Clinical trial results:
A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects With HIV and With Hyperlipidemia and/or Mixed Dyslipidemia

Summary

EudraCT number	2015-004735-12
Trial protocol	FR PT GB BE ES GR PL IT
Global end of trial date	27 January 2020

Results information

Result version number	v1 (current)
This version publication date	28 January 2021
First version publication date	28 January 2021

Trial information

Trial identification

Sponsor protocol code	20130286

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02833844
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oks, California, United States,
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	27 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2020
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 24 weeks of subcutaneous (SC) evolocumab administered once monthly (QM) compared with placebo QM on percent change from baseline in low density lipoprotein cholesterol (LDL-C) in human immunodeficiency virus (HIV)-positive subjects with hyperlipidemia and/or mixed dyslipidemia.

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 regulations and guidelines set forth in 21 Code of Federal Regulations parts 11, 50, 54, 56, and 312. 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	22 May 2017
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	Australia: 28
Country: Number of subjects enrolled	South Africa: 20
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Switzerland: 25
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	United States: 121
Worldwide total number of subjects	467
EEA total number of subjects	190

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)	390
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 72 centers in Australia, Belgium, Brazil, Canada, France, Greece, Italy, Poland, Portugal, Romania, South Africa, Spain, Switzerland, United Kingdom, and United States. The first participant was enrolled on 22 May 2017, and the last participant was enrolled on 23 January 2019.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to evolocumab or placebo, respectively, in a double-blind manner. Randomization was stratified by entry statin treatment and hepatitis C status.

Period 1

Period 1 title	Double-Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Blinded individuals did not have access to unblinded information until the study was formally unblinded. Unblinding and potentially unblinding information was not distributed to the study team, investigators or subjects prior to the study being formally unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Placebo

Arm description:

Double-blind placebo subcutaneous (SC) injection every 4 weeks (QM) for 24 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:

Matching placebo administered QM at day 1 and weeks 4, 8, 12, 16, and 20 as an SC injection.

Arm title	Double-Blind Evolocumab

Arm description:

Double-blind evolocumab SC injection QM for 24 weeks.

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

Dosage and administration details:

Evolocumab 420 mg administered QM at day 1 and weeks 4, 8, 12, 16, and 20 as an SC injection.

Number of subjects in period 1	Double-Blind Placebo	Double-Blind Evolocumab
Started	157	310
Randomized and Treated	157	307
Completed	155	303
Not completed	2	7
Consent withdrawn by subject	2	3
Protocol deviation	-	4

Period 2

Period 2 title	Open-Label Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Placebo/Open-Label Evolocumab

Arm description:

Participants originally randomized to placebo in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

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

Dosage and administration details:

Evolocumab 420 mg QM at weeks 24, 28, 32, 36, 40, 44, and 48 as an SC injection.

Arm title	Double-Blind Evolocumab/Open-Label Evolocumab

Arm description:

Participants originally randomized to evolocumab in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

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

Dosage and administration details:

Evolocumab 420 mg QM at weeks 24, 28, 32, 36, 40, 44, and 48 as an SC injection.

Number of subjects in period 2[1]	Double-Blind Placebo/Open-Label Evolocumab	Double-Blind Evolocumab/Open-Label Evolocumab
Started	152	303
Received Open-Label Study Drug	152	299 [2]
Completed	150	301
Not completed	2	2
Adverse event, serious fatal	-	2
Consent withdrawn by subject	1	-
Lost to follow-up	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 3 participants did not continue into the open-label period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 4 participants did not receive open-label study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Placebo
Reporting group description:	
Double-blind placebo subcutaneous (SC) injection every 4 weeks (QM) for 24 weeks.	
Reporting group title	Double-Blind Evolocumab
Reporting group description:	
Double-blind evolocumab SC injection QM for 24 weeks.	

Reporting group values	Double-Blind Placebo	Double-Blind Evolocumab	Total
Number of subjects	157	310	467
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.2	56.5	
standard deviation	± 8.0	± 9.1	-
Sex: Female, Male Units:			
Female	37	45	82
Male	120	265	385
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	21	41	62
Not Hispanic or Latino	136	269	405
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	3	3	6
Black or African American	25	54	79
White	125	246	371
Multiple Races	1	0	1
Other, Not Specified	3	7	10
Stratification Factor: Statin Use at Baseline Units: Subjects			
Statin Use = Yes	128	256	384
Statin Use = No	29	54	83
Stratification Factor: Hepatitis C Virus (HCV) Status at Baseline Units: Subjects			
HCV = Yes	7	10	17
HCV = No	150	300	450
Low-Density Lipoprotein Cholesterol (LDL-C) Units: mg/dL			
arithmetic mean	133.26	133.25	

standard deviation	± 39.97	± 40.25	-

End points

End points reporting groups

Reporting group title	Double-Blind Placebo
Reporting group description:	
Double-blind placebo subcutaneous (SC) injection every 4 weeks (QM) for 24 weeks.	
Reporting group title	Double-Blind Evolocumab
Reporting group description:	
Double-blind evolocumab SC injection QM for 24 weeks.	
Reporting group title	Double-Blind Placebo/Open-Label Evolocumab
Reporting group description:	
Participants originally randomized to placebo in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.	
Reporting group title	Double-Blind Evolocumab/Open-Label Evolocumab
Reporting group description:	
Participants originally randomized to evolocumab in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.	

Primary: Percent Change From Baseline in LDL-C at Week 24

End point title	Percent Change From Baseline in LDL-C at Week 24
End point description:	
Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	295		
Units: percent change				
least squares mean (standard error)	1.68 (± 2.03)	-55.23 (± 1.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-56.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.55
upper limit	-52.28
Variability estimate	Standard error of the mean
Dispersion value	2.36

Notes:

[1] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Change From Baseline in LDL-C at Week 24

End point title	Change From Baseline in LDL-C at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	295		
Units: mg/dL				
least squares mean (standard error)	-2.3 (± 3.1)	-77.5 (± 2.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-75.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.1
upper limit	-68.4
Variability estimate	Standard error of the mean
Dispersion value	3.5

Notes:

[2] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percentage of Participants Acheiving LDL-C < 70 mg/dL (1.8 mmol/L) at Week 24

End point title	Percentage of Participants Acheiving LDL-C < 70 mg/dL (1.8 mmol/L) at Week 24

End point description:

End point type	Secondary

End point timeframe:

Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	296		
Units: percentage of participants				
number (confidence interval 95%)	7.9 (4.6 to 13.4)	73.3 (68.0 to 78.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference
Point estimate	65.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.8
upper limit	71.1

Notes:

[3] - Based on Cochran-Mantel-Haenszel test stratified by statin use stratification factor. For testing, nonachievement was imputed for participants with a missing value.

Secondary: Percentage of Participants With an LDL-C Response (50% Reduction of LDL-C From Baseline) at Week 24

End point title	Percentage of Participants With an LDL-C Response (50% Reduction of LDL-C From Baseline) at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	295		
Units: percentage of participants				
number (confidence interval 95%)	0.7 (0.1 to 3.7)	72.5 (67.2 to 77.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference
Point estimate	71.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	65.7
upper limit	76.7

Notes:

[4] - Based on Cochran-Mantel-Haenszel test stratified by statin use stratification factor. For testing, nonachievement was imputed for participants with a missing value.

Secondary: Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (HDL-C) at Week 24

End point title	Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (HDL-C) at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	296		
Units: percent change				
least squares mean (standard error)	2.86 (± 1.74)	-48.07 (± 1.31)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-50.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.88
upper limit	-46.99
Variability estimate	Standard error of the mean
Dispersion value	2.01

Notes:

[5] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percent Change From Baseline in Apolipoprotein B (ApoB) at Week 24

End point title	Percent Change From Baseline in Apolipoprotein B (ApoB) at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	302		
Units: percent change				
least squares mean (standard error)	2.59 (± 1.50)	-45.14 (± 1.13)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-47.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.11
upper limit	-44.35
Variability estimate	Standard error of the mean
Dispersion value	1.72

Notes:

[6] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percent Change From Baseline in Total Cholesterol (TC) at Week 24

End point title	Percent Change From Baseline in Total Cholesterol (TC) at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	296		
Units: percent change				
least squares mean (standard error)	2.34 (± 1.40)	-35.78 (± 1.06)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-38.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.3
upper limit	-34.94
Variability estimate	Standard error of the mean
Dispersion value	1.62

Notes:

[7] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percent Change From Baseline in Lipoprotein(a) (Lp[a]) at Week 24

End point title	Percent Change From Baseline in Lipoprotein(a) (Lp[a]) at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	302		
Units: percent change				
least squares mean (standard error)	10.35 (± 3.34)	-16.44 (± 2.57)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-26.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.17
upper limit	-19.4
Variability estimate	Standard error of the mean
Dispersion value	3.76

Notes:

[8] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percent Change From Baseline in Triglycerides at Week 24

End point title	Percent Change From Baseline in Triglycerides at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	296		
Units: percent change				
least squares mean (standard error)	13.21 (± 3.80)	-9.25 (± 2.89)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-22.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.03
upper limit	-13.88
Variability estimate	Standard error of the mean
Dispersion value	4.36

Notes:

[9] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percent Change From Baseline in HDL-C at Week 24

End point title	Percent Change From Baseline in HDL-C at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Bseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	296		
Units: percent change				
least squares mean (standard error)	2.73 (± 1.57)	11.08 (± 1.20)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	8.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.83
upper limit	11.89
Variability estimate	Standard error of the mean
Dispersion value	1.8

Notes:

[10] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Secondary: Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Week 24

End point title	Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Week 24

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-Blind Placebo	Double-Blind Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	284		
Units: percent change				
least squares mean (standard error)	12.34 (± 3.54)	-9.81 (± 2.65)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Evolocumab
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	repeated measures linear effects model
Parameter estimate	treatment difference
Point estimate	-22.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.04
upper limit	-14.26
Variability estimate	Standard error of the mean
Dispersion value	4.01

Notes:

[11] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind Treatment Period: From first dose of study drug to up to week 24. Open-label Extension Period: From first dose of study drug in the OLE up to 30 days after last dose, or end of study, whichever was earlier.

Adverse event reporting additional description:

Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Double-Blind Placebo

Reporting group description:

Double-blind placebo SC injection QM for 24 weeks.

Reporting group title	Double-Blind Evolocumab

Reporting group description:

Double-blind evolocumab SC injection QM for 24 weeks.

Reporting group title	Double-Blind Placebo/Open-Label Evolocumab

Reporting group description:

Participants originally randomized to placebo in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

Reporting group title	Double-Blind Evolocumab/Open-Label Evolocumab

Reporting group description:

Participants originally randomized to evolocumab in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

Serious adverse events	Double-Blind Placebo	Double-Blind Evolocumab	Double-Blind Placebo/Open-Label Evolocumab
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 157 (5.10%)	10 / 307 (3.26%)	8 / 152 (5.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basosquamous carcinoma of skin			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer stage 0, with cancer in situ			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hair follicle tumour benign			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma stage II			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcomatoid carcinoma			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Non-cardiac chest pain			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis constrictive			

subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery thrombosis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Blood loss anaemia			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Lipohypertrophy			

subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 157 (1.27%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 307 (0.33%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis bacterial			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 157 (0.00%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 307 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind Evolocumab/Open-Label Evolocumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 299 (4.68%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			

subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basosquamous carcinoma of skin				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder cancer stage 0, with cancer in situ				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hair follicle tumour benign				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipoma				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma stage II				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sarcomatoid carcinoma				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive emergency				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Non-cardiac chest pain			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchiectasis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain contusion			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	0 / 299 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis constrictive				

subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral artery thrombosis			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Blood loss anaemia			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Lipohypertrophy			

subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis bacterial			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Helicobacter gastritis			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus bronchitis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-Blind Placebo	Double-Blind Evolocumab	Double-Blind Placebo/Open-Label Evolocumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 157 (26.11%)	78 / 307 (25.41%)	23 / 152 (15.13%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 157 (3.18%)	0 / 307 (0.00%)	3 / 152 (1.97%)
occurrences (all)	5	0	3
Nervous system disorders			
Headache			

subjects affected / exposed	5 / 157 (3.18%)	6 / 307 (1.95%)	3 / 152 (1.97%)
occurrences (all)	6	6	4
Paraesthesia			
subjects affected / exposed	0 / 157 (0.00%)	7 / 307 (2.28%)	0 / 152 (0.00%)
occurrences (all)	0	8	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 157 (3.18%)	2 / 307 (0.65%)	0 / 152 (0.00%)
occurrences (all)	5	2	0
Influenza like illness			
subjects affected / exposed	4 / 157 (2.55%)	12 / 307 (3.91%)	2 / 152 (1.32%)
occurrences (all)	4	15	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 157 (2.55%)	3 / 307 (0.98%)	0 / 152 (0.00%)
occurrences (all)	4	3	0
Diarrhoea			
subjects affected / exposed	7 / 157 (4.46%)	11 / 307 (3.58%)	1 / 152 (0.66%)
occurrences (all)	7	12	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 157 (1.91%)	9 / 307 (2.93%)	1 / 152 (0.66%)
occurrences (all)	3	10	1
Back pain			
subjects affected / exposed	4 / 157 (2.55%)	12 / 307 (3.91%)	4 / 152 (2.63%)
occurrences (all)	4	13	4
Myalgia			
subjects affected / exposed	6 / 157 (3.82%)	6 / 307 (1.95%)	0 / 152 (0.00%)
occurrences (all)	6	6	0
Pain in extremity			
subjects affected / exposed	3 / 157 (1.91%)	7 / 307 (2.28%)	0 / 152 (0.00%)
occurrences (all)	3	7	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 157 (1.27%)	10 / 307 (3.26%)	6 / 152 (3.95%)
occurrences (all)	2	10	6

Upper respiratory tract infection			
subjects affected / exposed	4 / 157 (2.55%)	7 / 307 (2.28%)	1 / 152 (0.66%)
occurrences (all)	4	7	1
Bronchitis			
subjects affected / exposed	3 / 157 (1.91%)	5 / 307 (1.63%)	2 / 152 (1.32%)
occurrences (all)	3	5	2
Sinusitis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 307 (0.33%)	1 / 152 (0.66%)
occurrences (all)	1	1	1

Non-serious adverse events	Double-Blind Evolocumab/Open-Label Evolocumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 299 (16.72%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 299 (1.34%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 299 (0.00%)		
occurrences (all)	0		
Diarrhoea			

subjects affected / exposed	8 / 299 (2.68%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 299 (1.67%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 299 (3.01%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	5 / 299 (1.67%)		
occurrences (all)	5		
Bronchitis			
subjects affected / exposed	7 / 299 (2.34%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	8 / 299 (2.68%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2017	- To address regulatory concerns that subjects without clinical atherosclerotic cardiovascular disease (ASCVD) would be eligible, entry criteria were modified such that subjects without clinical ASCVD were required to have an LDL-C >/= 100 mg/dL. - Modified enrollment criteria such that a subpopulation of subjects not on statin background therapy could be included - Added a section to clarify that human immunodeficiency virus (HIV) worsening be recorded as an adverse event - The pregnancy test schedule was revised to address regulatory agency concerns, and details were provided to clarify when serum and urine pregnancy tests were performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported