Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Summary

EudraCT number	2014-004464-38
Trial protocol	FI SE CZ DE SK AT PL HU BE NL
Global end of trial date	19 June 2017

Results information

Result version number	v1 (current)
This version publication date	05 July 2018
First version publication date	05 July 2018

Trial information

Trial identification

Sponsor protocol code	20120296

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02456740
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
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	19 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of erenumab (AMG 334) compared to placebo on the change from baseline in mean monthly migraine days, in subjects with episodic migraine.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the GCPs applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. All centers complied with local regulations.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to subjects were reviewed and approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), as appropriate, at each center/country.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	United States: 449
Country: Number of subjects enrolled	Austria: 34
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Czech Republic: 74
Country: Number of subjects enrolled	Finland: 45
Country: Number of subjects enrolled	Germany: 148
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Sweden: 57
Country: Number of subjects enrolled	Turkey: 22
Country: Number of subjects enrolled	United Kingdom: 29
Worldwide total number of subjects	955
EEA total number of subjects	456

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)	951
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 121 centers in Canada, Austria, Belgium, Czech Republic, Finland, Germany, Poland, Slovakia, Sweden, the United Kingdom, Turkey, the Netherlands and USA.
The study consisted of a 24-week double-blind treatment phase (DBTP) and a 28-week active treatment phase (ATP).

Pre-assignment

Screening details:

At the end of the baseline phase, participants were randomized 1:1:1 to receive placebo, erenumab 70 mg, or erenumab 140 mg monthly for 24 weeks. Randomization was stratified by region and treatment status with migraine prophylactic medication.
Participants were re-randomized at week 24 to erenumab 70 mg or 140 mg for 28 weeks.

Period 1

Period 1 title	Double-blind Treatment Phase (24 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo once a month (QM) by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.

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:

Administered by subcutaneous injection once a month

Arm title	Erenumab 70 mg QM

Arm description:

Participants received erenumab 70 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Erenumab 140 mg QM

Arm description:

Participants received erenumab 140 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.

Arm type	Experimental

Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Number of subjects in period 1	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM
Started	319	317	319
Received Study Drug	319	314	319
Completed	282	284	292
Not completed	37	33	27
Consent withdrawn by subject	27	28	21
Decision by Sponsor	1	1	1
Lost to follow-up	9	4	5

Period 2

Period 2 title	Active Treatment Phase (Weeks 24 - 52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / Erenumab 70 mg

Arm description:

Participants originally randomized to receive placebo in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Erenumab 70 mg / Erenumab 70 mg

Arm description:

Participants originally randomized to receive erenumab 70 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Erenumab 140 mg / Erenumab 70 mg

Arm description:

Participants originally randomized to receive erenumab 140 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Placebo / Erenumab 140 mg

Arm description:

Participants originally randomized to receive placebo QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Erenumab 70 mg / Erenumab 140 mg

Arm description:

Participants originally randomized to receive erenumab 70 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Erenumab 140 mg / Erenumab 140 mg

Arm description:

Participants originally randomized to receive erenumab 140 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Arm type	Experimental

Investigational medicinal product name	Erenumab
Investigational medicinal product code	AMG 334
Other name	Aimovig™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Number of subjects in period 2[1]	Placebo / Erenumab 70 mg	Erenumab 70 mg / Erenumab 70 mg	Erenumab 140 mg / Erenumab 70 mg
Started	138	140	143
Completed	124	123	130
Not completed	14	17	13
Consent withdrawn by subject	10	11	9
Protocol specified criteria	1	4	-
Death	-	-	-
Lost to follow-up	3	2	4

Number of subjects in period 2[1]	Placebo / Erenumab 140 mg	Erenumab 70 mg / Erenumab 140 mg	Erenumab 140 mg / Erenumab 140 mg
Started	140	140	144
Completed	131	128	126
Not completed	9	12	18
Consent withdrawn by subject	8	8	9
Protocol specified criteria	-	-	5
Death	-	1	-
Lost to follow-up	1	3	4

Notes:

[1] - 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: Fourteen subjects who completed the double-blind treatment phase did not continue onto the active treatment phase.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once a month (QM) by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.	
Reporting group title	Erenumab 70 mg QM
Reporting group description:	
Participants received erenumab 70 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.	
Reporting group title	Erenumab 140 mg QM
Reporting group description:	
Participants received erenumab 140 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.	

Reporting group values	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM
Number of subjects	319	317	319
Age Categorical Units: Subjects			
18 - 64 years	317	317	317
65 - 74 years	2	0	2
Age Continuous Units: years			
arithmetic mean	41.3	41.1	40.4
standard deviation	± 11.2	± 11.3	± 11.1
Gender Categorical Units: Subjects			
Female	274	268	272
Male	45	49	47
Race Units: Subjects			
American Indian or Alaska Native	2	0	1
Asian	8	5	4
Black or African American	24	24	18
Multiple	2	1	0
Native Hawaiian or Other Pacific Islander	0	0	1
White	277	281	293
Other	6	6	2
Ethnicity Units: Subjects			
Hispanic or Latino	32	26	22
Not Hispanic or Latino	287	291	297
Region Units: Subjects			
North America	158	159	160
Other	161	158	159
Treatment Status with Migraine Prophylactic Medication			

Units: Subjects			
Current migraine prophylactic treatment	8	6	7
Prior migraine prophylactic treatment only	119	119	120
No prior / current migraine prophylactic treatment	192	192	192
Monthly Migraine Days			
A migraine day was any calendar day in which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine without aura or a migraine with aura. Monthly migraine days were calculated as the number of migraine days in the 4-week baseline phase. Data are reported for participants with non-missing data (318, 316, and 319 subjects in each treatment group respectively).			
Units: migraine days / month			
arithmetic mean	8.23	8.29	8.34
standard deviation	± 2.51	± 2.47	± 2.48

Reporting group values	Total		
Number of subjects	955		
Age Categorical Units: Subjects			
18 - 64 years	951		
65 - 74 years	4		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	814		
Male	141		
Race Units: Subjects			
American Indian or Alaska Native	3		
Asian	17		
Black or African American	66		
Multiple	3		
Native Hawaiian or Other Pacific Islander	1		
White	851		
Other	14		
Ethnicity Units: Subjects			
Hispanic or Latino	80		
Not Hispanic or Latino	875		
Region Units: Subjects			
North America	477		
Other	478		
Treatment Status with Migraine Prophylactic Medication Units: Subjects			
Current migraine prophylactic treatment	21		

Prior migraine prophylactic treatment only	358		
No prior / current migraine prophylactic treatment	576		
Monthly Migraine Days			
A migraine day was any calendar day in which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine without aura or a migraine with aura. Monthly migraine days were calculated as the number of migraine days in the 4-week baseline phase. Data are reported for participants with non-missing data (318, 316, and 319 subjects in each treatment group respectively).			
Units: migraine days / month			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo once a month (QM) by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.	
Reporting group title	Erenumab 70 mg QM
Reporting group description:	
Participants received erenumab 70 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.	
Reporting group title	Erenumab 140 mg QM
Reporting group description:	
Participants received erenumab 140 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.	
Reporting group title	Placebo / Erenumab 70 mg
Reporting group description:	
Participants originally randomized to receive placebo in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.	
Reporting group title	Erenumab 70 mg / Erenumab 70 mg
Reporting group description:	
Participants originally randomized to receive erenumab 70 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.	
Reporting group title	Erenumab 140 mg / Erenumab 70 mg
Reporting group description:	
Participants originally randomized to receive erenumab 140 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.	
Reporting group title	Placebo / Erenumab 140 mg
Reporting group description:	
Participants originally randomized to receive placebo QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.	
Reporting group title	Erenumab 70 mg / Erenumab 140 mg
Reporting group description:	
Participants originally randomized to receive erenumab 70 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.	
Reporting group title	Erenumab 140 mg / Erenumab 140 mg
Reporting group description:	
Participants originally randomized to receive erenumab 140 mg QM in the 24-week double-blind treatment phase were re-randomized at week 24 to receive erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.	

Primary: Change From Baseline in Mean Monthly Migraine Days to the Last 3 Months of the Double-blind Treatment Period

End point title	Change From Baseline in Mean Monthly Migraine Days to the Last 3 Months of the Double-blind Treatment Period
End point description:	
A migraine day was any calendar day in which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine with or without aura.	

The change from baseline in monthly migraine days was calculated as the average number of migraine days per month during the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase – the number of migraine days during the 4-week baseline phase.
The analysis was conducted in the efficacy analysis set which includes participants who received at least 1 dose of study drug and had at least 1 change from baseline measurement in monthly migraine days in the double-blind treatment phase.

End point type	Primary

End point timeframe:

4-week baseline phase and the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	312	318	
Units: migraine days / month				
least squares mean (standard error)	-1.83 (± 0.18)	-3.23 (± 0.18)	-3.67 (± 0.18)	

Statistical analyses

Statistical analysis title	Analysis of Monthly Migraine Days

Statistical analysis description:

The primary endpoint was analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.88
upper limit	-0.92

Notes:

[1] - The primary endpoint was tested independently for each erenumab dose at an alpha level of 0.04 for 70 mg and of 0.01 for 140 mg to maintain the type 1 error rate at an alpha level of 0.05.

Statistical analysis title	Analysis of Monthly Migraine Days

Statistical analysis description:

The primary endpoint was analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 140 mg QM

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.33
upper limit	-1.37

Notes:

[2] - The primary endpoint was tested independently for each erenumab dose at an alpha level of 0.04 for 70 mg and of 0.01 for 140 mg to maintain the type 1 error rate at an alpha level of 0.05.

Secondary: Percentage of Participants with at Least a 50% Reduction From Baseline in Monthly Migraine Days in the Last 3 Months of the Double-blind Treatment Phase

End point title	Percentage of Participants with at Least a 50% Reduction From Baseline in Monthly Migraine Days in the Last 3 Months of the Double-blind Treatment Phase

End point description:

A migraine day was any calendar day in which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine without aura or a migraine with aura.
At least a 50% reduction from baseline in monthly migraine days was determined if the change in monthly migraine days from the 4-week baseline phase to the last 3 months (mean of months 4, 5 and 6) of the 24-week double-blind treatment phase * 100 / baseline monthly migraine days was less than or equal to -50%.
The analysis was conducted in the efficacy analysis set which includes participants who received at least 1 dose of study drug and had at least 1 change from baseline measurement in monthly migraine days in the double-blind treatment phase. Participants with missing data at months 4, 5, and 6 were counted as non-responders.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	312	318	
Units: percentage of participants				
number (not applicable)	26.6	43.3	50.0	

Statistical analyses

Statistical analysis title	Analysis of Migraine Response

Statistical analysis description:

Analyzed using a Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors (region and prior/current treatment with migraine prophylactic medication).

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	2.98

Notes:

[3] - If the primary endpoint was statistically significant for the erenumab 70 mg group, using a gate-keeping strategy, the first two (first tier) secondary endpoints were tested using the Hochberg method at an alpha level of 0.04.

Statistical analysis title	Analysis of Migraine Response

Statistical analysis description:

Analyzed using a Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors (region and prior/current treatment with migraine prophylactic medication).

Comparison groups	Placebo v Erenumab 140 mg QM
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.01
upper limit	3.94

Notes:

[4] - If the primary endpoint was statistically significant for the erenumab 140 mg group, using a gate-keeping strategy, the first two (first tier) secondary endpoints were tested using the Hochberg method at an alpha level of 0.01.

Secondary: Change From Baseline in Mean Monthly Acute Migraine-specific Medication Treatment Days to the Last 3 Months of the Double-blind Treatment Period

End point title	Change From Baseline in Mean Monthly Acute Migraine-specific Medication Treatment Days to the Last 3 Months of the Double-blind Treatment Period

End point description:

Monthly acute migraine-specific medication treatment days is the number of days on which migraine specific medications were used between monthly doses of study drug. Migraine-specific medications includes two categories of medications: triptan-based migraine medications and ergotamine-based migraine medications.
The change from baseline in monthly acute migraine-specific treatment days was calculated as the average number of migraine-specific treatment days per month during the last 3 months of the 24-week double-blind treatment phase – the number of migraine-specific treatment days during the 4-week baseline phase.
The analysis was conducted in the efficacy analysis set which includes participants who received at least 1 dose of study drug and had at least 1 change from baseline measurement in monthly acute migraine-

specific treatment days in the double-blind treatment phase.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	312	318	
Units: Acute migraine-specific med days/mo				
least squares mean (standard error)	-0.20 (± 0.11)	-1.13 (± 0.11)	-1.61 (± 0.11)	

Statistical analyses

Statistical analysis title	Analysis of Migraine Treatment Days

Statistical analysis description:

Analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	-0.64

Notes:

[5] - If the primary endpoint was statistically significant for the erenumab 70 mg group, using a gate-keeping strategy, the first two (first tier) secondary endpoints were tested using the Hochberg method at an alpha level of 0.04.

Statistical analysis title	Analysis of Migraine Treatment Days

Statistical analysis description:

Analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, (stratification factors region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 140 mg QM

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	-1.12

Notes:

[6] - If the primary endpoint was statistically significant for the erenumab 140 mg group, using a gate-keeping strategy, the first two (first tier) secondary endpoints were tested using the Hochberg method at an alpha level of 0.01.

Secondary: Change From Baseline in Mean Monthly Average Physical Impairment Domain Score Measured by MPFID in the Last 3 Months of the Double-blind Treatment Phase

End point title	Change From Baseline in Mean Monthly Average Physical Impairment Domain Score Measured by MPFID in the Last 3 Months of the Double-blind Treatment Phase

End point description:

The Migraine Physical Function Impact Diary (MPFID) is a self-administered 13-item instrument measuring physical functioning. It has two domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and a stand-alone global question. Participants completed the MPFID daily based on the past 24 hours. Difficulty items ranged from "Without any difficulty" (1) to "Unable to do" (5) and frequency items ranged from "None of the time" (1) to "All of the time" (5). For each domain, response scores were summed and rescaled to 0 – 100, where higher scores represent greater impact of migraine.
Change from baseline was calculated as mean monthly average physical impairment score over the last 3 months of the DBTP - baseline monthly average physical impairment score.
The analysis was conducted in the efficacy analysis set including participants who received ≥ 1 dose of study drug and had ≥ 1 change from baseline in MPFID average physical impairment domain score in the DBTP.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	312	318	
Units: units on a scale				
least squares mean (standard error)	-2.38 (± 0.40)	-4.24 (± 0.40)	-4.81 (± 0.40)	

Statistical analyses

Statistical analysis title	Analysis of Average Physical Impairment Score

Statistical analysis description:

Analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 140 mg QM
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	-1.35

Notes:

[7] - If the first tier secondary endpoints were statistically significant for both erenumab doses the erenumab 140 mg group for the 2 remaining MPFID secondary endpoints was tested using the Hochberg method at a level of 0.05; If only the erenumab 70 mg group or 140 mg group showed statistical significance for the first tier secondary endpoints then the erenumab 140 group for the 2 remaining MPFID secondary endpoints was tested for significance at a level of either 0.04 or 0.01 respectively.

Statistical analysis title	Analysis of Average Physical Impairment Score

Statistical analysis description:

Analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.95
upper limit	-0.77

Notes:

[8] - If the erenumab 140 mg group for both remaining MPFID secondary endpoints was statistically significant, then the erenumab 70 mg group for the two remaining MPFID secondary endpoints was tested for significance using the Hochberg method with the same alpha level carried over from 140 mg group.

Secondary: Change From Baseline in Mean Monthly Average Impact on Everyday Activities Score Measured by MPFID in the Last 3 Months of the Double-blind Treatment Phase

End point title	Change From Baseline in Mean Monthly Average Impact on Everyday Activities Score Measured by MPFID in the Last 3 Months of the Double-blind Treatment Phase

End point description:

The MPFID is a self-administered 13-item instrument measuring physical functioning. It has two domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and a stand-alone

global question. Participants completed the MPFID daily based on the past 24 hours. Difficulty items ranged from "Without any difficulty" (1) to "Unable to do" (5) and frequency items ranged from "None of the time" (1) to "All of the time" (5). For each domain, response scores were summed and rescaled to 0 – 100, where higher scores represent greater impact of migraine.
Change from baseline was calculated as mean monthly impact on everyday activities score over the last 3 months of the DBTP – baseline monthly impact on everyday activities score.
The analysis was conducted in the efficacy analysis set including participants who received ≥ 1 dose of study drug and had ≥ 1 change from baseline measurement in MPFID average impact on everyday activities domain score in the DBTP.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM	Erenumab 140 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	312	318	
Units: units on a scale				
least squares mean (standard error)	-3.30 (± 0.39)	-5.52 (± 0.39)	-5.86 (± 0.39)	

Statistical analyses

Statistical analysis title	Analysis of Impact on Everyday Activities Score

Statistical analysis description:

Analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 140 mg QM
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.62
upper limit	-1.51

Notes:

[9] - If the first tier secondary endpoints were statistically significant for both erenumab doses the erenumab 140 mg group for the 2 remaining MPFID secondary endpoints was tested using the Hochberg method at a level of 0.05; If only the erenumab 70 mg group or 140 mg group showed statistical significance for the first tier secondary endpoints then the erenumab 140 group for the 2 remaining MPFID secondary endpoints was tested for significance at a level of either 0.04 or 0.01 respectively.

Statistical analysis title	Analysis of Impact on Everyday Activities Score

Statistical analysis description:

Analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors (region and prior/current treatment with migraine prophylactic

medication), and baseline value as covariates.

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001
Method	Generalized Linear Mixed Model
Parameter estimate	LS Mean Difference
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	-1.16

Notes:

[10] - If the erenumab 140 mg group for both remaining MPFID secondary endpoints was statistically significant, then the erenumab 70 mg group for the two remaining MPFID secondary endpoints was tested for significance using the Hochberg method with the same alpha level carried over from 140 mg group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 16 weeks after the last dose.
The double-blind treatment phase was 24 weeks and the open-label treatment phase was 28 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Double-blind Treatment Phase: Placebo

Reporting group description:

Participants received placebo once a month (QM) by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.

Reporting group title	Double-blind Treatment Phase: Erenumab 70 mg

Reporting group description:

Participants received erenumab 70 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.

Reporting group title	Double-blind Treatment Phase: Erenumab 140 mg

Reporting group description:

Participants received erenumab 140 mg QM by subcutaneous injection on day 1 and weeks 4, 8, 12, 16, and 20 in the 24-week double-blind treatment phase.

Reporting group title	Active Treatment Phase: Erenumab 70 mg

Reporting group description:

Participants received erenumab 70 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Reporting group title	Active Treatment Phase: Erenumab 140 mg

Reporting group description:

Participants received erenumab 140 mg subcutaneously at weeks 24, 28, 32, 36, 40, 44, and 48 in the active treatment phase.

Serious adverse events	Double-blind Treatment Phase: Placebo	Double-blind Treatment Phase: Erenumab 70 mg	Double-blind Treatment Phase: Erenumab 140 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 319 (2.19%)	8 / 314 (2.55%)	8 / 319 (2.51%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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 fibroma			

subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Prolactin-producing pituitary tumour			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 319 (0.31%)	1 / 314 (0.32%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 319 (0.31%)	0 / 314 (0.00%)	0 / 319 (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
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Endometriosis			

subjects affected / exposed	1 / 319 (0.31%)	0 / 314 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 319 (0.00%)	1 / 314 (0.32%)	0 / 319 (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
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 319 (0.31%)	0 / 314 (0.00%)	0 / 319 (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
Femur fracture			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Intentional overdose			

subjects affected / exposed	1 / 319 (0.31%)	0 / 314 (0.00%)	0 / 319 (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
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 319 (0.00%)	1 / 314 (0.32%)	0 / 319 (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
Radius fracture			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Subdural haematoma			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Wound			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Arrhythmogenic right ventricular dysplasia			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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			
Pericarditis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Nervous system disorders			
Cerebral venous thrombosis			

subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic intracranial hypertension			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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 / 319 (0.00%)	1 / 314 (0.32%)	0 / 319 (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
Migraine with aura			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Syncope			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Eye disorders			
Idiopathic orbital inflammation			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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			
Dyspepsia			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Gastritis			

subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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 / 319 (0.00%)	2 / 314 (0.64%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 319 (0.31%)	0 / 314 (0.00%)	0 / 319 (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
Back pain			
subjects affected / exposed	0 / 319 (0.00%)	1 / 314 (0.32%)	0 / 319 (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
Osteoarthritis			
subjects affected / exposed	1 / 319 (0.31%)	0 / 314 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
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	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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

Clostridium difficile colitis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Erysipelas			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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
Pyelonephritis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 319 (0.00%)	1 / 314 (0.32%)	0 / 319 (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
Sepsis			

subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 319 (0.00%)	0 / 314 (0.00%)	0 / 319 (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	Active Treatment Phase: Erenumab 70 mg	Active Treatment Phase: Erenumab 140 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 421 (3.33%)	14 / 424 (3.30%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast fibroma			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolactin-producing pituitary tumour			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (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			
Breast cyst			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (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 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			

subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural haematoma			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arrhythmogenic right ventricular dysplasia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral venous thrombosis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic intracranial hypertension			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			

subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Idiopathic orbital inflammation			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (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 / 421 (0.00%)	0 / 424 (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			
Arthralgia			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (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	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 421 (0.00%)	2 / 424 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis viral			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 421 (0.24%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 421 (0.00%)	0 / 424 (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			
Dehydration			
subjects affected / exposed	0 / 421 (0.00%)	1 / 424 (0.24%)	
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	Double-blind Treatment Phase: Placebo	Double-blind Treatment Phase: Erenumab 70 mg	Double-blind Treatment Phase: Erenumab 140 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 319 (16.61%)	53 / 314 (16.88%)	54 / 319 (16.93%)
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	19 / 319 (5.96%)	21 / 314 (6.69%)	15 / 319 (4.70%)
occurrences (all)	26	26	18
Viral upper respiratory tract infection			
subjects affected / exposed	34 / 319 (10.66%)	32 / 314 (10.19%)	39 / 319 (12.23%)
occurrences (all)	44	40	46

Non-serious adverse events	Active Treatment Phase: Erenumab 70 mg	Active Treatment Phase: Erenumab 140 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 421 (19.71%)	63 / 424 (14.86%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	25 / 421 (5.94%)	19 / 424 (4.48%)	
occurrences (all)	27	21	
Viral upper respiratory tract infection			
subjects affected / exposed	58 / 421 (13.78%)	44 / 424 (10.38%)	
occurrences (all)	73	56	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2015	• Allowed patients to be on 1 stable migraine prophylactic treatment while on-study to evaluate the effect of AMG 334 in a broader patient population. • Updated C-SSRS language to provide guidance to physician or study center staff in case of any suicidal ideation or behavior. • Removed several exploratory endpoints from inclusion in supplemental statistical analysis. • Updated pregnancy and lactation reporting. • Added collection of menses start date each month to allow for subgroup analysis of the effect of AMG 334 on menstrual-related migraine
03 June 2016	• Revised and reordered 2 MPFID-related secondary objectives/endpoints to include a definition of treatment response. - On the basis of the results of the observational validation study 20140136, a within-subject reduction in MPFID score of ≥ 5 points from month 1 to month 4 was determined to represent a clinically meaningful change for each MPFID domain. This a priori responder definition was therefore incorporated into the 2 MPFID-related secondary endpoints of this study protocol. • Included an unblinded, interim analysis (safety data only) of the active treatment period that would only be implemented in the event that 140 mg SC QM is selected as the dose for commercialization. This analysis would provide long-term safety data on subjects exposed to 140 mg AMG 334 SC QM. • Revised 2 MPFID-related exploratory objectives/endpoints. • Allowed for the collection of data on: - use of triptans or ergotamine-derivatives before the study - employment status - migraine triggers • Updated AMG 334 safety and tolerability data. • Made minor text clarifications, additions, and edits throughout the protocol.
18 October 2016	• Reverted the 2 MPFID-related secondary objectives/endpoints to those in in the original protocol. • On the basis of the primary analysis of phase 3 study 20120297 in episodic migraine, it was found that the responder definition in the 2 MPFID-related secondary dichotomous endpoints (ie, ≥ 5 point reduction in the physical impairment domain and impact on everyday activities domain as measured by the MPFID) derived from a previous observational study may not be as appropriate as the continuous measure of MPFID scores, as implemented in the MPFID-related exploratory endpoints. Therefore, the 2 MPFID-related secondary endpoints were switched with corresponding exploratory endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported