EU Clinical Trials Register

Clinical trial results:

A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia (BANTING)

Summary

EudraCT number	2015-004711-21
Trial protocol	PL BE ES IT
Global end of trial date	05 September 2017

Results information

Result version number	v1 (current)
This version publication date	18 August 2018
First version publication date	18 August 2018

Trial information

Trial identification

Sponsor protocol code	20130287

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02739984
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	03 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2017
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 12 weeks of subcutaneous evolocumab once a month (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated dose of statin of at least moderate-intensity oral daily.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, and Food and Drug Administration (FDA) regulations and guidelines set forth in 21 Code of Federal Regulations parts 11, 50, 54, 56, and 312.
The study and all amendments were reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each center.
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	17 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	United States: 327
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Mexico: 10
Worldwide total number of subjects	424
EEA total number of subjects	64

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	245
From 65 to 84 years	179
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 853 patients screened, a total of 424 participants were randomized at 58 centers in Belgium, Canada, Italy, Mexico, Poland, Spain and the United States from 17 May 2016 to 05 May 2017.

Pre-assignment

Screening details:

Participants received subcutaneous placebo during a 6-week screening period. Participants who completed the screening period and met final eligibility criteria were randomized in a 1:2 ratio to placebo or evolocumab. Randomization was stratified by low-density lipoprotein cholesterol (LDL-C) level (> or < 130 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneous injection once every month (QM) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Arm title	Evolocumab

Arm description:

Participants received 420 mg evolocumab subcutaneous injection once every 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 in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once a month

Number of subjects in period 1	Placebo	Evolocumab
Started	143	281
Received Study Drug	141	280
Completed	138	279
Not completed	5	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	1
Sponsor Decision	1	-
Lost to follow-up	3	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injection once every month (QM) for 12 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received 420 mg evolocumab subcutaneous injection once every month (QM) for 12 weeks.	

Reporting group values	Placebo	Evolocumab	Total
Number of subjects	143	281	424
Age, Customized			
Units: Subjects			
< 65 years	86	159	245
65 - < 85 years	57	122	179
≥ 85 years	0	0	0
Age Continuous			
Units: years			
arithmetic mean	62.3	62.5	
standard deviation	± 8.5	± 8.5	-
Sex: Female, Male			
Units: Subjects			
Female	65	121	186
Male	78	160	238
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	7	8	15
Asian	2	4	6
Black (or African American)	32	41	73
Native Hawaiian or Other Pacific Islander	0	2	2
White	102	223	325
Multiple	0	1	1
Other	0	2	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	24	54	78
Not Hispanic or Latino	119	227	346
Unknown or Not Reported	0	0	0
Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C) Level			
Units: Subjects			
< 130 mg/dL	108	213	321
≥ 130 mg/dL	35	68	103
LDL-C Concentration			

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), 141 and 280 subjects in each treatment group respectively.

Units: mg/dL			

arithmetic mean	110.4	108.6	
standard deviation	± 33.0	± 31.0	-

Non-High-density Lipoprotein Cholesterol (non-HDL-C) Concentration

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), 141 and 280 subjects in each treatment group respectively.

Units: mg/dL			
arithmetic mean	145.5	144.6	
standard deviation	± 33.9	± 34.9	-

Apolipoprotein B Concentration

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), and with available baseline data, 138 and 272 subjects in each treatment group respectively.

Units: mg/dL			
arithmetic mean	98.1	97.1	
standard deviation	± 22.1	± 23.3	-

Total Cholesterol Concentration

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), 141 and 280 subjects in each treatment group respectively.

Units: mg/dL			
arithmetic mean	190.7	188.2	
standard deviation	± 35.0	± 36.8	-

Lipoprotein(a) Concentration

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), and with available baseline data, 137 and 273 subjects in each treatment group respectively.

Units: nmol/L			
arithmetic mean	99.4	88.0	
standard deviation	± 122.8	± 111.5	-

Triglycerides Concentration

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), 141 and 280 subjects in each treatment group respectively.

Units: mg/dL			
arithmetic mean	177.3	184.2	
standard deviation	± 89.2	± 102.2	-

High-density Lipoprotein Cholesterol (HDL-C) Concentraion

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), 141 and 280 subjects in each treatment group respectively.

Units: mg/dL			
arithmetic mean	45.2	43.6	
standard deviation	± 12.2	± 12.9	-

Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration

Data are reported for all participants in the full analysis set, consisting of randomized participants who received at least 1 dose of the study drug (placebo or evolocumab), and with available baseline data, 138 and 276 subjects in each treatment group respectively.

Units: mg/dL			
arithmetic mean	33.6	34.8	
standard deviation	± 14.3	± 15.4	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injection once every month (QM) for 12 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received 420 mg evolocumab subcutaneous injection once every month (QM) for 12 weeks.	

Primary: Percent Change From Baseline in LDL-C at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in LDL-C at the Mean of Weeks 10 and 12
End point description:	
End point type	Primary
End point timeframe:	
Baseline and Weeks 10 and 12	

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	-0.84 (± 1.76)	-64.98 (± 1.31)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-64.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.16
upper limit	-60.12

Variability estimate	Standard error of the mean
Dispersion value	2.05

Notes:

[1] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[2] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Primary: 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:

End point type	Primary

End point timeframe:

Baseline and week 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	-1.14 (± 1.92)	-54.28 (± 1.42)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-53.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.56
upper limit	-48.71
Variability estimate	Standard error of the mean
Dispersion value	2.25

Notes:

[3] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[4] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Change From Baseline in LDL-C at the Mean of Weeks 10 and 12

End point title	Change From Baseline in LDL-C at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: mg/dL				
least squares mean (standard error)	-8.3 (± 2.2)	-75.5 (± 1.6)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-67.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-72.1
upper limit	-62.2
Variability estimate	Standard error of the mean
Dispersion value	2.5

Notes:

[5] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[6] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

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

End point title	Change From Baseline in LDL-C 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	141	280		
Units: mg/dL				
least squares mean (standard error)	-8.6 (± 2.3)	-64.4 (± 1.7)		

Statistical analyses

Statistical analysis title	Treatment Difference	
Comparison groups	Placebo v Evolocumab	
Number of subjects included in analysis	421	
Analysis specification	Pre-specified	
Analysis type	superiority[7]	
P-value	< 0.0001 [8]	
Method	Repeated measures linear effects model	
Parameter estimate	LS Mean Treatment Difference	
Point estimate	-55.8	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	-61	
upper limit	-50.5	
Variability estimate	Standard error of the mean	
Dispersion value	2.7	

Notes:

[7] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[8] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in Non-HDL-C at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in Non-HDL-C at the Mean of Weeks 10 and 12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and weeks 10 and 12	

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	-0.05 (± 1.63)	-56.62 (± 1.21)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-56.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.28
upper limit	-52.85
Variability estimate	Standard error of the mean
Dispersion value	1.89

Notes:

[9] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[10] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in Non-HDL-C at Week 12

End point title	Percent Change From Baseline in Non-HDL-C 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	141	280		
Units: percent change				
least squares mean (standard error)	-0.60 (± 1.79)	-46.89 (± 1.33)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-46.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.42
upper limit	-42.15
Variability estimate	Standard error of the mean
Dispersion value	2.1

Notes:

[11] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[12] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in Apolipoprotein B at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in Apolipoprotein B at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	2.31 (± 1.58)	-50.17 (± 1.18)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-52.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.1
upper limit	-48.85
Variability estimate	Standard error of the mean
Dispersion value	1.85

Notes:

[13] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[14] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

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

End point title	Percent Change From Baseline in Apolipoprotein B 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	141	280		
Units: percent change				
least squares mean (standard error)	1.78 (± 1.73)	-40.34 (± 1.29)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-42.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.13
upper limit	-38.11
Variability estimate	Standard error of the mean
Dispersion value	2.04

Notes:

[15] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[16] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in Total Cholesterol at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in Total Cholesterol at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	-1.13 (± 1.24)	-42.19 (± 0.92)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001 [18]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-41.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.9
upper limit	-38.22
Variability estimate	Standard error of the mean
Dispersion value	1.44

Notes:

[17] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[18] - The model includes treatment group, stratification factor (screening LDL-C level), 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	141	280		
Units: percent change				
least squares mean (standard error)	-1.23 (± 1.36)	-34.97 (± 1.01)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-33.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.87
upper limit	-30.6
Variability estimate	Standard error of the mean
Dispersion value	1.59

Notes:

[19] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[20] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percentage of Participants With Mean LDL-C at Weeks 10 and 12 of Less Than 70 mg/dL (1.8 mmol/L)

End point title	Percentage of Participants With Mean LDL-C at Weeks 10 and 12 of Less Than 70 mg/dL (1.8 mmol/L)

End point description:

End point type	Secondary

End point timeframe:

Weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percentage of participants				
number (confidence interval 95%)	14.8 (9.8 to 21.8)	92.7 (89.0 to 95.2)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	77.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	70
upper limit	83.5

Notes:

[21] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[22] - Cochran Mantel Haenszel (CMH) test adjusted by the stratification factor (screening LDL-C level).

Secondary: Percentage of Participants With LDL-C at Week 12 of Less Than 70 mg/dL (1.8 mmol/L)

End point title	Percentage of Participants With LDL-C at Week 12 of Less Than 70 mg/dL (1.8 mmol/L)

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percentage of participants				
number (confidence interval 95%)	15.4 (10.2 to 22.6)	84.5 (79.5 to 88.5)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.0001 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	69.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	60.4
upper limit	75.7

Notes:

[23] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[24] - Cochran Mantel Haenszel (CMH) test adjusted by the stratification factor (screening LDL-C level).

Secondary: Percentage of Participants With at Least a 50% Reduction from Baseline in Mean LDL-C at Weeks 10 and 12

End point title	Percentage of Participants With at Least a 50% Reduction from Baseline in Mean LDL-C at Weeks 10 and 12
End point description:	

End point type	Secondary
End point timeframe:	

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percentage of participants				
number (confidence interval 95%)	0.7 (0.1 to 4.1)	84.2 (79.5 to 88.1)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.0001 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	83.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	77.7
upper limit	87.4

Notes:

[25] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[26] - Cochran Mantel Haenszel (CMH) test adjusted by the stratification factor (screening LDL-C level).

Secondary: Percentage of Participants With at Least a 50% Reduction from Baseline in LDL-C at Week 12

End point title	Percentage of Participants With at Least a 50% Reduction from Baseline in LDL-C 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	141	280		
Units: percentage of participants				
number (confidence interval 95%)	0.8 (0.1 to 4.2)	65.5 (59.4 to 71.1)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.0001 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	64.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.7
upper limit	70.3

Notes:

[27] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[28] - Cochran Mantel Haenszel (CMH) test adjusted by the stratification factor (screening LDL-C level).

Secondary: Percent Change From Baseline in Lipoprotein(a) at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in Lipoprotein(a) at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	9.63 (± 3.29)	-30.87 (± 2.43)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.0001 [30]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-40.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.11
upper limit	-32.9
Variability estimate	Standard error of the mean
Dispersion value	3.87

Notes:

[29] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[30] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

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

End point title	Percent Change From Baseline in Lipoprotein(a) 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	141	280		
Units: percent change				
least squares mean (standard error)	7.38 (± 3.06)	-25.18 (± 2.28)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001 [32]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-32.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.58
upper limit	-25.53
Variability estimate	Standard error of the mean
Dispersion value	3.57

Notes:

[31] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[32] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in Triglycerides at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in Triglycerides at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	6.61 (± 2.94)	-12.64 (± 2.19)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.0001 [34]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-19.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.95
upper limit	-12.54
Variability estimate	Standard error of the mean
Dispersion value	3.41

Notes:

[33] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[34] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in Triglycerides at Week 12

End point title	Percent Change From Baseline in Triglycerides 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	141	280		
Units: percent change				
least squares mean (standard error)	4.81 (± 3.41)	-8.90 (± 2.52)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.0001 [36]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-13.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.6
upper limit	-5.8
Variability estimate	Standard error of the mean
Dispersion value	4.02

Notes:

[35] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[36] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in HDL-C at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in HDL-C at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	-2.57 (± 1.25)	7.23 (± 0.93)		

Statistical analyses

Statistical analysis title	Treatment Difference	
Comparison groups	Placebo v Evolocumab	
Number of subjects included in analysis	421	
Analysis specification	Pre-specified	
Analysis type	superiority[37]	
P-value	< 0.0001 [38]	
Method	Repeated measures linear effects model	
Parameter estimate	LS Mean Treatment Difference	
Point estimate	9.8	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	6.95	
upper limit	12.64	
Variability estimate	Standard error of the mean	
Dispersion value	1.45	

Notes:

[37] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[38] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in HDL-C at Week 12

End point title	Percent Change From Baseline in HDL-C 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	141	280		
Units: percent change				
least squares mean (standard error)	-1.41 (± 1.38)	5.96 (± 1.02)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001 [40]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	7.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.19
upper limit	10.56
Variability estimate	Standard error of the mean
Dispersion value	1.62

Notes:

[39] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[40] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in VLDL-C at the Mean of Weeks 10 and 12

End point title	Percent Change From Baseline in VLDL-C at the Mean of Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and weeks 10 and 12

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	280		
Units: percent change				
least squares mean (standard error)	3.42 (± 2.57)	-13.64 (± 1.89)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.0001 [42]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-17.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.91
upper limit	-11.21
Variability estimate	Standard error of the mean
Dispersion value	2.98

Notes:

[41] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[42] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Secondary: Percent Change From Baseline in VLDL-C at Week 12

End point title	Percent Change From Baseline in VLDL-C 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	141	280		
Units: percent change				
least squares mean (standard error)	3.02 (± 2.94)	-10.31 (± 2.15)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	< 0.0001 [44]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-13.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.09
upper limit	-6.56
Variability estimate	Standard error of the mean
Dispersion value	3.44

Notes:

[43] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

[44] - The model includes treatment group, stratification factor (screening LDL-C level), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
From the first dose of study drug (placebo or evolocumab) to week 12.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injection once every month (QM) for 12 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received 420 mg evolocumab subcutaneous injection once every month (QM) for 12 weeks.	

Serious adverse events	Placebo	Evolocumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 141 (1.42%)	14 / 280 (5.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)	
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			
Fracture displacement			
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)	
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 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery disease		
subjects affected / exposed	0 / 141 (0.00%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorders		
Haemorrhagic stroke		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions		
Sudden cardiac death		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gastrointestinal disorders		
Peptic ulcer		
subjects affected / exposed	1 / 141 (0.71%)	0 / 280 (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		
Chronic obstructive pulmonary disease		
subjects affected / exposed	0 / 141 (0.00%)	4 / 280 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Sleep apnoea syndrome		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infections and infestations		

Cellulitis		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis viral		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis chronic		
subjects affected / exposed	1 / 141 (0.71%)	0 / 280 (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	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia bacterial		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders		
Dehydration		
subjects affected / exposed	0 / 141 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Evolocumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 141 (13.48%)	37 / 280 (13.21%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 141 (0.00%)	11 / 280 (3.93%)	
occurrences (all)	0	11	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 141 (2.13%)	6 / 280 (2.14%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 141 (2.84%)	6 / 280 (2.14%)	
occurrences (all)	9	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 141 (2.13%)	2 / 280 (0.71%)	
occurrences (all)	3	2	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	3 / 141 (2.13%)	0 / 280 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	2 / 141 (1.42%)	6 / 280 (2.14%)	
occurrences (all)	2	6	
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 141 (2.84%)	5 / 280 (1.79%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	5 / 141 (3.55%)	8 / 280 (2.86%)	
occurrences (all)	5	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2016	- clarified timing of randomization in relation to first dose. - added clarification that subjects must tolerate SC injection of placebo with device anticipated to be used (either AI/pen or AMD) - added clinical research associate as an additional contact for the investigator prior to unblinding of subject's treatment assignment. - added non-clinic investigational product injection at Week 4 to the Schedule of Assessments table for clarity. - removed text specifying kilograms and centimeters for body weight and height so sites can record in pounds and inches. - added that triglycerides > 1000 mg/dL would be reported to the investigators to allow appropriate follow-up to be initiated. - revised reasons for removal from treatment to be consistent with template text. - updated reporting requirements for adverse events for consistency throughout the protocol. - added appendix E of Child-Pugh Score to provide additional information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported