Clinical trial results:
A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Chronic Migraine Prevention

Summary

EudraCT number	2013-001707-36
Trial protocol	DE SE NO FI DK PL CZ GB
Global end of trial date	28 April 2016

Results information

Result version number	v1 (current)
This version publication date	14 May 2017
First version publication date	14 May 2017

Trial information

Trial identification

Sponsor protocol code	20120295

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02066415
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, 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	28 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of AMG 334 compared to placebo on the change from baseline in monthly migraine days, in subjects with chronic 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	05 March 2014
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: 14
Country: Number of subjects enrolled	United States: 301
Country: Number of subjects enrolled	Czech Republic: 54
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 38
Country: Number of subjects enrolled	Germany: 72
Country: Number of subjects enrolled	Norway: 35
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Sweden: 64
Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	667
EEA total number of subjects	352

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)	666
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 69 centers in Canada, Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, United Kingdom, and the United States of America (USA).
The First subject was enrolled on 05 March 2014 and the last subject enrolled on 05 November 2015.

Pre-assignment

Screening details:

Of the 953 subjects screened, 286 were enrolled but not randomized; 667 subjects were randomized in a 3:2:2 ratio to receive placebo, AMG 334 70 mg, or AMG 334 140 mg. Randomization was stratified by region (North America vs Other) and medication overuse at baseline (Yes vs No).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

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.

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

Dosage and administration details:

Administered once a month subcutaneously by authorized investigational site study staff.

Arm title	AMG 334 70 mg

Arm description:

Participants received AMG 334 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.

Arm type	Experimental
Investigational medicinal product name	AMG 334
Investigational medicinal product code	AMG 334
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered once a month subcutaneously by authorized investigational site study staff.

Arm title	AMG 334 140 mg

Arm description:

Participants received AMG 334 140 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.

Arm type	Experimental

Investigational medicinal product name	AMG 334
Investigational medicinal product code	AMG 334
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered once a month subcutaneously by authorized investigational site study staff.

Number of subjects in period 1	Placebo	AMG 334 70 mg	AMG 334 140 mg
Started	286	191	190
Received Study Drug	282	190	188
Completed	265	184	182
Not completed	21	7	8
Consent withdrawn by subject	9	1	4
Lost to follow-up	7	2	2
Decision by sponsor	5	4	2

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.	
Reporting group title	AMG 334 70 mg
Reporting group description:	
Participants received AMG 334 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.	
Reporting group title	AMG 334 140 mg
Reporting group description:	
Participants received AMG 334 140 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.	

Reporting group values	Placebo	AMG 334 70 mg	AMG 334 140 mg
Number of subjects	286	191	190
Age Categorical Units: Subjects			
Adults (18-64 years)	285	191	190
From 65-84 years	1	0	0
Age Continuous Units: years			
arithmetic mean	42.1	41.4	42.9
standard deviation	± 11.3	± 11.3	± 11.1
Gender Categorical Units: Subjects			
Female	226	166	160
Male	60	25	30
Race Units: Subjects			
Asian	4	4	0
Black or African American	11	10	6
White	268	176	184
Other	3	1	0
Ethnicity Units: Subjects			
Hispanic/Latino	9	7	10
Not Hispanic/Latino	277	184	180
Prior Migraine Prophylactic Medication Units: Subjects			
Yes	218	138	136
No	68	53	54
Prior Migraine Prophylactic Treatment Failure Units: Subjects			
Yes	200	127	126
No	86	64	64
Region Units: Subjects			
North America	135	91	89

Other	151	100	101
Medication Overuse			
Medication overuse was defined as any of the following criteria being met during the baseline (BL) phase: • ≥ 15 days of simple analgesics (>3 days/week in each week during BL with at least 5 diary days), • ≥ 10 days of triptans (> 2 days/week in each week during BL with at least 5 diary days), • ≥ 10 days of ergots (> 2 days/week in each week during BL with at least 5 diary days), • ≥ 10 days of combination therapy intake of any combination of ergots, triptans, opiates, combination-analgesic medications or simple analgesics (> 2 days/week in each week during BL with at least 5 diary days).			
Units: Subjects			
Yes	117	79	78
No	169	112	112
Monthly Migraine Days			
A migraine day is any calendar day in which the subject experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined either as a migraine without aura or a migraine with aura. Monthly migraine days are the number of migraine days in the 28-consecutive day baseline phase.			
Units: days			
arithmetic mean	18.22	17.85	17.78
standard deviation	± 4.73	± 4.39	± 4.72

Reporting group values	Total		
Number of subjects	667		
Age Categorical Units: Subjects			
Adults (18-64 years)	666		
From 65-84 years	1		
Age Continuous Units: years arithmetic mean standard deviation	- -		
Gender Categorical Units: Subjects			
Female	552		
Male	115		
Race Units: Subjects			
Asian	8		
Black or African American	27		
White	628		
Other	4		
Ethnicity Units: Subjects			
Hispanic/Latino	26		
Not Hispanic/Latino	641		
Prior Migraine Prophylactic Medication Units: Subjects			
Yes	492		
No	175		
Prior Migraine Prophylactic Treatment Failure Units: Subjects			
Yes	453		

No	214		
Region Units: Subjects			
North America	315		
Other	352		
Medication Overuse			
Medication overuse was defined as any of the following criteria being met during the baseline (BL) phase: • ≥ 15 days of simple analgesics (>3 days/week in each week during BL with at least 5 diary days), • ≥ 10 days of triptans (> 2 days/week in each week during BL with at least 5 diary days), • ≥ 10 days of ergots (> 2 days/week in each week during BL with at least 5 diary days), • ≥ 10 days of combination therapy intake of any combination of ergots, triptans, opiates, combination-analgesic medications or simple analgesics (> 2 days/week in each week during BL with at least 5 diary days).			
Units: Subjects			
Yes	274		
No	393		
Monthly Migraine Days			
A migraine day is any calendar day in which the subject experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined either as a migraine without aura or a migraine with aura. Monthly migraine days are the number of migraine days in the 28-consecutive day baseline phase.			
Units: days arithmetic mean standard deviation	- -		

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.	
Reporting group title	AMG 334 70 mg
Reporting group description:	
Participants received AMG 334 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.	
Reporting group title	AMG 334 140 mg
Reporting group description:	
Participants received AMG 334 140 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.	

Primary: Change From Baseline in Monthly Migraine Days

End point title	Change From Baseline in Monthly Migraine Days
End point description:	
Participants recorded migraines in an eDiary on a daily basis. A migraine without aura is defined as a headache lasting continuously for ≥ 4 hours and meeting either criteria a and/or b: a) ≥ 2 of the following pain features: • Unilateral • Throbbing • Moderate to severe • Exacerbated with exercise or physical activity b) ≥ 1 of the associated symptoms: • Nausea and/or vomiting • Photophobia and phonophobia A migraine with aura met the following criteria c and d: c) ≥ 1 of the following fully reversible aura symptoms: • Visual • Sensory • Speech and/or language • Retinal • Brainstem d) Aura with, or followed by within 1 hour, headache for ≥ 4 hours. The endpoint was calculated as: Migraine days during the last 4 weeks of treatment - migraine days during the 4-week baseline phase. The endpoint was analyzed in the efficacy analysis set which includes subjects who received at least 1 dose of study drug and completed at least 1 post-baseline monthly eDiary measurement.	
End point type	Primary
End point timeframe:	
Baseline and the last 4 weeks of the 12-week treatment period	

End point values	Placebo	AMG 334 70 mg	AMG 334 140 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	188	187	
Units: migraine days / month				
least squares mean (confidence interval 95%)	-4.18 (-4.86 to -3.5)	-6.64 (-7.47 to -5.81)	-6.63 (-7.45 to -5.8)	

Statistical analyses

Statistical analysis title	Primary Analysis of AMG 334 70 mg vs Placebo
Statistical analysis description:	
The primary endpoint was analyzed using a linear mixed effects model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit. The analysis included all participants in the efficacy analysis set (656 subjects).	
Comparison groups	Placebo v AMG 334 70 mg
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear mixed model
Parameter estimate	Difference in LS means
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.52
upper limit	-1.39

Statistical analysis title	Primary Analysis of AMG 334 140 mg vs Placebo
Statistical analysis description:	
The primary endpoint was analyzed using a linear mixed effects model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit. The analysis included all participants in the efficacy analysis set (656 subjects).	
Comparison groups	Placebo v AMG 334 140 mg
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear mixed model
Parameter estimate	Difference in LS means
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	-1.38

Secondary: Percentage of Participants with at Least a 50% Reduction in Monthly

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

End point description:

This analysis was performed using the efficacy analysis set with non-responder imputation.

End point type	Secondary

End point timeframe:

Baseline and week 12

End point values	Placebo	AMG 334 70 mg	AMG 334 140 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	188	187	
Units: percentage of participants				
number (not applicable)	23.5	39.9	41.2	

Statistical analyses

Statistical analysis title	AMG 334 70 mg vs Placebo

Statistical analysis description:

This endpoint was analyzed using a Cochran-Mantel-Haenszel test after the missing data were imputed as non-response, stratified by stratification factors region and medication overuse. The analysis included all participants in the efficacy analysis set (656 subjects).

Comparison groups	Placebo v AMG 334 70 mg
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	3.27

Statistical analysis title	AMG 334 140 mg vs Placebo

Statistical analysis description:

This endpoint was analyzed using a Cochran-Mantel-Haenszel test after the missing data were imputed as non-response, stratified by stratification factors region and medication overuse. The analysis included all participants in the efficacy analysis set (656 subjects).

Comparison groups	Placebo v AMG 334 140 mg

Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	3.51

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

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

End point description:

Monthly acute migraine-specific medication treatment days is the number of days on which migraine specific medications were used between each monthly dose 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:

Baseline and week 12

End point values	Placebo	AMG 334 70 mg	AMG 334 140 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	188	187	
Units: acute migraine treatment days / month				
least squares mean (confidence interval 95%)	-1.58 (-2.05 to -1.11)	-3.45 (-4.02 to -2.87)	-4.13 (-4.7 to -3.56)	

Statistical analyses

Statistical analysis title	AMG 334 70 mg vs Placebo

Statistical analysis description:

This endpoint was analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assuming a first-order autoregressive covariance structure. The analysis included all participants in the efficacy analysis set (656 subjects).

Comparison groups	Placebo v AMG 334 70 mg

Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear mixed model
Parameter estimate	Difference in LS means
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-1.13

Statistical analysis title	AMG 334 140 mg vs Placebo

Statistical analysis description:

This endpoint was analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assuming a first-order autoregressive covariance structure. The analysis included all participants in the efficacy analysis set (656 subjects).

Comparison groups	Placebo v AMG 334 140 mg
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Generalized linear mixed model
Parameter estimate	Difference in LS means
Point estimate	-2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	-1.82

Secondary: Change From Baseline in Cumulative Monthly Headache Hours

End point title	Change From Baseline in Cumulative Monthly Headache Hours

End point description:

The cumulative duration of any qualified headache between each monthly dose of study drug regardless of acute treatment use.
A qualified headache is defined as follows:
• a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
• a qualified non-migraine headache, which is a headache that lasts continuously for ≥ 4 hours and is not a qualified migraine headache, or
• a headache of any duration for which acute headache treatment is administered.
This analysis was performed using the efficacy analysis set.

End point type	Secondary

End point timeframe:

Baseline and week 12

End point values	Placebo	AMG 334 70 mg	AMG 334 140 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	188	187	
Units: hours / month				
least squares mean (confidence interval 95%)	-55.22 (-66.38 to -44.06)	-64.76 (-78.34 to -51.17)	-74.53 (-88.05 to -61.01)	

Statistical analyses

Statistical analysis title	AMG 334 70 mg vs Placebo

Statistical analysis description:

This endpoint was analyzed using a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assuming a first-order autoregressive covariance structure. The analysis included all participants in the efficacy analysis set (656 subjects).

Comparison groups	Placebo v AMG 334 70 mg
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Generalized linear mixed model
Parameter estimate	Difference in LS means
Point estimate	-9.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.98
upper limit	7.9

Statistical analysis title	AMG 334 140 mg vs Placebo

Statistical analysis description:

A generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assuming a first-order autoregressive covariance structure. The analysis included all participants in the efficacy analysis set (656 subjects).

Comparison groups	Placebo v AMG 334 140 mg
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Generalized linear mixed model
Parameter estimate	Difference in LS means
Point estimate	-19.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.71
upper limit	-1.92

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.
Adverse events were assessed in all randomized subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 16 weeks after the last dose (24 weeks)

End point values	Placebo	AMG 334 70 mg	AMG 334 140 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	282	190	188	
Units: participants				
number (not applicable)				
Any adverse event	110	83	88	
Grade ≥ 2	65	45	42	
Grade ≥ 3	13	11	4	
Grade ≥ 4	0	1	0	
Serious adverse events	7	6	2	
AEs leading to discontinuation of study drug	2	0	2	
Fatal adverse events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Antibodies to AMG 334

End point title	Number of Participants who Developed Antibodies to AMG

End point description:

Blood samples were first tested in an electrochemiluminescence (ECL)-based bridging immunoassay to detect anti-drug antibodies (ADA) against AMG 334. Samples confirmed to be positive for binding antibodies were subsequently tested in a cell-based bioassay to determine neutralizing activity against AMG 334 (Neutralizing Antibody Assay). 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.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8, 12 and 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed in the AMG 334 treatment groups only.

End point values	AMG 334 70 mg	AMG 334 140 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: participants				
number (not applicable)				
Binding antibody positive	11	3		
Neutralizing antibody positive	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug up to 16 weeks after the last dose (24 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo on day 1 and at weeks 4 and 8 by subcutaneous injection.	
Reporting group title	AMG 334 140 mg
Reporting group description:	
Participants received AMG 334 140 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.	
Reporting group title	AMG 334 70 mg
Reporting group description:	
Participants received AMG 334 70 mg on day 1 and at weeks 4 and 8 by subcutaneous injection.	

Serious adverse events	Placebo	AMG 334 140 mg	AMG 334 70 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 282 (2.48%)	2 / 188 (1.06%)	6 / 190 (3.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	0 / 282 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
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			
Cartilage injury			
subjects affected / exposed	0 / 282 (0.00%)	1 / 188 (0.53%)	0 / 190 (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 / 282 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
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 / 282 (0.35%)	0 / 188 (0.00%)	0 / 190 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 282 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
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 adhesions			
subjects affected / exposed	0 / 282 (0.00%)	1 / 188 (0.53%)	0 / 190 (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
Abdominal pain			
subjects affected / exposed	0 / 282 (0.00%)	1 / 188 (0.53%)	0 / 190 (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
Pancreatitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 188 (0.00%)	0 / 190 (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
Vomiting			
subjects affected / exposed	1 / 282 (0.35%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 282 (0.35%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 282 (0.35%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 282 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 188 (0.00%)	0 / 190 (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
Urinary tract infection			
subjects affected / exposed	1 / 282 (0.35%)	0 / 188 (0.00%)	0 / 190 (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	Placebo	AMG 334 140 mg	AMG 334 70 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 282 (5.67%)	3 / 188 (1.60%)	6 / 190 (3.16%)
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed occurrences (all)	16 / 282 (5.67%) 17	3 / 188 (1.60%) 3	6 / 190 (3.16%) 6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2014	• A DMC replaced the Data Review Team (DRT) and the Interim Analysis Review Steering Committee (IARSC). The DMC reviewed both safety data and futility analysis results. • The plans for the interim analyses were refined, and text was added to describe the 2 interim analysis time points: Interim analyses for futility will occur after approximately 65% and 80% of subjects have been randomized. • Introduced an Event Adjudication Committee, which covered the overall AMG 334 clinical development program, to ensure a thorough and systematic review and classification of all cardiovascular and cerebrovascular events that have might occurred during the studies. • US-specific protocol supplement included (Protocol Supplement Version 1.0, dated 12 February 2015) o Major change included an addition of optional novel patient-reported outcome (Migraine Physical Function Impact Diary [MPFID]) substudy for English-speaking subjects in the USA.
23 July 2015	• 2 exploratory objectives and endpoints were elevated to secondary objectives and endpoints. • The number of randomized subjects was increased from 490 to 651 subjects to increase the power for each treatment arm and to adjust for multiplicity. • The plans for the interim analyses were refined, interim analyses for futility were removed, and text was added to describe that an administrative interim analysis may be performed after all randomized subjects have completed the double-blind treatment phase. • An optional novel patient-reported outcome MPFID substudy added globally.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported