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	2014-004463-20
Trial protocol	PT GR DK ES
Global end of trial date	20 March 2017

Results information

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

Trial information

Trial identification

Sponsor protocol code	20120297

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02483585
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	20 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of erenumab (AMG 334) compared to placebo on the change from baseline in 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	20 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	United States: 338
Country: Number of subjects enrolled	Denmark: 99
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Switzerland: 15
Worldwide total number of subjects	577
EEA total number of subjects	191

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)	573
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 69 centers in Denmark, France, Greece, Portugal, Russia, Spain, Switzerland, and the USA. Participants were enrolled from 20 July 2015 to 19 April 2016.

Pre-assignment

Screening details:

Participants were randomized 1:1 to placebo or erenumab 70 mg once a month (QM). Randomization was stratified by region (North America vs Other) and treatment status with migraine prophylactic medication (current, prior, or no prior or current migraine prophylactic medication treatment).

Period 1

Period 1 title	Double-blind Treatment Phase
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 on day 1 and at weeks 4 and 8 by subcutaneous injection in the 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 once a month by subcutaneous injection

Arm title	Erenumab 70 mg QM

Arm description:

Participants received erenumab 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection in the 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 once a month by subcutaneous injection

Number of subjects in period 1	Placebo	Erenumab 70 mg QM
Started	291	286
Received Treatment	289	283
Completed	275	271
Not completed	16	15
Consent withdrawn by subject	12	12
Decision by Sponsor	1	1
Lost to follow-up	3	2

Period 2

Period 2 title	Open-label Treatment Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Erenumab

Arm description:

Participants who received placebo in the double-blind treatment phase received erenumab 70 mg administered by subcutaneous injection at weeks 12, 16, 20, 24, 28, 32, and 36 in the open-label 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 once a month by subcutaneous injection

Arm title	Erenumab/Erenumab

Arm description:

Participants who received erenumab in the double-blind treatment phase received erenumab 70 mg administered by subcutaneous injection at weeks 12, 16, 20, 24, 28, 32, and 36 in the open-label 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 once a month by subcutaneous injection

Number of subjects in period 2[1]	Placebo/Erenumab	Erenumab/Erenumab
Started	270	268
Completed	243	243
Not completed	27	25
Consent withdrawn by subject	18	14
Protocol specified criteria	6	5
Decision by Sponsor	-	1
Lost to follow-up	3	5

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: Eight subjects who completed the double-blind treatment phase did not continue onto the open-label treatment phase: 4 subjects withdrew consent and 4 subjects did not continue in the study due to 'protocol specified criteria'.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo on day 1 and at weeks 4 and 8 by subcutaneous injection in the double-blind treatment phase.	
Reporting group title	Erenumab 70 mg QM
Reporting group description:	
Participants received erenumab 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection in the double-blind treatment phase.	

Reporting group values	Placebo	Erenumab 70 mg QM	Total
Number of subjects	291	286	577
Age Categorical Units: Subjects			
Adults (18-64 years)	290	283	573
From 65-84 years	1	3	4
Age Continuous Units: years			
arithmetic mean	42.2	42.3	
standard deviation	± 11.5	± 11.4	-
Gender Categorical Units: Subjects			
Female	247	245	492
Male	44	41	85
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	2	2
Black or African American	27	24	51
Multiple	2	1	3
Native Hawaiian or Other Pacific Islander	1	0	1
White	259	259	518
Other	2	0	2
Ethnicity Units: Subjects			
Hispanic/Latino	34	23	57
Not Hispanic/Latino	257	263	520
Region Units: Subjects			
North America	170	168	338
Other	121	118	239
Treatment Status with Migraine Prophylactic Medication Units: Subjects			
Current migraine prophylactic medication treatment	18	17	35

Prior migraine prophylactic treatment only	120	119	239
No prior / current migraine prophylactic treatment	153	150	303
Disease Duration of Migraine With or Without Aura			
Units: years			
arithmetic mean	20.03	21.70	
standard deviation	± 12.08	± 12.62	-
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.			
Units: days			
arithmetic mean	8.38	8.14	
standard deviation	± 2.60	± 2.65	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo on day 1 and at weeks 4 and 8 by subcutaneous injection in the double-blind treatment phase.	
Reporting group title	Erenumab 70 mg QM
Reporting group description:	
Participants received erenumab 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection in the double-blind treatment phase.	
Reporting group title	Placebo/Erenumab
Reporting group description:	
Participants who received placebo in the double-blind treatment phase received erenumab 70 mg administered by subcutaneous injection at weeks 12, 16, 20, 24, 28, 32, and 36 in the open-label treatment phase.	
Reporting group title	Erenumab/Erenumab
Reporting group description:	
Participants who received erenumab in the double-blind treatment phase received erenumab 70 mg administered by subcutaneous injection at weeks 12, 16, 20, 24, 28, 32, and 36 in the open-label treatment phase.	
Subject analysis set title	Double-blind Treatment Phase: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least 1 dose of placebo by subcutaneous injection in the double-blind treatment period.	
Subject analysis set title	Double-blind Treatment Phase: Erenumab 70 mg QM
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least 1 dose of erenumab 70 mg by subcutaneous injection in the double-blind treatment period.	
Subject analysis set title	Open-label Treatment Phase: Erenumab 70 mg QM
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least 1 dose of erenumab 70 mg by subcutaneous injection in the open-label treatment period.	

Primary: Change from Baseline in Monthly Migraine Days at Week 12

End point title	Change from Baseline in Monthly Migraine Days at Week 12
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 number of migraine days during the last 4 weeks of the 12-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 day in the double-blind treatment phase.	
End point type	Primary
End point timeframe:	
4-week baseline phase and the last 4 weeks of the 12-week double-blind treatment phase	

End point values	Placebo	Erenumab 70 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288[1]	282[2]		
Units: migraine days / month				
least squares mean (standard error)	-1.84 (± 0.21)	-2.88 (± 0.21)		

Notes:

[1] - Participants in the efficacy analysis set

[2] - Participants in the efficacy analysis set

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The primary endpoint was analyzed using a linear mixed effects model including treatment group, baseline value, stratification factors (region and prior/current treatment with migraine prophylactic medication), scheduled visit, and the interaction of treatment group with scheduled visit.

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Generalized linear mixed model
Parameter estimate	Difference in LS Means
Point estimate	-1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	-0.47

Notes:

[3] - A sequential testing procedure, specifically, the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the 2-sided study-wise type I error at 0.05 between the primary and efficacy secondary endpoints.

Secondary: Percentage of Participants with at Least a 50% Reduction From Baseline in Monthly Migraine Days at Week 12

End point title	Percentage of Participants with at Least a 50% Reduction From Baseline in Monthly Migraine Days at Week 12

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. Monthly migraine days were calculated as the number of migraine days in the 4-week baseline phase and during the last 4 weeks of treatment.
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 4 weeks of the 12-week double-blind treatment phase * 100 / baseline monthly migraine days was less than or equal to -50%.
This analysis was performed using the efficacy analysis set; participants with missing post-baseline data were counted as non-responders.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 4 weeks of the 12-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	282		
Units: percentage of participants				
number (not applicable)	29.5	39.7		

Statistical analyses

Statistical analysis title	Analysis of Reduction in Monthly Migraine Days

Statistical analysis description:

Analyzed using a Cochran-Mantel-Haenszel (CMH) test after the missing data were imputed as non-response, stratified by 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	570
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	2.27

Secondary: Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days at Week 12

End point title	Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days at Week 12

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.
This analysis was performed using the efficacy analysis set.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 4 weeks of the 12-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288[4]	282[5]		
Units: acute migraine treatment days / month				
least squares mean (standard error)	-0.62 (± 0.14)	-1.21 (± 0.14)		

Notes:

[4] - Efficacy analysis set

[5] - Efficacy analysis set

Statistical analyses

Statistical analysis title	Analysis of Acute Migraine-specific Treatment

Statistical analysis description:

Analyzed using a linear mixed effects model including treatment group, baseline value, stratification factors (region and prior/current treatment with migraine prophylactic medication), scheduled visit, and the interaction of treatment group with scheduled visit.

Comparison groups	Placebo v Erenumab 70 mg QM
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Generalized linear mixed model
Parameter estimate	Difference in LS Means
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.21

Secondary: Percentage of Participants with at Least a 5-point Reduction from Baseline in Average Impact on Everyday Activities Domain Score Measured by MPFID at Week 12

End point title	Percentage of Participants with at Least a 5-point Reduction from Baseline in Average Impact on Everyday Activities Domain Score Measured by MPFID at Week 12

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 one stand-alone global question. Participants respond to items on a 5-point scale, with difficulty items ranging from "Without any difficulty" (0) to "Unable to do" (5) and frequency items ranging from "None of the time" (0) to "All of the time" (5). For each domain, the scores were calculated as the sum of the responses and rescaled to a 0 – 100 scale, with higher scores representing greater impact of migraine.
Monthly average MPFID score is the sum of observed MPFID scores divided by the total number of observed MPFID scores between monthly doses of study drug.
The analysis was conducted in the efficacy analysis set; participants with missing post-baseline data were counted as non-responders.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 4 weeks of the 12-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	282		
Units: percentage of participants				
number (not applicable)	35.8	40.4		

Statistical analyses

Statistical analysis title	Analysis of Impact on Everyday Activities

Statistical analysis description:

Analyzed using a Cochran-Mantel-Haenszel (CMH) test after the missing data were imputed as non-response, stratified by 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	570
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.71

Secondary: Percentage of Participants with at Least a 5 Point Reduction from Baseline in Average Impact on Physical Impairment Domain Score Measured by MPFID at Week 12

End point title	Percentage of Participants with at Least a 5 Point Reduction from Baseline in Average Impact on Physical Impairment Domain Score Measured by MPFID at Week 12

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 one stand-alone global question. Participants respond to items on a 5-point scale, with difficulty items ranging from "Without any difficulty" (0) to "Unable to do" (5) and frequency items ranging from "None of the time" (0) to "All of the time" (5). For each domain, the scores were calculated as the sum of the responses and rescaled to a 0 – 100 scale, with higher scores representing greater impact of migraine.
Monthly average MPFID score is the sum of observed MPFID scores divided by the total number of observed MPFID scores between monthly doses of study drug.
The analysis was conducted in the efficacy analysis set; participants with missing post-baseline data were counted as non-responders.

End point type	Secondary

End point timeframe:

4-week baseline phase and the last 4 weeks of the 12-week double-blind treatment phase

End point values	Placebo	Erenumab 70 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	282		
Units: percentage of participants				
number (not applicable)	27.1	33.0		

Statistical analyses

Statistical analysis title	Analysis of Reduction in Physical Impairment

Statistical analysis description:

Analyzed using a Cochran-Mantel-Haenszel (CMH) test after the missing data were imputed as non-response, stratified by 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	570
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.9

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4, where:
Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);
Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL;
Grade 4 = Life-threatening consequences; urgent intervention indicated
Grade 5 = Death related to AE.
For the double-blind treatment phase adverse events were analyzed for all randomized participants who received at least one dose of study drug. For the open-label treatment phase adverse events were analyzed for all participants who received at least one dose of study drug in the open-label treatment phase.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 12 weeks after the last dose.
The double-blind treatment phase was 12 weeks and the open-label treatment phase was 28 weeks.

End point values	Double-blind Treatment Phase: Placebo	Double-blind Treatment Phase: Erenumab 70 mg QM	Open-label Treatment Phase: Erenumab 70 mg QM	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	289	283	538	
Units: participants				
Any adverse event	158	136	337	
Adverse event Grade ≥ 2	96	72	245	
Adverse event Grade ≥ 3	8	6	34	
Adverse event Grade ≥ 4	0	0	2	
Serious adverse events	5	3	15	
AE leading to discontinuation of study drug	1	5	13	
Fatal adverse events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Antibodies to Erenumab

End point title	Number of Participants who Developed Antibodies to Erenumab

End point description:

Blood samples were first tested in an electrochemiluminescence (ECL)-based bridging immunoassay to detect anti-drug antibodies (ADA) against erenumab. Samples confirmed to be positive for binding antibodies were subsequently tested in a cell-based bioassay to determine neutralizing activity against erenumab (Neutralizing Antibody Assay).
Developing antibody incidence indicates participants with a negative or no result at baseline and a positive result at any time post-baseline.
If a sample was positive for binding antibodies and demonstrated neutralizing activity at the same time point, the sample was defined as positive for neutralizing antibodies.
Transient indicates negative result at the subject's last time point tested, for those subjects with a positive binding/neutralizing result post-baseline.
Participants who received at least one dose of erenumab and with post-baseline data are included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (the period prior to the first dose erenumab 70 mg) and post-baseline (the period after the first dose of erenumab 70 mg until 12 weeks after last dose)

End point values	Placebo	Erenumab 70 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269[6]	279[7]		
Units: participants				
Binding antibody positive	25	24		
-Transient binding antibody positive	10	11		
Neutralizing antibody positive	0	2		
-Transient neutralizing antibody positive	0	2		

Notes:

[6] - Participants who received at least one dose of erenumab 70 mg and with a post-baseline result

[7] - Participants who received at least one dose of erenumab 70 mg and with a post-baseline result

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 12 weeks after the last dose.
The double-blind treatment phase was 12 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 (12 weeks): Placebo

Reporting group description:

Participants received placebo on day 1 and at weeks 4 and 8 by subcutaneous injection during the double-blind treatment phase.

Reporting group title	Double-blind Treatment Phase (12 weeks): Erenumab 70 mg QM

Reporting group description:

Participants received erenumab 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.

Reporting group title	Open-label Treatment Phase (28 weeks): Erenumab 70 mg QM

Reporting group description:

Participants received erenumab 70 mg administered by subcutaneous injection at weeks 12, 16, 20, 24, 28, 32, and 36 during the open-label treatment phase.

Serious adverse events	Double-blind Treatment Phase (12 weeks): Placebo	Double-blind Treatment Phase (12 weeks): Erenumab 70 mg QM	Open-label Treatment Phase (28 weeks): Erenumab 70 mg QM
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 289 (1.73%)	3 / 283 (1.06%)	15 / 538 (2.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	2 / 538 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 289 (0.35%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Nasal septal operation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 289 (0.35%)	0 / 283 (0.00%)	0 / 538 (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			
Endometriosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haematoma			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural pulmonary embolism			

subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 289 (0.35%)	1 / 283 (0.35%)	0 / 538 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			

subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 289 (0.35%)	0 / 283 (0.00%)	0 / 538 (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
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 289 (0.35%)	0 / 283 (0.00%)	0 / 538 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 289 (0.00%)	1 / 283 (0.35%)	0 / 538 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			

subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 289 (0.00%)	0 / 283 (0.00%)	1 / 538 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 289 (0.00%)	1 / 283 (0.35%)	0 / 538 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 289 (0.35%)	0 / 283 (0.00%)	0 / 538 (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

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

Non-serious adverse events	Double-blind Treatment Phase (12 weeks): Placebo	Double-blind Treatment Phase (12 weeks): Erenumab 70 mg QM	Open-label Treatment Phase (28 weeks): Erenumab 70 mg QM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 289 (15.92%)	54 / 283 (19.08%)	140 / 538 (26.02%)
Nervous system disorders			
Migraine			
subjects affected / exposed	7 / 289 (2.42%)	5 / 283 (1.77%)	28 / 538 (5.20%)
occurrences (all)	7	6	35
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	12 / 289 (4.15%)	17 / 283 (6.01%)	30 / 538 (5.58%)
occurrences (all)	14	32	95
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed	14 / 289 (4.84%)	18 / 283 (6.36%)	41 / 538 (7.62%)
occurrences (all)	14	20	45
Viral upper respiratory tract infection			
subjects affected / exposed	17 / 289 (5.88%)	17 / 283 (6.01%)	53 / 538 (9.85%)
occurrences (all)	18	18	61

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2015	Major changes included: - Allowed subjects to be on 1 stable migraine prophylactic treatment while on study. This would allow evaluation of the effect of AMG 334 in a broader patient population. - Updated C-SSRS language to provide guidance to physician or site staff in case of any suicidal ideation or behavior. - Removed several exploratory endpoints to be included in the supplemental statistical analysis. - Updated pregnancy and lactation reporting guidance. - Added collection of menses start date each month to allow for subgroup analysis of effect of AMG 334 on menstrual-related migraine. - Added a blinded interim analysis to evaluate the new MPFID PRO instrument.
26 May 2016	- Refined and reordered 2 MPFID-related secondary objectives/endpoints to include a definition of treatment response. - On the basis of the results of the PRO 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. - Revised 2 PRO-related exploratory objectives/endpoints. - Allowed for the collection of data on use of triptans or ergotamine-derivatives prior to the study, employment status, and migraine triggers. - Updated AMG 334 safety and tolerability data. - Minor text clarifications, additions, and edits throughout the protocol were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported