Clinical trial results:
A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Long-term Tolerability and Durable Efficacy of AMG 145 on LDL-C in Hyperlipidemic Subjects

Summary

EudraCT number	2011-003827-37
Trial protocol	CZ HU BE AT DK
Global end of trial date	07 November 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	20110109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01516879
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	07 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of 52 weeks of subcutaneous evolocumab monthly (QM), compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) when added to background lipid-lowering therapy.

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:

All eligible subjects received 1 of 4 background therapies based upon their LDL-C goal derived from National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP) risk, screening LDL-C, current lipid lowering therapy, and level of LDL-C lowering required to achieve their individual LDL-C goal:
1. no drug therapy required - diet alone
2. low dose drug therapy required - diet plus atorvastatin 10 mg orally once daily
3. high dose drug therapy required - diet plus atorvastatin 80 mg orally once daily
4. maximal drug therapy required - diet plus atorvastatin 80 mg plus ezetimibe 10 mg orally once daily.

Evidence for comparator: -

Actual start date of recruitment	05 January 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: 155
Country: Number of subjects enrolled	United States: 369
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 102
Country: Number of subjects enrolled	Denmark: 87
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	South Africa: 121

Worldwide total number of subjects	905
EEA total number of subjects	243

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)	699
From 65 to 84 years	206
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adults with fasting low-density lipoprotein cholesterol (LDL-C) ≥ 75 mg/dL and triglycerides ≤ 400 mg/dL were eligible. The first patient enrolled on 5 January 2012 and the last patient enrolled on 12 October 2012. All patients were counseled on the National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet.

Pre-assignment

Screening details:

Patients were assigned to 1 of 4 background lipid-lowering regimens for a 4-12 week stabilization period: diet alone, diet and 10 mg atorvastatin daily, diet and 80 mg atorvastatin daily, or diet, 80 mg atorvastatin and 10 mg ezetimibe daily. Patients meeting criteria were randomized 2:1 to evolocumab or placebo, stratified by background therapy.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneously once a month for 52 weeks.

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:

Placebo subcutaneous injection one a month

Arm title	Evolocumab

Arm description:

Participants received evolocumab 420 mg subcutaneously once a month for 52 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:

Evolocumab 420 mg subcutaneously once a month

Number of subjects in period 1	Placebo	Evolocumab
Started	303	602
Received Treatment	302	599
Completed	287	568
Not completed	16	34
Consent withdrawn by subject	9	11
Other	5	10
Death	-	2
Lost to follow-up	2	11

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously once a month for 52 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received evolocumab 420 mg subcutaneously once a month for 52 weeks.	

Reporting group values	Placebo	Evolocumab	Total
Number of subjects	303	602	905
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.6	55.9	
standard deviation	± 10.3	± 10.9	-
Gender, Male/Female Units: participants			
Female	162	312	474
Male	141	290	431
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	3	3
Asian	16	41	57
Black or African American	23	53	76
Native Hawaiian or Other Pacific Islander	0	1	1
White	249	478	727
Other	13	26	39
Mixed Race	2	0	2
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	17	33	50
Not Hispanic/Latino	286	569	855
Background Therapy Units: Subjects			
Diet Only	38	74	112
Diet + Atorvastatin 10 mg	129	256	385
Diet + Atorvastatin 80 mg	73	146	219
Diet + Atorvastatin 80 mg + Ezetimibe 10 mg	63	126	189
Low-density Lipoprotein Cholesterol (LDL-C) Concentration			
Cholesterol was measured by means of ultracentrifugation. Data are provided for the Full Analysis Set (all participants who were randomized and received at least 1 dose of study treatment).			
Units: mg/dL			
arithmetic mean	104	104.2	

standard deviation	± 21.6	± 22.1	-
Total Cholesterol			
Data are provided for the Full Analysis Set			
Units: mg/dL			
arithmetic mean	179.1	176.8	
standard deviation	± 27.2	± 27.5	-
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Concentration			
Data are provided for the Full Analysis Set			
Units: mg/dL			
arithmetic mean	125.6	124.2	
standard deviation	± 26.9	± 25.6	-
Apolipoprotein B Concentration			
Data are provided for the Full Analysis Set			
Units: mg/dL			
arithmetic mean	87.5	87	
standard deviation	± 16.3	± 16.3	-
Total Cholesterol/High Density Lipoprotein-Cholesterol (HDL-C) Ratio			
Data are provided for the Full Analysis Set			
Units: ratio			
arithmetic mean	3.603	3.597	
standard deviation	± 1.11	± 1.04	-
Apolipoprotein B/Apolipoprotein A-1 Ratio			
Data are provided for the Full Analysis Set			
Units: ratio			
arithmetic mean	0.586	0.593	
standard deviation	± 0.17	± 0.17	-
Lipoprotein(a) Concentration			
Data are provided for the Full Analysis Set			
Units: nmol/L			
arithmetic mean	89.3	84	
standard deviation	± 108.6	± 98.5	-
Triglycerides Concentration			
Data are provided for the Full Analysis Set			
Units: mg/dL			
arithmetic mean	127.8	119.8	
standard deviation	± 65.8	± 63.2	-
High-density Lipoprotein Cholesterol (HDL-C) Concentration			
Data are providedfor the Full Analysis Set			
Units: mg/dL			
arithmetic mean	53.5	52.6	
standard deviation	± 16.1	± 15.5	-
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration			
Data are provided for the Full Analysis Set			
Units: mg/dL			
arithmetic mean	21.5	20	
standard deviation	± 13.4	± 11.4	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously once a month for 52 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received evolocumab 420 mg subcutaneously once a month for 52 weeks.	

Primary: Percent Change from Baseline in LDL-C at Week 52

End point title	Percent Change from Baseline in LDL-C at Week 52
End point description:	
Cholesterol was measured by means of ultracentrifugation. The full analysis set (FAS) included all randomized subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[1]	599[2]		
Units: percent change				
least squares mean (standard error)	6.83 (± 1.75)	-50.14 (± 1.24)		

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
The null hypothesis was that there was no mean difference in the percent change from Baseline at Week 52 in LDL-C between evolocumab 420 mg and placebo, and the alternative hypothesis was that a mean difference did exist.	
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-56.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.08
upper limit	-52.85
Variability estimate	Standard error of the mean
Dispersion value	2.1

Notes:

[3] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Change from Baseline in LDL-C at Week 52

End point title	Change from Baseline in LDL-C at Week 52

End point description:

Cholesterol was measured by means of ultracentrifugation.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[4]	599[5]		
Units: mg/dL				
least squares mean (standard error)	5.1 (± 1.9)	-52.7 (± 1.4)		

Notes:

[4] - Full Analysis Set

[5] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-57.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.3
upper limit	-53.3
Variability estimate	Standard error of the mean
Dispersion value	2.3

Notes:

[6] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percentage of Participants with an LDL-C Response at Week 52

End point title	Percentage of Participants with an LDL-C Response at Week 52

End point description:

An LDL-C response is defined as LDL-C level < 70 mg/dL (1.8 mmol/L) at Week 52.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[7]	599[8]		
Units: percentage of participants				
number (confidence interval 95%)	6.4 (4.1 to 10.1)	82.3 (78.8 to 85.3)		

Notes:

[7] - Full Analysis Set

[8] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	75.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.8
upper limit	79.7

Notes:

[9] - Based on CMH test stratified by the stratification factor. For testing, non-achievement was imputed for subjects with a missing value at Week 52.

Secondary: Percent Change from Baseline in LDL-C at Week 12

End point title	Percent Change from Baseline in LDL-C at Week 12

End point description:

Cholesterol was measured by means of ultracentrifugation.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[10]	599[11]		
Units: percent change				
least squares mean (standard error)	3.17 (± 1.31)	-54.35 (± 0.96)		

Notes:

[10] - Full analysis set

[11] - Full analysis set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-57.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.57
upper limit	-54.45
Variability estimate	Standard error of the mean
Dispersion value	1.56

Notes:

[12] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Total Cholesterol at Week 12

End point title	Percent Change from Baseline in Total Cholesterol at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[13]	599[14]		
Units: percent change				
least squares mean (standard error)	2.85 (± 0.87)	-32.3 (± 0.63)		

Notes:

[13] - Full Analysis Set

[14] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
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	-35.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.19
upper limit	-33.11
Variability estimate	Standard error of the mean
Dispersion value	1.04

Notes:

[15] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Total Cholesterol at Week 52

End point title	Percent Change from Baseline in Total Cholesterol at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[16]	599[17]		
Units: percent change				
least squares mean (standard error)	5.26 (± 1.16)	-28.18 (± 0.84)		

Notes:

[16] - Full Analysis Set

[17] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab

Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-33.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.21
upper limit	-30.68
Variability estimate	Standard error of the mean
Dispersion value	1.41

Notes:

[18] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Week 52

End point title	Percent Change from Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[19]	599[20]		
Units: percent change				
least squares mean (standard error)	8.44 (± 1.68)	-41.82 (± 1.21)		

Notes:

[19] - Full Analysis Set

[20] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [21]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-50.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.25
upper limit	-46.28
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[21] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Apolipoprotein B at Week 52

End point title	Percent Change from Baseline in Apolipoprotein B at Week 52
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[22]	599[23]		
Units: percent change				
least squares mean (standard error)	2.94 (± 1.41)	-41.26 (± 1.02)		

Notes:

[22] - Full Analysis Set

[23] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.004 [24]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-44.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.56
upper limit	-40.85
Variability estimate	Standard error of the mean
Dispersion value	1.71

Notes:

[24] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in the Total Cholesterol/HDL-C Ratio at Week 52

End point title	Percent Change from Baseline in the Total Cholesterol/HDL-C Ratio at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[25]	599[26]		
Units: percent change				
least squares mean (standard error)	6.47 (± 1.37)	-30.67 (± 0.99)		

Notes:

[25] - Full Analysis Set

[26] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [27]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-37.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.41
upper limit	-33.87
Variability estimate	Standard error of the mean
Dispersion value	1.67

Notes:

[27] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 52

End point title	Percent Change from Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[28]	599[29]		
Units: percent change				
least squares mean (standard error)	4.46 (± 1.5)	-41.75 (± 1.09)		

Notes:

[28] - Full Analysis Set

[29] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-46.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.79
upper limit	-42.63
Variability estimate	Standard error of the mean
Dispersion value	1.82

Notes:

[30] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Lipoprotein(a) at Week 52

End point title	Percent Change from Baseline in Lipoprotein(a) at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[31]	599[32]		
Units: percent change				
least squares mean (standard error)	-5.37 (± 1.62)	-27.72 (± 1.19)		

Notes:

[31] - Full Analysis Set

[32] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [33]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-22.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.15
upper limit	-18.55
Variability estimate	Standard error of the mean
Dispersion value	1.94

Notes:

[33] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Triglycerides at Week 52

End point title	Percent Change from Baseline in Triglycerides at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[34]	599[35]		
Units: percent change				
least squares mean (standard error)	8.99 (± 2.39)	-2.55 (± 1.72)		

Notes:

[34] - Full analysis set

[35] - Full analysis set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [36]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-11.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.21
upper limit	-5.86
Variability estimate	Standard error of the mean
Dispersion value	2.89

Notes:

[36] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 52

End point title	Percent Change from Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 52

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[37]	599[38]		
Units: percent change				
least squares mean (standard error)	0.35 (± 0.9)	5.77 (± 0.65)		

Notes:

[37] - Full Analysis Set

[38] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab

Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [39]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	5.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.28
upper limit	7.56
Variability estimate	Standard error of the mean
Dispersion value	1.09

Notes:

[39] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Week 52

End point title	Percent Change from Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Week 52

End point description:

Cholesterol was measured by means of ultracentrifugation.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[40]	599[41]		
Units: percent change				
least squares mean (standard error)	31.89 (± 4.69)	2.74 (± 3.36)		

Notes:

[40] - Full Analysis Set

[41] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [42]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-29.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.23
upper limit	-18.08
Variability estimate	Standard error of the mean
Dispersion value	5.64

Notes:

[42] - The model includes treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change from Week 12 to Week 52 in LDL-C

End point title	Percent Change from Week 12 to Week 52 in LDL-C

End point description:

Cholesterol was measured by means of ultracentrifugation.
Analysis was peformed in the effect durability analysis set which included subjects in the FAS who adhered to the scheduled study drug and have nonmissing LDL-C values at Baseline, Week 12 and Week 52.

End point type	Secondary

End point timeframe:

Week 12 and Week 52

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253[43]	514[44]		
Units: percent change				
least squares mean (standard error)	2.57 (± 1.56)	2.44 (± 1.14)		

Notes:

[43] - Effect Durability Analysis Set

[44] - Effect Durability Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	767
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [45]
Method	ANCOVA
Parameter estimate	LS Mean Treatment Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	3.48
Variability estimate	Standard error of the mean
Dispersion value	1.84

Notes:
[45] - Model includes treatment group and stratification factor as covariates

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first dose of study drug until 28 days after the last dose (52 weeks).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Evolocumab
Reporting group description: Participants received evolocumab 420 mg subcutaneously once a month for 52 weeks.	
Reporting group title	Placebo
Reporting group description: Participants received placebo subcutaneously once a month for 52 weeks.	

Serious adverse events	Evolocumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 599 (5.51%)	13 / 302 (4.30%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal neoplasm			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Breast prosthesis implantation			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device breakage			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	2 / 599 (0.33%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 599 (0.17%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint injury			

subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 599 (0.33%)	2 / 302 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Palpitations			
subjects affected / exposed	2 / 599 (0.33%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 599 (0.33%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	2 / 599 (0.33%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis of external ear canal			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract disorder			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 599 (0.33%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 599 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 599 (0.17%)	0 / 302 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Evolocumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 599 (29.55%)	76 / 302 (25.17%)	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	36 / 599 (6.01%)	17 / 302 (5.63%)	
occurrences (all)	38	17	
Infections and infestations			
Influenza			
subjects affected / exposed	45 / 599 (7.51%)	19 / 302 (6.29%)	
occurrences (all)	54	21	
Upper respiratory tract infection			
subjects affected / exposed	56 / 599 (9.35%)	19 / 302 (6.29%)	
occurrences (all)	66	21	
Nasopharyngitis			
subjects affected / exposed	63 / 599 (10.52%)	29 / 302 (9.60%)	
occurrences (all)	66	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2012	- added a vitamin E substudy - updated the study schema - added additional clarity on the definition of CHD risk equivalents - removed the term "absolute" from all endpoints - added information on drug dispensation and reconciliation - added information on retesting - added a rescreening cap - added steroid testing at day 1 and weeks 12, 24, and 52 - added a process for updating the DMC for consecutive LDL values below 25 mg/dl - better defined end of study (EOS) - updated blood pressure and waist circumference language to add additional clarity - clarified that doses should be split - updated the interim analysis guidelines
03 May 2012	- changed the sample size from 600 to 900 subjects in order to increase long-term safety and tolerability data supporting registration - updated the evolocumab background section with the most currently available data - added information to the 420 mg dose selection with data from the most recent evolocumab interim analysis - changed "hypercholesterolemia" to "hyperlipidemia" to be consistent with Amgen's phase 3 protocols - updated the statistics section to align the hypothesis-testing secondary endpoints with Amgen's phase 3 protocols, adjusted for multiplicity - added language that allowed Amgen to limit the enrollment of patients in certain NCEP risk categories or background therapy arms in order to prevent overly skewed enrollment in these groups - allowed down titration for subjects randomized to maximal background therapy who overshoot the LDL entry cutoff - updated the vital sign and waist circumference sections to align the language with that used in Amgen's phase 3 protocols - changed the SAE reporting requirements from 1 business day to 24 hours - added additional information on pregnancy and lactation
09 December 2012	- requirements reclassified the study from a phase 2 study to a phase 3 study - changed the dosing terminology from Q4W to QM - updated the list of completed and ongoing studies
21 February 2013	- updated three secondary endpoints - updated the study schema - added an alert threshold for elevated triglycerides - added new Amgen safety template AE & SAE language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported