Clinical trial results:
A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache

Summary

EudraCT number	2018-003342-16
Trial protocol	CZ ES PL PT FI HU GB AT IT
Global end of trial date	23 June 2023

Results information

Result version number	v1 (current)
This version publication date	09 March 2024
First version publication date	09 March 2024

Trial information

Trial identification

Sponsor protocol code	20170703

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03971071
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	13 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to evaluate the effect of erenumab compared with placebo on achieving medication overuse headache (MOH) remission during the double-blind treatment period (DBTP).

Protection of trial subjects:

The study was conducted in accordance with International Council for Harmonisation Good Clinical Practice regulations/guidelines. All participants provided written informed consent before undergoing any study-related procedures, including screening procedures. The study protocol, and all amendments, the informed consent form and any accompanying materials provided to the participants were reviewed and approved by the Institutional Review Boards or Independent Ethics Committee at each study center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 October 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	United States: 47
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Czechia: 121
Country: Number of subjects enrolled	Finland: 33
Country: Number of subjects enrolled	France: 105
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Poland: 88
Country: Number of subjects enrolled	Portugal: 46
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	620
EEA total number of subjects	566

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)	598
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 67 study centers in North America, Europe, and Australia, and participated from 07 October 2019 to 13 June 2023.

Pre-assignment

Screening details:

Adults with chronic migraine and medication overuse headaches according to the International Classification of Headache Disorders 3rd Edition criteria were randomized 1:1:1 to receive erenumab 70 mg or 140 mg or matching placebo. Prior to enrollment and randomization, participants completed a 4-week baseline period to evaluate eligibility.

Period 1

Period 1 title	Double-blind Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (DBTP)

Arm description:

Participants were randomized to receive matching placebo subcutaneously (SC) every 4 weeks (QM) for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to the optional OLTP and were randomized 1:1 to receive erenumab 70 mg or 140 mg SC QM in the OLTP for up to 28 weeks.

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:

Matching placebo was administered SC QM for 24 weeks in the DBTP.

Arm title	Erenumab 70 mg (DBTP)

Arm description:

Participants were randomized to receive 1 mL of erenumab 70 mg/mL SC QM for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to receive erenumab 70 mg in the optional OLTP for up to 28 weeks.

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

Dosage and administration details:

Erenumab was administered SC QM for 24 weeks in the DBTP.

Arm title	Erenumab 140 mg (DBTP)

Arm description:

Participants were randomized to receive 1 mL of erenumab 140 mg/mL SC QM for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to receive erenumab 140 mg in

the optional OLTP for up to 28 weeks.

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

Dosage and administration details:

Erenumab was administered SC QM for 24 weeks in the DBTP.

Number of subjects in period 1	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (DBTP)
Started	206	207	207
Opioid-treated: > 4 days/month	12 [1]	12 [2]	12 [3]
Nonopioid-treated: ≤ 4 days/month	194 [4]	195	195 [5]
Completed	197	193	201
Not completed	9	14	6
Consent withdrawn by subject	7	11	6
Not specified	2	2	-
Sponsor decision	-	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents the opioid-treated cohort and included participants with > 4 days/ month of opioid medication use during the baseline period, and is included for purposes of exploratory analyses only.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents the opioid-treated cohort and included participants with > 4 days/ month of opioid medication use during the baseline period, and is included for purposes of exploratory analyses only.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents the opioid-treated cohort and included participants with > 4 days/ month of opioid medication use during the baseline period, and is included for purposes of exploratory analyses only.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents the nonopioid-treated cohort and included participants with ≤ 4 days/ month of opioid medication use during the baseline period.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents the nonopioid-treated cohort and included participants with ≤ 4 days/ month of opioid medication use during the baseline period.

Period 2

Period 2 title	Open-label Treatment Period (OLTP)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Erenumab 70 mg (OLTP)

Arm description:

Eligible participants continued to the Open-label Treatment Period (OLTP) and received erenumab 70 mg SC QM for 28 weeks (up to Week 52).
Eligible participants included participants randomized to erenumab 70 mg in the DBTP and participants randomized to placebo in the DBTP, re-randomized to erenumab 70 mg in the OLTP.

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

Dosage and administration details:

Erenumab was administered SC QM for 28 weeks in the OLTP.

Arm title	Erenumab 140 mg (OLTP)

Arm description:

Eligible participants continued to the OLTP and received erenumab 140 mg SC QM for 28 weeks (up to Week 52).
Eligible participants included participants randomized to erenumab 140 mg in the DBTP and participants randomized to placebo in the DBTP, re-randomized to erenumab 140 mg in the OLTP.

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

Dosage and administration details:

Erenumab was administered SC QM for 28 weeks in the OLTP.

Number of subjects in period 2[6]	Erenumab 70 mg (OLTP)	Erenumab 140 mg (OLTP)
Started	291	296
Completed	281	281
Not completed	10	15
Consent withdrawn by subject	10	13
Sponsor decision	-	1
Lost to follow-up	-	1

Notes:

[6] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The number of participants starting the OLTP included eligible participants who completed the DBTP, and not all participants proceeded to the optional OLTP.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (DBTP)
Reporting group description:	
Participants were randomized to receive matching placebo subcutaneously (SC) every 4 weeks (QM) for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to the optional OLTP and were randomized 1:1 to receive erenumab 70 mg or 140 mg SC QM in the OLTP for up to 28 weeks.	
Reporting group title	Erenumab 70 mg (DBTP)
Reporting group description:	
Participants were randomized to receive 1 mL of erenumab 70 mg/mL SC QM for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to receive erenumab 70 mg in the optional OLTP for up to 28 weeks.	
Reporting group title	Erenumab 140 mg (DBTP)
Reporting group description:	
Participants were randomized to receive 1 mL of erenumab 140 mg/mL SC QM for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to receive erenumab 140 mg in the optional OLTP for up to 28 weeks.	

Reporting group values	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (DBTP)
Number of subjects	206	207	207
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	200	201	197
From 65-84 years	6	6	10
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	44.3	43.1	43.5
standard deviation	± 12.5	± 11.6	± 12.2
Gender Categorical Units: Subjects			
Female	166	170	174
Male	40	37	33
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	4	2
White	196	187	187
More than one race	0	0	0

Unknown or Not Reported	6	15	17
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	10	13
Not Hispanic or Latino	196	197	194
Unknown or Not Reported	1	0	0

Reporting group values	Total		
Number of subjects	620		
Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	598		
From 65-84 years	22		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	510		
Male	110		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	570		
More than one race	0		
Unknown or Not Reported	38		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	32		
Not Hispanic or Latino	587		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	Placebo (DBTP)
Reporting group description:	
Participants were randomized to receive matching placebo subcutaneously (SC) every 4 weeks (QM) for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to the optional OLTP and were randomized 1:1 to receive erenumab 70 mg or 140 mg SC QM in the OLTP for up to 28 weeks.	
Reporting group title	Erenumab 70 mg (DBTP)
Reporting group description:	
Participants were randomized to receive 1 mL of erenumab 70 mg/mL SC QM for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to receive erenumab 70 mg in the optional OLTP for up to 28 weeks.	
Reporting group title	Erenumab 140 mg (DBTP)
Reporting group description:	
Participants were randomized to receive 1 mL of erenumab 140 mg/mL SC QM for 24 weeks in the DBTP. Participants who successfully completed the DBTP could continue to receive erenumab 140 mg in the optional OLTP for up to 28 weeks.	
Reporting group title	Erenumab 70 mg (OLTP)
Reporting group description:	
Eligible participants continued to the Open-label Treatment Period (OLTP) and received erenumab 70 mg SC QM for 28 weeks (up to Week 52). Eligible participants included participants randomized to erenumab 70 mg in the DBTP and participants randomized to placebo in the DBTP, re-randomized to erenumab 70 mg in the OLTP.	
Reporting group title	Erenumab 140 mg (OLTP)
Reporting group description:	
Eligible participants continued to the OLTP and received erenumab 140 mg SC QM for 28 weeks (up to Week 52). Eligible participants included participants randomized to erenumab 140 mg in the DBTP and participants randomized to placebo in the DBTP, re-randomized to erenumab 140 mg in the OLTP.	

Primary: Number of Participants with Absence of Medication Overuse Headaches at Month 6

End point title	Number of Participants with Absence of Medication Overuse Headaches at Month 6
End point description:	
Absence of medication overuse headaches at month 6 was defined as mean monthly acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 (weeks 13 through 24) or mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 (weeks 13 through 24) of the DBTP where an AHMD was defined as a calendar day in which the participant takes at least 1 acute headache medication. Efficacy analysis set (nonopioid-treated cohort): randomized participants with an opioid medication use of ≤ 4 days per month during the baseline period and who received at least 1 dose of IP during DBTP.	
End point type	Primary
End point timeframe:	
Months 4, 5, and 6 (weeks 13 through 24) of the DBTP	

End point values	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (DBTP)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194	194	194	
Units: participants	102	117	134	

Statistical analyses

Statistical analysis title	Erenumab 140 mg versus Placebo

Statistical analysis description:

Common odds ratio and p-value were obtained from a Cochran-Mantel-Haenszel test, stratified by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No).

Comparison groups	Placebo (DBTP) v Erenumab 140 mg (DBTP)
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	3.05

Statistical analysis title	Erenumab 70 mg versus Placebo

Statistical analysis description:

Common odds ratio and p-value were obtained from a Cochran-Mantel-Haenszel test, stratified by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No).

Comparison groups	Placebo (DBTP) v Erenumab 70 mg (DBTP)
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Odds Ratio
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.05

Secondary: Change from Baseline in Mean Monthly AHMDs Over Months 4, 5, and 6

End point title	Change from Baseline in Mean Monthly AHMDs Over Months 4, 5, and 6

End point description:

An AHMD was defined as a calendar day in which the participant takes at least 1 acute headache medication. Acute headache medications included triptan-based, ergotamine-based and ditan-based migraine medications, non-opioid and opioid-containing acute headache medications, non-opioid butalbital and opioid-containing butalbital containing medications.
Efficacy analysis set (nonopioid-treated cohort): randomized participants with an opioid medication use of ≤ 4 days per month during the baseline period and who received at least 1 dose of IP during DBTP. Participants with evaluable data from weeks 13 through 24 are included.

End point type	Secondary

End point timeframe:

Baseline and months 4, 5, and 6 (weeks 13 through 24) of the DBTP

End point values	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (DBTP)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194	193	194	
Units: days per month				
least squares mean (standard error)	-6.61 (± 0.41)	-7.83 (± 0.41)	-9.35 (± 0.41)	

Statistical analyses

Statistical analysis title	Erenumab 70 mg versus Placebo

Statistical analysis description:

Covariates: treatment, visit, treatment-by-visit, concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), and baseline value.

Comparison groups	Placebo (DBTP) v Erenumab 70 mg (DBTP)
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 [1]
Method	Linear Mixed Model
Parameter estimate	Least squares mean difference
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	-0.1

Notes:

[1] - Nominal p-value is presented without multiplicity adjustment.

Statistical analysis title	Erenumab 140 mg versus Placebo

Statistical analysis description:

Covariates: treatment, visit, treatment-by-visit, concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), and baseline value.

Comparison groups	Placebo (DBTP) v Erenumab 140 mg (DBTP)
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Linear Mixed Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.87
upper limit	-1.62

Notes:

[2] - Nominal p-value is presented without multiplicity adjustment.

Secondary: Change from Baseline in Mean Headache Impact Test 6 (HIT-6) Score Over Months 4, 5, and 6

End point title	Change from Baseline in Mean Headache Impact Test 6 (HIT-6) Score Over Months 4, 5, and 6

End point description:

The HIT-6 is a 6-item short-form self-administered questionnaire to assess headache severity in the previous month, with a total score ranging from 36 to 78, with higher scores representing greater impact of headache, i.e., higher burden.

Efficacy analysis set (nonopioid-treated cohort): randomized participants with an opioid medication use of ≤ 4 days per month during the baseline period and who received at least 1 dose of IP during DBTP. Participants with evaluable data from weeks 13 through 24 are included.

End point type	Secondary

End point timeframe:

Baseline and months 4, 5, and 6 (weeks 13 through 24) of the DBTP

End point values	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (DBTP)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	189	188	
Units: score on a scale				
least squares mean (standard error)	-5.02 (± 0.49)	-6.18 (± 0.48)	-8.82 (± 0.48)	

Statistical analyses

Statistical analysis title	Erenumab 140 mg versus Placebo

Statistical analysis description:

Covariates: treatment, visit, treatment-by-visit, concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), and baseline value.

Comparison groups	Placebo (DBTP) v Erenumab 140 mg (DBTP)

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Linear Mixed Model
Parameter estimate	Least squares mean difference
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.12
upper limit	-2.47

Notes:

[3] - Nominal p-value is presented without multiplicity adjustment.

Statistical analysis title	Erenumab 70 mg versus Placebo

Statistical analysis description:

Covariates: treatment, visit, treatment-by-visit, concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), and baseline value.

Comparison groups	Placebo (DBTP) v Erenumab 70 mg (DBTP)
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086 [4]
Method	Linear Mixed Model
Parameter estimate	Least squares mean difference
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	0.17

Notes:

[4] - Nominal p-value is presented without multiplicity adjustment.

Secondary: Number of Participants with Sustained MOH Remission at Month 6

End point title	Number of Participants with Sustained MOH Remission at Month 6

End point description:

Sustained MOH remission was defined as the absence of MOH at month 3 (week 12) and month 6 (week 24) of the DBTP. Absence of MOH was achieved when mean monthly AHMD < 10 days or mean monthly headache days < 14 days over the 3-month period (weeks 12 to 24).
Efficacy analysis set (nonopioid-treated cohort): randomized participants with an opioid medication use of ≤ 4 days per month during the baseline period and who received at least 1 dose of IP during DBTP.

End point type	Secondary

End point timeframe:

Month 3 (week 12) to month 6 (week 24) of the DBTP

End point values	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (DBTP)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194	194	194	
Units: participants	73	96	119	

Statistical analyses

Statistical analysis title	Erenumab 140 mg versus Placebo

Statistical analysis description:

Common odds ratio and p-value were obtained from a Cochran-Mantel-Haenszel test, stratified by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No).

Comparison groups	Placebo (DBTP) v Erenumab 140 mg (DBTP)
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common odds ratio
Point estimate	2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	3.96

Statistical analysis title	Erenumab 70 mg versus Placebo

Statistical analysis description:

Common odds ratio and p-value were obtained from a Cochran-Mantel-Haenszel test, stratified by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No).

Comparison groups	Placebo (DBTP) v Erenumab 70 mg (DBTP)
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common odds ratio
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.43

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:

TEAEs were defined as any adverse event (AE) that started on or after first dose of IP, and up to the end of the study (52 weeks).
Any clinically significant changes in vital signs were included as TEAEs.
Safety analysis set: randomized participants who received at least 1 dose of IP.

End point type	Secondary

End point timeframe:

Day 1 to Week 24 (DBTP) and Week 25 to 52 weeks (OLTP)

End point values	Placebo (DBTP)	Erenumab 70 mg (OLTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (OLTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	206	291	206	296
Units: participants	130	178	139	182

End point values	Erenumab 140 mg (DBTP)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: participants	142			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 24 (DBTP) and Week 25 to 52 weeks (OLTP).

Adverse event reporting additional description:

Deaths, serious AEs and other AEs are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo (DBTP)

Reporting group description:

Participants were randomized to receive matching placebo SC QM for 24 weeks in the DBTP.

Reporting group title	Erenumab 70 mg (DBTP)

Reporting group description:

Participants were randomized to receive 1 mL of erenumab 70 mg/mL SC QM for 24 weeks in the DBTP.

Reporting group title	Erenumab 140 mg (OLTP)

Reporting group description:

Eligible participants continued to the OLTP and received erenumab 140 mg SC QM for 28 weeks (up to Week 52).
Eligible participants included participants randomized to erenumab 140 mg in the DBTP and participants randomized to placebo in the DBTP, re-randomized to erenumab 140 mg in the OLTP.

Reporting group title	Erenumab 70 mg (OLTP)

Reporting group description:

Eligible participants continued to the OLTP and received erenumab 70 mg SC QM for 28 weeks (up to Week 52).
Eligible participants included participants randomized to erenumab 70 mg in the DBTP and participants randomized to placebo in the DBTP, re-randomized to erenumab 70 mg in the OLTP.

Reporting group title	Erenumab 140 mg (DBTP)

Reporting group description:

Participants were randomized to receive 1 mL of erenumab 140 mg/mL SC QM for 24 weeks in the DBTP.

Serious adverse events	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (OLTP)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 206 (3.88%)	3 / 206 (1.46%)	12 / 296 (4.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine carcinoma metastatic			

subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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 I			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
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			
Endometrial hyperplasia			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Multiple fractures			

subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
Head injury			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
Contusion			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
Ventricular arrhythmia			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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
Migraine			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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
Gastrointestinal disorders			
Volvulus			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal prolapse			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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			
Cholelithiasis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 296 (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
Sphincter of Oddi dysfunction			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 296 (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
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
Musculoskeletal and connective tissue disorders			
Periarthritis			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
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			
Appendicitis			

subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
COVID-19 pneumonia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	2 / 296 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 296 (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
Periorbital cellulitis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
Mastoiditis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (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
Embolic pneumonia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			

subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Erenumab 70 mg (OLTP)	Erenumab 140 mg (DBTP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 291 (2.06%)	3 / 206 (1.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	0 / 291 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 291 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage I			
subjects affected / exposed	1 / 291 (0.34%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			

subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Multiple fractures			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 291 (0.34%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 291 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Migraine			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 291 (0.34%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Volvulus			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal prolapse			
subjects affected / exposed	1 / 291 (0.34%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sphincter of Oddi dysfunction			
subjects affected / exposed	1 / 291 (0.34%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Periarthritis			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic pneumonia			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sinusitis			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 291 (0.00%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo (DBTP)	Erenumab 70 mg (DBTP)	Erenumab 140 mg (OLTP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 206 (14.08%)	67 / 206 (32.52%)	75 / 296 (25.34%)
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 206 (4.37%)	31 / 206 (15.05%)	24 / 296 (8.11%)
occurrences (all)	14	36	26
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 206 (1.94%)	8 / 206 (3.88%)	3 / 296 (1.01%)
occurrences (all)	4	8	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 206 (1.94%)	12 / 206 (5.83%)	14 / 296 (4.73%)
occurrences (all)	6	14	16
COVID-19			
subjects affected / exposed	14 / 206 (6.80%)	25 / 206 (12.14%)	39 / 296 (13.18%)
occurrences (all)	14	26	41

Non-serious adverse events	Erenumab 70 mg (OLTP)	Erenumab 140 mg (DBTP)	

Total subjects affected by non-serious adverse events subjects affected / exposed	65 / 291 (22.34%)	72 / 206 (34.95%)	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	22 / 291 (7.56%) 22	34 / 206 (16.50%) 35	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 291 (0.34%) 1	12 / 206 (5.83%) 15	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all)	15 / 291 (5.15%) 17 31 / 291 (10.65%) 32	9 / 206 (4.37%) 12 33 / 206 (16.02%) 34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2019	- Primary, secondary, and exploratory endpoints were modified and estimands added. - Study procedures and eligibility requirements were simplified.
27 May 2020	- Updated study duration to approximately 59 weeks. - Updated the Schedule of Activities to clarify the baseline period, information collected and processed by IRT, the clinical outcome assessment or patient reported outcomes to be done post-randomization on day 1 in the clinic, informed consent, and timing of the entry and exit interviews. - Updated key exclusion criteria to update changes in drug regimen of an allowed migraine preventive medication within 2 months from screening, to remove criterion for body mass index > 40 kg/m^2 at screening, to clarify if participant has a known hypersensitivity to any of the components to be administered during dosing to be excluded from the study, and to update the participants taking short-acting opioids or opioid-containing analgesic for any indication as exclusion criteria. - Clarified that the blinding will be continued in both double-blind and open-label treatment periods. - Updated exploratory objectives and endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported