-blind Phase: Fremanezumab	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	177	176	153	155
Units: participants				
Baseline: Incomplete (n=177,176,0,0)	0	0	99999	99999
Baseline: Negative (n=177,176,0,0)	177	176	99999	99999
Baseline: Positive (n=177,176,0,0)	0	0	99999	99999
Week 4: Incomplete (n=169,169,0,0)	1	0	99999	99999
Week 4: Negative (n=169,169,0,0)	168	168	99999	99999
Week 4: Positive (n=169,169,0,0)	0	1	99999	99999
Week 8: Incomplete (n=170,164,0,0)	0	0	99999	99999
Week 8: Negative (n=170,164,0,0)	170	164	99999	99999
Week 8: Positive (n=170,164,0,0)	0	0	99999	99999
Week 12: Incomplete (n=165,163,0,0)	0	0	99999	99999
Week 12: Negative (n=165,163,0,0)	165	163	99999	99999
Week 12: Positive (n=165,163,0,0)	0	0	99999	99999
Week 24: Incomplete (n=0,0,153,155)	99999	99999	0	0
Week 24: Negative (n=0,0,153,155)	99999	99999	152	153
Week 24: Positive (n=0,0,153,155)	99999	99999	1	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Baseline up to Week 24

Adverse event reporting additional description:

DB safety analysis set and OL safety analysis set (all randomized participants who received at least 1 dose of study drug during the DB period and the OL period).
One participant was randomized to Placebo and received placebo in DB period but was summarized in the Fremanezumab group in all safety summaries due to an error in recording treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Double-blind Phase: Placebo

Reporting group description:

Participants received placebo matched to fremanezumab SC during the 12-week DB period.

Reporting group title	Open-label Phase: Placebo/Fremanezumab Dose 2

Reporting group description:

Participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.

Reporting group title	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2

Reporting group description:

Participants received a single quarterly dose of fremanezumab Dose 2 SC on Day 85.

Reporting group title	Double-blind Phase: Fremanezumab

Reporting group description:

Participants received monthly doses of fremanezumab Dose 1 SC during the 12-week DB period.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious AEs were reported in this study.

Serious adverse events	Double-blind Phase: Placebo	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 177 (0.56%)	3 / 165 (1.82%)	1 / 165 (0.61%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 177 (0.00%)	0 / 165 (0.00%)	0 / 165 (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
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	0 / 177 (0.00%)	1 / 165 (0.61%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 165 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 177 (0.00%)	1 / 165 (0.61%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 177 (0.00%)	0 / 165 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 165 (0.61%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 177 (0.00%)	0 / 165 (0.00%)	0 / 165 (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

Serious adverse events	Double-blind Phase: Fremanezumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 176 (1.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 176 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 176 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 176 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 176 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 176 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 176 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 176 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-blind Phase: Placebo	Open-label Phase: Placebo/Fremanezumab Dose 2	Open-label Phase: Fremanezumab Dose 1/Fremanezumab Dose 2
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 177 (0.00%)	0 / 165 (0.00%)	0 / 165 (0.00%)

Non-serious adverse events	Double-blind Phase: Fremanezumab		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 176 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2019	The following major procedural changes (not all-inclusive) were made to the protocol: • The primary reason for this amendment was to specify that the suicidality assessment to be used was the eC-SSRS in conjunction with the clinical judgment of a qualified psychiatrist.
10 October 2019	The following major procedural changes (not all-inclusive) were made to the protocol: • The primary reason for this amendment was to update the protocol based on feedback received from the Voluntary Harmonisation Procedure.
04 November 2019	The following major procedural changes (not all-inclusive) were made to the protocol: • The primary reasons for this amendment were to update the protocol to allow a qualified staff member to complete the HAM-A and HAM-D 17 assessments and to allow a qualified clinician’s judgment to be used in conjunction with the eC-SSRS instead of a psychiatrist.
04 May 2020	The following major procedural changes (not all-inclusive) were made to the protocol: • The primary reason for this amendment was to revise an exclusion criterion to exclude participants with a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome and to allow rescreening of participants once. • Coronavirus 2019 (COVID-19) pandemic-related operational updates were added to the study as a new appendix.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported