Clinical trial results:
Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double-blind, Placebo-controlled Phase 4 Study

Summary

EudraCT number	2019-003646-33
Trial protocol	PL PT HU BG CZ IT RO
Global end of trial date	26 October 2023

Results information

Result version number	v1 (current)
This version publication date	23 August 2024
First version publication date	23 August 2024

Trial information

Trial identification

Sponsor protocol code	20190008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04252742
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 Inc., MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen Inc., 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	26 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the treatment benefit of erenumab on headache duration of at least moderate pain intensity.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice and other applicable ICH laws and regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2020
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: 23
Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Czechia: 66
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Poland: 278
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 11
Worldwide total number of subjects	512
EEA total number of subjects	489

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)	501
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 61 study centers in North America and Europe from September 2020 to October 2023.

Pre-assignment

Screening details:

Eligible adult participants with high frequency episodic migraine (EP) who met specific eligibility criteria during a 2-week run-in period and 4-week baseline period entered the double-blind treatment period (DBTP). The DBTP included a 12-week main-DBTP (M-DBTP) and a 4-week exploratory DBTP (E-DBTP)

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	Placebo

Arm description:

Participants were randomized to receive matching placebo subcutaneously (SC) every 4 weeks (Q4W) for up to 16 weeks in the DBTP.

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

Dosage and administration details:

Placebo was administered SC Q4W for up to 16 weeks.

Arm title	Erenumab 140 mg SC Q4W

Arm description:

Participants were randomized to receive 140 mg erenumab SC Q4W for up to 16 weeks in the DBTP.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Erenumab was administered SC Q4W for up to 16 weeks.

Number of subjects in period 1	Placebo	Erenumab 140 mg SC Q4W
Started	256	256
Received investigational product (IP)	256	254
Completed	241	244
Not completed	15	12
Consent withdrawn by subject	15	9
Lost to follow-up	-	1
Decision by sponsor	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive matching placebo subcutaneously (SC) every 4 weeks (Q4W) for up to 16 weeks in the DBTP.	
Reporting group title	Erenumab 140 mg SC Q4W
Reporting group description:	
Participants were randomized to receive 140 mg erenumab SC Q4W for up to 16 weeks in the DBTP.	

Reporting group values	Placebo	Erenumab 140 mg SC Q4W	Total
Number of subjects	256	256	512
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)	250	251	501
From 65-84 years	6	5	11
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	42.5	41.9	
standard deviation	± 10.2	± 10.9	-
Sex: Female, Male Units: participants			
Female	222	220	442
Male	34	36	70
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	7	14
Not Hispanic or Latino	248	249	497
Unknown or Not Reported	1	0	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	253	252	505
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Monthly Hours of at Least Moderate Headache Pain Intensity			
At least moderate headache pain intensity was defined as headache pain intensity reported as 'Moderate' or 'Severe' based on the 3-level headache pain intensity scale. Worst or peak pain intensity during a headache was collected using the e-diary in 3-levels (mild, moderate or severe). The duration of headaches with at least moderate pain intensity was collected. Participants with observed data within the 4-week baseline period are included (N=255 for Placebo and N=256 for Erenumab 140 mg SC Q4W).			
Units: hours/month			
arithmetic mean	47.382	48.843	
standard deviation	± 29.302	± 29.502	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive matching placebo subcutaneously (SC) every 4 weeks (Q4W) for up to 16 weeks in the DBTP.	
Reporting group title	Erenumab 140 mg SC Q4W
Reporting group description:	
Participants were randomized to receive 140 mg erenumab SC Q4W for up to 16 weeks in the DBTP.	

Primary: Change from Baseline in Mean Monthly Hours of at Least Moderate Headache Pain Intensity Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Hours of at Least Moderate Headache Pain Intensity Over Months 1, 2, and 3
End point description:	
At least moderate headache pain intensity was defined as headache pain intensity reported as 'Moderate' or 'Severe' based on the 3-level headache pain intensity scale. Worst or peak pain intensity during a headache was collected using the e-diary in 3-levels (mild, moderate or severe). The duration of headaches with at least moderate pain intensity was collected. A negative change from baseline indicates a reduction in mean monthly hours of at least moderate headache pain intensity. Change from baseline in mean monthly measurement is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value. The least squares mean (LSM) estimates of change from baseline in reported headache pain intensity utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.	
End point type	Primary
End point timeframe:	
Baseline, Month 1, Month 2, and Month 3	

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251[1]	253[2]		
Units: hours/month				
least squares mean (standard error)	-23.38 (± 1.26)	-31.33 (± 1.25)		

Notes:

[1] - The M-DBTP efficacy analysis set.

[2] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [3]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-7.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.45
upper limit	-4.46

Notes:

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

Secondary: Change from Baseline in Mean Monthly Physical Function Domain Score as Measured by the Migraine Functional Impact Questionnaire (MFIQ) Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Physical Function Domain Score as Measured by the Migraine Functional Impact Questionnaire (MFIQ) Over Months 1, 2, and 3

End point description:

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including on Physical Functioning (5 items). Participants responded to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. Each domain score was calculated as the sum of the item responses and rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period was the past 7 days. A negative change from baseline indicates an improvement in burden. Change from baseline in mean monthly scores is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value.
The LSM estimates utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2, and Month 3

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[4]	244[5]		
Units: score on a scale				
least squares mean (standard error)	-22.92 (± 1.25)	-30.28 (± 1.23)		

Notes:

[4] - The M-DBTP efficacy analysis set.

[5] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [6]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-7.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	-3.92

Notes:

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

Secondary: Change from Baseline in Mean Monthly Usual Activities Domain Score as Measured by the MFIQ Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Usual Activities Domain Score as Measured by the MFIQ Over Months 1, 2, and 3

End point description:

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including Impact on Usual Activities (10 items). Participants responded to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. Each domain score was calculated as the sum of the item responses and rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period was the previous 7 days. A negative change from baseline indicates an improvement in burden. Change from baseline in mean monthly scores is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value.
The LSM estimates utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2, and Month 3

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[7]	244[8]		
Units: score on a scale				
least squares mean (standard error)	-23.98 (± 1.17)	-31.08 (± 1.16)		

Notes:

[7] - The M-DBTP efficacy analysis set.

[8] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [9]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.34
upper limit	-3.87

Notes:

[9] - Nominal p-value is presented without multiplicity adjustment

Secondary: Change from Baseline in Mean Monthly Emotional Functioning Domain Score as Measured by the MFIQ Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Emotional Functioning Domain Score as Measured by the MFIQ Over Months 1, 2, and 3

End point description:

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including Impact on Emotional Functioning (5 items). Participants responded to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. Each domain score was calculated as the sum of the item responses and rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period was the previous 7 days. A negative change from baseline indicates an improvement in burden. Change from baseline in mean monthly scores is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value.
The LSM estimates utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2, and Month 3

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[10]	244[11]		
Units: score on a scale				
least squares mean (standard error)	-22.77 (± 1.34)	-29.83 (± 1.33)		

Notes:

[10] - The M-DBTP efficacy analysis set.

[11] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [12]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-7.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.76
upper limit	-3.34

Notes:

[12] - Nominal p-value is presented without multiplicity adjustment

Secondary: Change from Baseline in Mean Monthly Social Functioning Domain Score as Measured by the MFIQ Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Social Functioning Domain Score as Measured by the MFIQ Over Months 1, 2, and 3

End point description:

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including Impact on Social Functioning (5 items). Participants responded to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. Each domain score was calculated as the sum of the item responses and rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period was the previous 7 days. A negative change from baseline indicates an improvement in burden. Change from baseline in mean monthly scores is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value.
The LSM estimates utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2, and Month 3

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[13]	244[14]		
Units: score on a scale				
least squares mean (standard error)	-25.05 (± 1.28)	-31.87 (± 1.27)		

Notes:

[13] - The M-DBTP efficacy analysis set.

[14] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [15]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-6.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.37
upper limit	-3.27

Notes:

[15] - Nominal p-value is presented without multiplicity adjustment

Secondary: Change from Baseline in Mean Monthly Average Duration of at Least Moderate Headache Pain Intensity in Migraine Attacks Occurring Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Average Duration of at Least Moderate Headache Pain Intensity in Migraine Attacks Occurring Over Months 1, 2, and 3

End point description:

At least moderate headache pain intensity was defined as headache pain intensity reported as 'Moderate' or 'Severe' based on the 3-level headache pain intensity scale. Worst or peak pain intensity during a headache was collected using the e-diary in 3-levels (mild, moderate or severe). The duration of headaches with at least moderate pain intensity during a migraine attack was collected. A negative change from baseline indicates a reduction in mean monthly average duration of at least moderate headache pain intensity during a migraine attack. Change from baseline in mean monthly measurement is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value.
The LSM estimates utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2, and Month 3

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251[16]	253[17]		
Units: hours				
least squares mean (standard error)	-2.78 (± 0.31)	-3.86 (± 0.30)		

Notes:

[16] - The M-DBTP efficacy analysis set.

[17] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.013 [18]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	-0.22

Notes:

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

Secondary: Change from Baseline in Mean Monthly Average Peak Migraine Pain Intensity as Assessed by the 11-point Numeric Rating Scale (NRS) Over Months 1, 2, and 3

End point title	Change from Baseline in Mean Monthly Average Peak Migraine Pain Intensity as Assessed by the 11-point Numeric Rating Scale (NRS) Over Months 1, 2, and 3

End point description:

The NRS assesses headache pain intensity ranging from 0 to 10 with a higher score indicating more severe pain. Participants recorded the pain intensity using the e-diary at the headache end-time or in an evening diary entry on a daily basis for an ongoing headache. A negative change from baseline indicates an improvement in pain intensity. Change from baseline in mean monthly scores is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there was at least one observed monthly value.
The LSM estimates utilized a linear mixed model which included treatment, visit, treatment-by-visit interaction, and baseline value as covariates and assumed a first-order auto regression covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2, and Month 3

End point values	Placebo	Erenumab 140 mg SC Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251[19]	253[20]		
Units: score on a scale				
least squares mean (standard error)	-1.48 (± 0.13)	-1.96 (± 0.13)		

Notes:

[19] - The M-DBTP efficacy analysis set.

[20] - The M-DBTP efficacy analysis set.

Statistical analyses

Statistical analysis title	LSM Difference: Erenumab - Placebo
Comparison groups	Placebo v Erenumab 140 mg SC Q4W

Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011 [21]
Method	Mixed models analysis
Parameter estimate	LSM difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.11

Notes:

[21] - Nominal p-value is presented without multiplicity adjustment

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Day 1 to end of the DBTP (up to 16 weeks)

Adverse event reporting additional description:

Serious adverse events and other adverse events 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	Erenumab 140 mg SC Q4W

Reporting group description:

Participants were randomized to receive 140 mg erenumab SC Q4W for up to 16 weeks in the DBTP.

Reporting group title	Placebo

Reporting group description:

Participants were randomized to receive matching placebo SC QW4 for up to 16 weeks in the DBTP.

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 participants experienced any non-serious adverse events above the indicated threshold.

Serious adverse events	Erenumab 140 mg SC Q4W	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 254 (0.00%)	2 / 256 (0.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Psychiatric disorders			
Psychogenic tremor			
subjects affected / exposed	0 / 254 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Erenumab 140 mg SC Q4W	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 256 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2022	- Updated the secondary and exploratory objectives and endpoints language. - Updated overall design language to incorporate the qualifying oral triptan-treated migraine attack definition; updated eligibility criteria for the end of the run-in period. - Updated the key eligibility criteria language. - Updated schedule of activities language. - Clarified IP background language. - Updated the benefit/risk assessment section. - Updated the prohibited medications section and prior treatment section. - Clarified that the run-in and baseline periods could not be extended for more than 18 days and 35 days, respectively. - Updated the subgroup language for the primary and secondary endpoints. - Updated the statistical analysis methods language.
29 June 2022	Updated the language in the endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported