Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Summary

EudraCT number	2015-002322-40
Trial protocol	SK BG DE LV CZ PL
Global end of trial date	13 April 2017

Results information

Result version number	v1 (current)
This version publication date	28 April 2018
First version publication date	28 April 2018

Trial information

Trial identification

Sponsor protocol code	20140254

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02575833
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	13 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of erenumab compared to placebo on exercise capacity in subjects with stable angina as measured by total exercise time during an exercise treadmill test.

Protection of trial subjects:

This study was conducted in accordance with International Council of 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	23 November 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: 20
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Slovakia: 34
Country: Number of subjects enrolled	South Africa: 2
Worldwide total number of subjects	89
EEA total number of subjects	66

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)	44
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 35 centers across the United States, South Africa, New Zealand, and the European Union (EU). Participants were enrolled from November 2015 to January 2017.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to receive either a single dose of erenumab 140 mg or placebo intravenously (IV) prior to starting an exercise treadmill test. Randomization was stratified by the total exercise time average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying exercise treadmill tests performed during screening.

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, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to receive a single dose of placebo administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.

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

Dosage and administration details:

A single dose of a matching volume of placebo infused over approximately 60 minutes.

Arm title	Erenumab 140 mg

Arm description:

Participants randomized to receive a single dose of erenumab 140 mg administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.

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

Dosage and administration details:

A single dose of erenumab 140 mg was infused over approximately 60 minutes.

Number of subjects in period 1	Placebo	Erenumab 140 mg
Started	44	45
Received study drug	44	44
Completed	43	44
Not completed	1	1
Consent withdrawn by subject	-	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive a single dose of placebo administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.	
Reporting group title	Erenumab 140 mg
Reporting group description:	
Participants randomized to receive a single dose of erenumab 140 mg administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.	

Reporting group values	Placebo	Erenumab 140 mg	Total
Number of subjects	44	45	89
Age Categorical			
Units: Subjects			
Adults (18-64 years)	21	23	44
From 65-84 years	23	22	45
Age Continuous			
Units: years			
arithmetic mean	63.5	61.8	
standard deviation	± 9.6	± 10.1	-
Gender Categorical			
Units: Subjects			
Female	11	9	20
Male	33	36	69
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Black (or African American)	5	1	6
Native Hawaiian or Other Pacific Islander	0	0	0
White	37	43	80
Multiple	0	0	0
Other	2	0	2
Ethnicity			
Units: Subjects			
Hispanic/Latino	2	1	3
Not Hispanic/Latino	42	44	86
Baseline Total Exercise Time			
Measured by an exercise treadmill test. Data are provided for 44 and 43 participants in each treatment group respectively with non-missing data.			
Units: seconds			
arithmetic mean	474.8	490.7	
standard deviation	± 149.5	± 149.7	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive a single dose of placebo administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.	
Reporting group title	Erenumab 140 mg
Reporting group description:	
Participants randomized to receive a single dose of erenumab 140 mg administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.	

Primary: Change from Baseline in Total Exercise Time

End point title	Change from Baseline in Total Exercise Time
End point description:	
Total exercise time was assessed using an exercise treadmill test. The analysis includes participants who received study drug and completed the baseline and post-randomization exercise treadmill tests.	
End point type	Primary
End point timeframe:	
Baseline and day 1, after dosing	

End point values	Placebo	Erenumab 140 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	42		
Units: seconds				
least squares mean (standard error)	8.1 (± 14.4)	-2.9 (± 14.8)		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
The primary endpoint was analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or ≥ 7 minutes). If the lower bound of the 90% confidence interval (CI) of the difference in change from baseline in exercise duration was above the non-inferiority margin of -90 seconds, then the hypothesis that erenumab does not decrease exercise duration would be supported.	
Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment Difference
Point estimate	-11

Confidence interval	
level	90 %
sides	2-sided
lower limit	-44.9
upper limit	22.9
Variability estimate	Standard error of the mean
Dispersion value	20.4

Notes:

[1] - The non-inferiority margin was -90 seconds.

Secondary: Time to Onset of Exercise-induced Angina

End point title	Time to Onset of Exercise-induced Angina

End point description:

Time to onset of angina was defined as the time the participant received study drug to the time of event onset during the exercise treadmill test. If no event occurred the participant was censored at the exercise treadmill test stop time.
The analysis includes participants who received study drug and completed the post-randomization exercise treadmill test.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Erenumab 140 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: seconds				
median (confidence interval 90%)	508.0 (405.0 to 572.0)	500.0 (420.0 to 540.0)		

Statistical analyses

Statistical analysis title	Analysis of Time to Exercise-induced Angina
Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.69 [3]
Method	Stratified Log Rank

Notes:

[2] - The log-rank test statistic was used to compare the two treatment groups at a significance level of 0.10.
[3] - Log rank test stratified by baseline total exercise time strata (< 7 minutes or ≥ 7 minutes).

Statistical analysis title	Secondary Analysis

Statistical analysis description:

Hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced angina free survival for erenumab 140 mg relative to placebo.

Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69 [4]
Method	Cox Proportional Hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.69

Notes:

[4] - Adjusted by stratified baseline total exercise time strata (< 7 or ≥ 7 minutes)

Statistical analysis title	Secondary Analysis

Statistical analysis description:

Hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced angina free survival for erenumab 140 mg relative to placebo.

Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 [5]
Method	Cox Proportional Hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	1.26

Notes:

[5] - Adjusted by continuous baseline total exercise time

Statistical analysis title	Secondary Analysis

Statistical analysis description:

Hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced angina free survival for erenumab 140 mg relative to placebo.

Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47 [6]
Method	Cox Proportional Hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	1.28

Notes:

[6] - Adj1usted by baseline total exercise time strata (< 7 or ≥ 7 minutes), age group (< 65, ≥ 65), and sex.

Secondary: Time to Onset of ≥ 1 mm ST-segment Depression

End point title	Time to Onset of ≥ 1 mm ST-segment Depression

End point description:

Time to onset of ≥ 1 mm ST-segment depression was defined as the time the participant received study drug to the time of event onset during the exercise treadmill test. If no event occurred the participant was censored at the exercise treadmill test stop time.
Heart rate and rhythm were monitored during the exercise treadmill test by electrocardiography (ECG).
The analysis includes participants who received study drug and completed the post-randomization exercise treadmill test.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Erenumab 140 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: seconds				
median (confidence interval 90%)	420.0 (409.0 to 480.0)	407.0 (380.0 to 443.0)		

Statistical analyses

Statistical analysis title	Analysis of Time to ≥ 1 mm ST-segment Depression
Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.59 [8]
Method	Stratified Log Rank

Notes:

[7] - The log-rank test statistic was used to compare the two treatment groups at a significance level of 0.10.
[8] - Log rank test stratified by baseline total exercise time strata (< 7 minutes or ≥ 7 minutes).

Statistical analysis title	Secondary Analysis

Statistical analysis description:

Hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced ST-segment depression free survival for erenumab 140 mg relative to placebo.

Comparison groups	Placebo v Erenumab 140 mg

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59 [9]
Method	Cox Proportional Hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.76
upper limit	1.69

Notes:

[9] - Adjusted by stratified baseline total exercise time strata (< 7 or ≥ 7 minutes)

Statistical analysis title	Secondary Analysis

Statistical analysis description:

Hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced ST-segment depression free survival for erenumab 140 mg relative to placebo.

Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75 [10]
Method	Cox Proportional Hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.6

Notes:

[10] - Adjusted by continuous baseline total exercise time

Statistical analysis title	Secondary Analysis

Statistical analysis description:

Hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced ST-segment depression free survival for erenumab 140 mg relative to placebo.

Comparison groups	Placebo v Erenumab 140 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39 [11]
Method	Cox Proportional Hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.82
upper limit	1.87

Notes:

[11] - Adjusted by baseline total exercise time strata (< 7 or ≥ 7 minutes), age group (< 65, ≥ 65), and sex.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Erenumab 140 mg
Reporting group description: Participants received a single dose of erenumab 140 mg administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.	
Reporting group title	Placebo
Reporting group description: Participants received a single dose of placebo administered by intravenous infusion on day 1 prior to starting an exercise treadmill test.	

Serious adverse events	Erenumab 140 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Erenumab 140 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 44 (9.09%)	6 / 44 (13.64%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 44 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 44 (4.55%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 44 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Viral infection			
subjects affected / exposed	0 / 44 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 44 (4.55%)	0 / 44 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2015	- Clarified language throughout the protocol and removed references to the storage of future research samples
17 November 2015	- Added a 12-lead electrocardiogram to be conducted 4 hours after the completion of the Exercise Treadmill Test on day 1 - Added an assessment of anti-AMG 334 antibodies at day 1, week 4, and End of Study - Added a summary of clinical safety data to the Background and Rationale section - Clarified language throughout the protocol
27 January 2016	- Increased the number of study centers - Supported decreasing the screen failure rate by: - Allowing for the use of 2 out of 3 screening exercise treadmill tests to qualify patients for enrollment - Removing the restriction for antianginal medication on the morning of the exercise treadmill test - Reworded inclusion criteria for clarification purposes - Clarified the background safety information of AMG 334 use in patients with migraine. - Clarified the definition of the Columbia-Suicidality Severity Scale - Clarified adverse event, drug related event, and serious adverse event reporting instructions - Aligned with changes made to the updated standard Amgen protocol template
28 October 2016	- Change in primary hypotheses, specifically to change the non-inferiority margin from -60 seconds to -90 seconds. - Sample size was changed from 120 subjects to at least 54 subjects. - Clarification of rescreening of screen failures due to technical difficulties will be reviewed by Amgen to determine if rescreening is permitted. - Clarification of text regarding dosage adjustments, delays, rules for withholding or restarting, or permanent discontinuation - Clarification of timing use of antianginals post exercise treadmill test - Clarification of who will be blinded and timing of unblinding - Clarification of primary analysis - Clarification of primary efficacy endpoint - Schedule of Assessments: Day 1 visits moved to occur within on study visits, as these were previously shown incorrectly within the screening period. An instructional footnote was also added for screening visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported