Clinical trial results:
A 2-part, Phase 2/3 Study to Assess the Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia. Part A – Open-label, Single-arm, Multicenter Pilot Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia. Part B – Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia

Summary

EudraCT number	2011-005399-40
Trial protocol	BE CZ ES IT NL Outside EU/EEA
Global end of trial date	31 January 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	03 August 2015

Trial information

Trial identification

Sponsor protocol code	20110233

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01588496
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	31 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterize the effect of 12 weeks of evolocumab on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with homozygous familial hypercholesterolemia (HoFH).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy:

Subjects were permitted to remain on a stable dose of lipid-lowering medications throughout the study.

Evidence for comparator: -

Actual start date of recruitment	05 April 2012
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: 2
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Lebanon: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	South Africa: 33

Worldwide total number of subjects	58
EEA total number of subjects	16

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)	11
Adults (18-64 years)	47
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female adults and adolescents ages ≥ 12 to ≤ 65 years (≥ 12 to ≤ 80 years in Part B) with a diagnosis of homozygous familial hypercholesterolemia (HoFH) were eligible for this study. The first participant enrolled on 05 April 2012and the last participant enrolled on 08 November 2013.

Pre-assignment

Screening details:

Part A was an open-label, single-arm, multicenter pilot study. Part B was a double-blind, randomized, placebo-controlled, multicenter study with expanded enrollment. In Part B participants were randomized in a 1:2 allocation stratified on the basis of screening low-density lipoprotein cholesterol (LDL-C) (< 420 mg/dL vs ≥ 420 mg/dL).

Period 1

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

Blinding implementation details:

Part A was an open-label, single-arm, multicenter pilot study where all enrolled subjects received open-label evolocumab.
Part B was a double-blind, randomized, placebo-controlled, multicenter study with expanded enrollment that was initiated after effective LDL-C reduction (defined as an average reduction in LDL-C of ≥ 15% at week 12) was demonstrated in Part A.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Evolocumab

Arm description:

Participants received open-label evolocumab 420 mg subcutaneously (SC) once a month (QM) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Evolocumab
Investigational medicinal product code	AMG 145
Other name	Repatha
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection

Arm title	Part B: Evolocumab

Arm description:

Participants received double-blind evolocumab 420 mg subcutaneously once a month for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Evolocumab
Investigational medicinal product code	AMG 145
Other name	Repatha
Pharmaceutical forms	Solution for injection, Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection

Arm title	Part B: Placebo

Arm description:	
Participants received double-blind placebo subcutaneously once a month for 12 weeks.	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection

Number of subjects in period 1	Part A: Evolocumab	Part B: Evolocumab	Part B: Placebo
Started	8	33	17
Received Treatment	8	33	16
Completed	8	33	16
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Evolocumab
Reporting group description:	
Participants received open-label evolocumab 420 mg subcutaneously (SC) once a month (QM) for 12 weeks.	
Reporting group title	Part B: Placebo
Reporting group description:	
Participants received double-blind placebo subcutaneously once a month for 12 weeks.	
Reporting group title	Part B: Evolocumab
Reporting group description:	
Participants received double-blind evolocumab 420 mg subcutaneously once a month for 12 weeks.	

Reporting group values	Part A: Evolocumab	Part B: Placebo	Part B: Evolocumab
Number of subjects	8	17	33
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	34.3	32.8	30.3
standard deviation	± 12.4	± 13.7	± 12.4
Gender, Male/Female Units: participants			
Female	2	8	16
Male	6	9	17
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	8	16	29
Other	0	0	3
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	8	17	32
Stratification Factor: Low-Density Lipoprotein Cholesterol (LDL-C) Level			
Participants in Part A were not stratified based on LDL-C level.			
Units: Subjects			
< 420 mg/dL	0	11	21
≥ 420 mg/dL	0	6	12
Missing	8	0	0

LDL-C Concentration			
LDL-C was quantified using the ultracentrifugation method. Data are provided for the full analysis set (all enrolled subjects who received at least 1 dose of evolocumab (Part A) or all randomized subjects who received at least 1 dose of investigational product (Part B).			
Units: mg/dL			
arithmetic mean	441.7	335.8	356
standard deviation	± 113.3	± 146	± 134.5
Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	470.6	358.9	374.9
standard deviation	± 117.8	± 149.1	± 136.9
Apolipoprotein B Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	269.1	208.6	208.3
standard deviation	± 53	± 79.5	± 68.4
Total Cholesterol/HDL-C Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	15.988	12.101	11.972
standard deviation	± 5.107	± 6.619	± 6.387
Apolipoprotein B/Apolipoprotein A1 Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	2.8	2.053	2.098
standard deviation	± 0.729	± 0.967	± 1.046
Lipoprotein(a) Concentration			
Data are provided for the full analysis set			
Units: nmol/L			
median	246.5	127.5	76
inter-quartile range (Q1-Q3)	61.5 to 276	79.5 to 200.5	25.5 to 145
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Concentration			
Data are provided for the full analysis set			
Units: ng/mL			
arithmetic mean	598.6	640.3	674.2
standard deviation	± 121.1	± 207.5	± 180

Reporting group values	Total		
Number of subjects	58		
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	26		

Male	32		

Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Black or African American	0		
Native Hawaiian or Other Pacific Islander	0		
White	53		
Other	3		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	57		
Stratification Factor: Low-Density Lipoprotein Cholesterol (LDL-C) Level			
Participants in Part A were not stratified based on LDL-C level.			
Units: Subjects			
< 420 mg/dL	32		
≥ 420 mg/dL	18		
Missing	8		
LDL-C Concentration			
LDL-C was quantified using the ultracentrifugation method. Data are provided for the full analysis set (all enrolled subjects who received at least 1 dose of evolocumab (Part A) or all randomized subjects who received at least 1 dose of investigational product (Part B).			
Units: mg/dL arithmetic mean standard deviation	- -		
Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL arithmetic mean standard deviation	- -		
Apolipoprotein B Concentration			
Data are provided for the full analysis set			
Units: mg/dL arithmetic mean standard deviation	- -		
Total Cholesterol/HDL-C Ratio			
Data are provided for the full analysis set			
Units: ratio arithmetic mean standard deviation	- -		
Apolipoprotein B/Apolipoprotein A1 Ratio			
Data are provided for the full analysis set			
Units: ratio arithmetic mean standard deviation	- -		
Lipoprotein(a) Concentration			

Data are provided for the full analysis set			
Units: nmol/L median inter-quartile range (Q1-Q3)	- 		
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Concentration			
Data are provided for the full analysis set			
Units: ng/mL arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Part A: Evolocumab
Reporting group description:	
Participants received open-label evolocumab 420 mg subcutaneously (SC) once a month (QM) for 12 weeks.	
Reporting group title	Part B: Evolocumab
Reporting group description:	
Participants received double-blind evolocumab 420 mg subcutaneously once a month for 12 weeks.	
Reporting group title	Part B: Placebo
Reporting group description:	
Participants received double-blind placebo subcutaneously once a month for 12 weeks.	

Primary: Part A: Percent Change From Baseline in Low Density Lipoprotein Cholesterol (LDL-C) at Week 12

End point title	Part A: Percent Change From Baseline in Low Density Lipoprotein Cholesterol (LDL-C) at Week 12[1][2]
End point description:	
LDL-C was quantified using the ultracentrifugation method. All endpoints are analyzed in the full analysis set.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Part A provided an estimate of the LDL-C reduction in this particular population and was used to guide the decision to initiate Part B; formal hypothesis testing was performed only in Part B.
[2] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent change				
arithmetic mean (standard error)	-16.5 (± 6.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Percent Change From Baseline in Low Density Lipoprotein Cholesterol (LDL-C) at Week 12

End point title	Part B: Percent Change From Baseline in Low Density Lipoprotein Cholesterol (LDL-C) at Week 12[3]

End point description:

LDL-C was quantified using the ultracentrifugation method.

End point type	Primary

End point timeframe:

Baseline and Week 12

Notes:

[3] - 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 pertains to subjects in Part B only

End point values	Part B: Placebo	Part B: Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	33		
Units: percent change				
least squares mean (standard error)	7.88 (± 5.26)	-23.05 (± 3.78)		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

LDL-C lowering was analyzed by comparing evolocumab and placebo. Statistical analysis was 2-sided with a significance level of 0.05.

Comparison groups	Part B: Placebo v Part B: Evolocumab
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-30.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.86
upper limit	-18
Variability estimate	Standard error of the mean
Dispersion value	6.42

Notes:

[4] - Model includes treatment group, baseline LDL-C level (< 420 mg/dL vs ≥ 420 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Part A: Change From Baseline in LDL-C at Week 12

End point title	Part A: Change From Baseline in LDL-C at Week 12[5]

End point description:

LDL-C was quantified using the ultracentrifugation method.

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[5] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg/dL				
arithmetic mean (standard error)	-70.6 (± 32.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (non-HDL-C) at Week 12

End point title	Part A: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (non-HDL-C) at Week 12 [6]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[6] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent change				
arithmetic mean (standard error)	-16.6 (± 6.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in the Total Cholesterol/HDL-C Ratio at Week 12

End point title	Part A: Percent Change From Baseline in the Total Cholesterol/HDL-C Ratio at Week 12[7]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[7] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent change				
arithmetic mean (standard error)	-18.319 (± 6.058)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in Apolipoprotein B at Week 12

End point title	Part A: Percent Change From Baseline in Apolipoprotein B at Week 12 [8]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[8] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent change				
arithmetic mean (standard error)	-14.9 (± 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12

End point title	Part A: Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12[9]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[9] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent change				
arithmetic mean (standard error)	-15.65 (± 4.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Participants With 15% or Greater Reduction in LDL-C From Baseline at Week 12

End point title	Part A: Percentage of Participants With 15% or Greater Reduction in LDL-C From Baseline at Week 12[10]

End point description:

LDL-C was quantified using the ultracentrifugation method.

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[10] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) at Week 12

End point title	Part A: Change From Baseline in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) at Week 12 [11]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[11] - 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 pertains to subjects in Part A only

End point values	Part A: Evolocumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
arithmetic mean (standard error)	-151.3 (± 81.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Mean Percent Change From Baseline in LDL-C at Weeks 6 and 12

End point title	Part B: Mean Percent Change From Baseline in LDL-C at Weeks 6 and 12[12]

End point description:

LDL-C was quantified using the ultracentrifugation method.

End point type	Secondary

End point timeframe:

Baseline and Weeks 6 and 12

Notes:

[12] - 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 pertains to subjects in Part B only

End point values	Part B: Placebo	Part B: Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	33		
Units: percent change				
least squares mean (standard error)	4.22 (± 4.56)	-25.56 (± 3.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Part B: Placebo v Part B: Evolocumab

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-29.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.94
upper limit	-18.62
Variability estimate	Standard error of the mean
Dispersion value	5.54

Notes:

[13] - Model includes treatment group, baseline LDL-C level (< 420 mg/dL vs ≥ 420 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Part B: Percent Change From Baseline in Apolipoprotein B at Week 12

End point title	Part B: Percent Change From Baseline in Apolipoprotein B at Week 12[14]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[14] - 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 pertains to subjects in Part B only

End point values	Part B: Placebo	Part B: Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	33		
Units: percent change				
least squares mean (standard error)	3.97 (± 4.74)	-19.17 (± 3.46)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Part B: Placebo v Part B: Evolocumab
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-23.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.83
upper limit	-11.45
Variability estimate	Standard error of the mean
Dispersion value	5.81

Notes:

[15] - Model includes treatment group, baseline LDL-C level (< 420 mg/dL vs ≥ 420 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Part B: Mean Percent Change From Baseline in Apolipoprotein B at Weeks 6 and 12

End point title	Part B: Mean Percent Change From Baseline in Apolipoprotein B at Weeks 6 and 12[16]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 6 and 12

Notes:

[16] - 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 pertains to subjects in Part B only

End point values	Part B: Placebo	Part B: Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	33		
Units: percent change				
least squares mean (standard error)	2.65 (± 4.42)	-20.24 (± 3.18)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Part B: Placebo v Part B: Evolocumab
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [17]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-22.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.72
upper limit	-12.05

Variability estimate	Standard error of the mean
Dispersion value	5.38

Notes:

[17] - Model includes treatment group, baseline LDL-C level (< 420 mg/dL vs ≥ 420 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Part B: Percent Change From Baseline in Lipoprotein (a) at Week 12

End point title	Part B: Percent Change From Baseline in Lipoprotein (a) at Week 12[18]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[18] - 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 pertains to subjects in Part B only

End point values	Part B: Placebo	Part B: Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	33		
Units: percent change				
least squares mean (standard error)	2.43 (± 5.49)	-9.4 (± 4.07)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Part B: Placebo v Part B: Evolocumab
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088 [19]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-11.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.48
upper limit	1.82
Variability estimate	Standard error of the mean
Dispersion value	6.77

Notes:

[19] - Model includes treatment group, baseline LDL-C level (< 420 mg/dL vs ≥ 420 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Part B: Mean Percent Change From Baseline in Lipoprotein (a) at Weeks

6 and 12

End point title	Part B: Mean Percent Change From Baseline in Lipoprotein (a) at Weeks 6 and 12[20]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 6 and 12

Notes:

[20] - 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 pertains to subjects in Part B only

End point values	Part B: Placebo	Part B: Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	33		
Units: percent change				
least squares mean (standard error)	-1.43 (± 4.78)	-12.71 (± 3.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Part B: Placebo v Part B: Evolocumab
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088 [21]
Method	Repeated measures linear effects
Parameter estimate	LS Mean Treatment Difference
Point estimate	-11.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.11
upper limit	0.56
Variability estimate	Standard error of the mean
Dispersion value	5.86

Notes:

[21] - Model includes treatment group, baseline LDL-C level (< 420 mg/dL vs ≥ 420 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first dose of study drug until 28 days after the last dose (12 weeks).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Part A: Evolocumab
Reporting group description: Participants received open-label evolocumab 420 mg subcutaneously (SC) once a month (QM) for 12 weeks.	
Reporting group title	Part B: Evolocumab
Reporting group description: Participants received double-blind evolocumab 420 mg subcutaneously once a month for 12 weeks.	
Reporting group title	Part B: Placebo
Reporting group description: Participants received double-blind placebo subcutaneously once a month for 12 weeks.	

Serious adverse events	Part A: Evolocumab	Part B: Evolocumab	Part B: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Part A: Evolocumab	Part B: Evolocumab	Part B: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	11 / 33 (33.33%)	10 / 16 (62.50%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 33 (3.03%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Medical device site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 33 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 33 (3.03%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Abdominal pain upper			

subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 33 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 33 (3.03%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 33 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 33 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 33 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 33 (6.06%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	3 / 33 (9.09%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 33 (6.06%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 33 (9.09%) 3	1 / 16 (6.25%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2012	- added optional visits for weeks 2 and 10, since more frequent visits would help mitigate against the risk of missing a detectable therapeutic effect - clarified that only phase 3 was blinded - added additional information about the analysis between the phases of the study - changed the sample size in phase 2 - updated safety reporting language
24 May 2013	- clarified that phase 2 was successfully completed and updated the primary, secondary and tertiary endpoints for phase 3 based on phase 2 data - added co-primary and co-secondary efficacy endpoints to include changes from baseline at the mean of weeks 6 and 12 and at the mean of weeks 8 and 12 for the lipid parameters (see Amendment 3 below for subsequent changes to these endpoints) - added treatment response (≥ 15% reduction in LDL-C at week 12) as an exploratory endpoint in phase 3 - added the LDLR Defective Analysis Set in phase 3 - added multiplicity adjustment methods - updated safety reporting language - allowed additional flexibility for specific visits - expanded age limit to include ≥ 12 to ≤ 80 years - added an exclusion criterion for lomitapide use - updated the list of participating countries - added new evolocumab formulation and autoinjector/pen (AI/pen) language - introduced the simplified terminology of monthly dosing (QM) - implemented minor editorial clarifications and corrections
12 November 2013	- removed the use of co-primary and co-secondary endpoints - made percent change in LDL-C from baseline to week 12 the primary endpoint - removed changes from baseline at the mean of weeks 8 and 12 from all endpoints, but kept changes from baseline to the mean of weeks 6 and 12 as secondary and exploratory endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported