Clinical trial results:
A Double-blind, Randomized, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor

Summary

EudraCT number	2012-001364-30
Trial protocol	BE ES DK NL PL GB DE
Global end of trial date	19 November 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	20110116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01763905
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	19 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks (Q2W) and monthly (QM), compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 99
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Denmark: 35
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Netherlands: 36
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Australia: 39
Country: Number of subjects enrolled	Hong Kong: 2

Worldwide total number of subjects	307
EEA total number of subjects	147

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)	180
From 65 to 84 years	127
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Men and women ≥ 18 to ≤ 80 years of age who have tried at least 2 statins and were unable to tolerate any dose or increase in statin dose due to muscle-related side effects were eligible for this study.
The first participant was enrolled on 24 January 2013 and the last participant enrolled on 29 August 2013.

Pre-assignment

Screening details:

Participants received subcutaneous placebo corresponding to the once monthly dose volume during a 6-week screening period. Those who completed the screening period and met final eligibility criteria were randomized 1:1:2:2 into 4 treatment groups. Randomization was stratified by LDL-C level (< 180 mg/dL vs ≥ 180 mg/dL) and statin use (yes vs no).

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	Ezetimibe (Q2W)

Arm description:

Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Zetia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg administered orally once a day

Investigational medicinal product name	Placebo to Evolocumab
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

Arm title	Ezetimibe (QM)

Arm description:

Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Zetia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 10 mg administered orally once a day	
Investigational medicinal product name	Placebo to Evolocumab
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	
Arm title	Evolocumab Q2W
Arm description: Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 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	
Investigational medicinal product name	Placebo to Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Self-administered orally once daily	
Arm title	Evolocumab QM
Arm description: Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 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	
Investigational medicinal product name	Placebo to Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Self-administered orally once daily	

Number of subjects in period 1	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W
Started	51	51	103
Completed	45	50	94
Not completed	6	1	9
Consent withdrawn by subject	1	1	-
Lost to follow-up	-	-	1
Decision by sponsor	5	-	8

Number of subjects in period 1	Evolocumab QM
Started	102
Completed	101
Not completed	1
Consent withdrawn by subject	1
Lost to follow-up	-
Decision by sponsor	-

Baseline characteristics

Reporting groups	
Reporting group title	Ezetimibe (Q2W)
Reporting group description:	
Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (QM)
Reporting group description:	
Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Evolocumab Q2W
Reporting group description:	
Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description:	
Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.	

Reporting group values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W
Number of subjects	51	51	103
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	61.7	60.2	60.5
standard deviation	± 10.1	± 8.7	± 9.7
Gender, Male/Female Units: participants			
Female	27	22	46
Male	24	29	57
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	3	5
Black or African American	0	1	3
Native Hawaiian or Other Pacific Islander	0	0	1
White	49	46	94
Other	1	1	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	50	49	100
Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C) Units: Subjects			
< 180 mg/dL	26	26	52
≥ 180 mg/dL	25	25	51

Stratification Factor: Baseline Statin Use Units: Subjects			
No	41	42	84
Yes	10	9	19
LDL-C Concentration Units: mg/dL			
arithmetic mean	194.7	195.2	192
standard deviation	± 63.8	± 51.8	± 57
Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration Units: mg/dL			
arithmetic mean	231.4	232.9	227.9
standard deviation	± 66	± 57	± 56.6
Apolipoprotein B Concentration Units: mg/dL			
arithmetic mean	140	140	140.2
standard deviation	± 37	± 31.1	± 32.1
Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio Units: ratio			
arithmetic mean	5.989	6.137	5.912
standard deviation	± 2.19	± 1.787	± 1.929
Apolipoprotein B/Apolipoprotein A1 Ratio Units: ratio			
arithmetic mean	0.943	1.005	0.98
standard deviation	± 0.282	± 0.294	± 0.318
Lipoprotein(a) Concentration Units: nmol/L			
arithmetic mean	106.3	76.6	66.2
standard deviation	± 101	± 96.7	± 72.5
Triglyceride Concentration Units: mg/dL			
arithmetic mean	183.4	187	179.8
standard deviation	± 79.8	± 81.5	± 80
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration Units: mg/dL			
arithmetic mean	36.7	37.1	35.2
standard deviation	± 16	± 15.8	± 14.5
High-Density Lipoprotein Cholesterol (HDL-C) Units: mg/dL			
arithmetic mean	52.4	48	51.1
standard deviation	± 18.3	± 11	± 16.4

Reporting group values	Evolocumab QM	Total	
Number of subjects	102	307	
Age categorical Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	62.9		
standard deviation	± 10.2	-	
Gender, Male/Female			
Units: participants			
Female	46	141	
Male	56	166	
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	10	
Black or African American	3	7	
Native Hawaiian or Other Pacific Islander	0	1	
White	98	287	
Other	0	2	
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	1	7	
Not Hispanic or Latino	101	300	
Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C)			
Units: Subjects			
< 180 mg/dL	52	156	
≥ 180 mg/dL	50	151	
Stratification Factor: Baseline Statin Use			
Units: Subjects			
No	82	249	
Yes	20	58	
LDL-C Concentration			
Units: mg/dL			
arithmetic mean	192.2		
standard deviation	± 61.2	-	
Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration			
Units: mg/dL			
arithmetic mean	222.1		
standard deviation	± 63.2	-	
Apolipoprotein B Concentration			
Units: mg/dL			
arithmetic mean	133.1		
standard deviation	± 32.2	-	
Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio			
Units: ratio			
arithmetic mean	5.506		
standard deviation	± 1.925	-	
Apolipoprotein B/Apolipoprotein A1 Ratio			
Units: ratio			
arithmetic mean	0.901		
standard deviation	± 0.283	-	

Lipoprotein(a) Concentration Units: nmol/L arithmetic mean standard deviation	 70.9 ± 99.9	 -	
Triglyceride Concentration Units: mg/dL arithmetic mean standard deviation	 149.3 ± 63.1	 -	
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration Units: mg/dL arithmetic mean standard deviation	 29.9 ± 12.6	 -	
High-Density Lipoprotein Cholesterol (HDL-C) Units: mg/dL arithmetic mean standard deviation	 54 ± 16	 -	

End points

End points reporting groups

Reporting group title	Ezetimibe (Q2W)
Reporting group description:	
Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (QM)
Reporting group description:	
Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Evolocumab Q2W
Reporting group description:	
Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description:	
Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.	

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:	
Calculated LDL-C was determined based on the Friedewald equation.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-18.08 (± 2.52)	-15.05 (± 2.13)	-56.14 (± 1.91)	-52.6 (± 1.58)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Statistical analysis description:	
The null hypothesis was that there is no mean difference in the percent change from Baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.	
Comparison groups	Evolocumab Q2W v Ezetimibe (Q2W)

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-38.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.73
upper limit	-32.99
Variability estimate	Standard error of the mean
Dispersion value	2.87

Notes:

[1] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)

Statistical analysis description:

The null hypothesis was that there is no mean difference in the percent change from baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-37.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.16
upper limit	-32.94
Variability estimate	Standard error of the mean
Dispersion value	2.33

Notes:

[2] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

Calculated LDL-C was determined based on the Friedewald equation.

End point type	Primary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-19.21 (± 2.4)	-16.62 (± 2.03)	-56.11 (± 1.83)	-55.31 (± 1.53)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)

Statistical analysis description:

The null hypothesis was that there is no mean difference in the mean percent change from Baseline at Weeks 10 and 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-36.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.26
upper limit	-31.55
Variability estimate	Standard error of the mean
Dispersion value	2.71

Notes:

[3] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)

Statistical analysis description:

The null hypothesis was that there is no mean difference in the percent change from baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-38.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.06
upper limit	-34.22
Variability estimate	Standard error of the mean
Dispersion value	2.21

Notes:

[4] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

Calculated LDL-C was determined based on the Friedewald equation.

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: mg/dL				
least squares mean (standard error)	-39.1 (± 5.1)	-33 (± 4.5)	-105.4 (± 3.9)	-103.6 (± 3.4)

Statistical analyses

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-70.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-80.5
upper limit	-60.7
Variability estimate	Standard error of the mean
Dispersion value	5

Notes:

[5] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-66.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.9
upper limit	-54.7
Variability estimate	Standard error of the mean
Dispersion value	5.9

Notes:

[6] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

End point title	Change From Baseline in LDL-C at Week 12
End point description:	
Calculated LDL-C was determined based on the Friedewald equation.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: mg/dL				
least squares mean (standard error)	-36.2 (± 5.4)	-30.2 (± 4.7)	-106 (± 4.1)	-99 (± 3.5)

Statistical analyses

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-68.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-79.2
upper limit	-58.4
Variability estimate	Standard error of the mean
Dispersion value	5.3

Notes:

[7] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-69.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82
upper limit	-57.5
Variability estimate	Standard error of the mean
Dispersion value	6.2

Notes:

[8] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

Mean low density lipoprotein-cholesterol response at Weeks 10 and 12 (low density lipoprotein-cholesterol < 70 mg/dL [1.8 mmol/L]).

End point type	Secondary

End point timeframe:

Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percentage of participants				
number (confidence interval 95%)	2 (0.4 to 10.5)	0 (0 to 7.3)	45.5 (36.2 to 55.2)	42 (32.8 to 51.8)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	43.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.9
upper limit	53.4

Notes:

[9] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	42
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.3
upper limit	51.8

Notes:

[10] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percentage of participants				
number (confidence interval 95%)	2 (0.4 to 10.7)	0 (0 to 7.9)	50 (40.3 to 59.7)	37.5 (28.5 to 47.5)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	48
Confidence interval	
level	95 %
sides	2-sided
lower limit	35
upper limit	57.8

Notes:

[11] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	37.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	25.5
upper limit	47.5

Notes:

[12] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05

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

End point title	Mean Percent Change From Baseline in Non-HDL-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	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-17.18 (± 2.15)	-14.54 (± 1.86)	-48.72 (± 1.64)	-49.13 (± 1.4)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-31.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.34
upper limit	-26.73
Variability estimate	Standard error of the mean
Dispersion value	2.43

Notes:

[13] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [14]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.63
upper limit	-30.54
Variability estimate	Standard error of the mean
Dispersion value	2.05

Notes:

[14] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: 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	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-16.53 (± 2.3)	-13.16 (± 1.93)	-48.62 (± 1.74)	-46.15 (± 1.43)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-32.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.28
upper limit	-26.9
Variability estimate	Standard error of the mean
Dispersion value	2.63

Notes:

[15] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [16]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-32.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.19
upper limit	-28.79
Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[16] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-13.67 (± 2.15)	-11.02 (± 2.21)	-45.88 (± 1.68)	-46.01 (± 1.65)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [17]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-32.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.92
upper limit	-27.49
Variability estimate	Standard error of the mean
Dispersion value	2.39

Notes:

[17] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.59
upper limit	-30.39
Variability estimate	Standard error of the mean
Dispersion value	2.33

Notes:

[18] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: 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	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-12.95 (± 2.32)	-9.97 (± 2.34)	-45.81 (± 1.79)	-43.07 (± 1.73)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-32.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.04
upper limit	-27.68
Variability estimate	Standard error of the mean
Dispersion value	2.62

Notes:

[19] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [20]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-33.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.04
upper limit	-28.17
Variability estimate	Standard error of the mean
Dispersion value	2.5

Notes:

[20] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-13.44 (± 2.14)	-11.2 (± 2.16)	-40.83 (± 1.65)	-41.14 (± 1.62)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [21]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-27.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.11
upper limit	-22.67
Variability estimate	Standard error of the mean
Dispersion value	2.39

Notes:

[21] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-29.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.72
upper limit	-25.17
Variability estimate	Standard error of the mean
Dispersion value	2.42

Notes:

[22] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Week 12

End point title	Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-14.13 (± 2.3)	-9.92 (± 2.34)	-40.42 (± 1.75)	-38.57 (± 1.73)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-26.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.42
upper limit	-21.15
Variability estimate	Standard error of the mean
Dispersion value	2.6

Notes:

[23] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-28.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.88
upper limit	-23.43
Variability estimate	Standard error of the mean
Dispersion value	2.64

Notes:

[24] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-13 (± 2.27)	-11.94 (± 2.56)	-47.86 (± 1.77)	-48.31 (± 1.92)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [25]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.84
upper limit	-29.88
Variability estimate	Standard error of the mean
Dispersion value	2.52

Notes:

[25] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [26]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-36.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.73
upper limit	-31.01
Variability estimate	Standard error of the mean
Dispersion value	2.71

Notes:

[26] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

End point title	Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-13.14 (± 2.47)	-11.37 (± 2.71)	-47.66 (± 1.9)	-45.51 (± 2.01)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [27]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.05
upper limit	-29
Variability estimate	Standard error of the mean
Dispersion value	2.79

Notes:

[27] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [28]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.87
upper limit	-28.39
Variability estimate	Standard error of the mean
Dispersion value	2.91

Notes:

[28] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-2.3 (± 3.36)	1.55 (± 4.01)	-26.2 (± 2.64)	-23.72 (± 2.97)

Statistical analyses

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-25.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.75
upper limit	-16.77
Variability estimate	Standard error of the mean
Dispersion value	4.3

Notes:

[29] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-23.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.27
upper limit	-16.54
Variability estimate	Standard error of the mean
Dispersion value	3.73

Notes:

[30] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: 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	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-1.74 (± 3.58)	5.81 (± 5.1)	-27.03 (± 2.78)	-22.07 (± 3.66)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [31]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-25.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.26
upper limit	-17.33
Variability estimate	Standard error of the mean
Dispersion value	4.03

Notes:

[31] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [32]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-27.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.21
upper limit	-16.56
Variability estimate	Standard error of the mean
Dispersion value	5.73

Notes:

[32] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

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

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-3.74 (± 3.88)	-0.32 (± 4.65)	-6.32 (± 2.94)	-6.73 (± 3.44)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [33]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-2.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.38
upper limit	6.2
Variability estimate	Standard error of the mean
Dispersion value	4.45

Notes:

[33] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Ezetimibe (QM) v Evolocumab QM
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [34]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-6.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.55
upper limit	3.71
Variability estimate	Standard error of the mean
Dispersion value	5.13

Notes:

[34] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: 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	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-5.47 (± 4.25)	2.16 (± 5.52)	-3.88 (± 3.18)	-2.53 (± 3.98)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [35]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.14
upper limit	11.31
Variability estimate	Standard error of the mean
Dispersion value	4.92

Notes:

[35] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [36]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-4.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.04
upper limit	7.67
Variability estimate	Standard error of the mean
Dispersion value	6.25

Notes:

[36] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-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	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	0.33 (± 1.98)	1.44 (± 2.03)	5.48 (± 1.51)	7.18 (± 1.51)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [37]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	5.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	9.56
Variability estimate	Standard error of the mean
Dispersion value	2.23

Notes:

[37] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [38]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	5.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	10.24
Variability estimate	Standard error of the mean
Dispersion value	2.28

Notes:

[38] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

End point title	Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	1.77 (± 2.22)	1.64 (± 2.22)	5.34 (± 1.67)	6.47 (± 1.63)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [39]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	3.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	8.63
Variability estimate	Standard error of the mean
Dispersion value	2.56

Notes:

[39] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [40]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	4.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	9.81
Variability estimate	Standard error of the mean
Dispersion value	2.52

Notes:

[40] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-5.76 (± 3.8)	-2.93 (± 4.41)	-7.6 (± 2.89)	-6.46 (± 3.21)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [41]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.43
upper limit	6.75
Variability estimate	Standard error of the mean
Dispersion value	4.35

Notes:

[41] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [42]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-3.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.12
upper limit	6.06
Variability estimate	Standard error of the mean
Dispersion value	4.85

Notes:

[42] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Week 12

End point title	Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Week 12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	103	102
Units: percent change				
least squares mean (standard error)	-5.49 (± 4.05)	-2.25 (± 5.11)	-6.16 (± 3.08)	-2.18 (± 3.6)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [43]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.96
upper limit	8.61
Variability estimate	Standard error of the mean
Dispersion value	4.7

Notes:

[43] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [44]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.24
upper limit	11.39
Variability estimate	Standard error of the mean
Dispersion value	5.72

Notes:

[44] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Adverse events

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Ezetimibe (Q2W)
Reporting group description: Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (QM)
Reporting group description: Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Evolocumab Q2W
Reporting group description: Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description: Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.	

Serious adverse events	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)	3 / 51 (5.88%)	5 / 103 (4.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma stage III			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	1 / 103 (0.97%)
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 / 51 (0.00%)	0 / 51 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cartilage graft			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	0 / 103 (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
Osteotomy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	0 / 103 (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
Spinal decompression			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	0 / 103 (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
Gastrointestinal disorders			
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	0 / 103 (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
Inguinal hernia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	0 / 103 (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 and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	0 / 103 (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

Serious adverse events	Evolocumab QM		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 102 (0.98%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma stage III			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipoma			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cartilage graft			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteotomy			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal decompression			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 102 (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: 5 %

Non-serious adverse events	Ezetimibe (Q2W)	Ezetimibe (QM)	Evolocumab Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 51 (39.22%)	29 / 51 (56.86%)	28 / 103 (27.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 51 (5.88%)	6 / 51 (11.76%)	4 / 103 (3.88%)
occurrences (all)	3	9	7
Paraesthesia			
subjects affected / exposed	1 / 51 (1.96%)	4 / 51 (7.84%)	0 / 103 (0.00%)
occurrences (all)	1	4	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 51 (7.84%)	6 / 51 (11.76%)	3 / 103 (2.91%)
occurrences (all)	4	7	3
Injection site erythema			
subjects affected / exposed	0 / 51 (0.00%)	3 / 51 (5.88%)	2 / 103 (1.94%)
occurrences (all)	0	3	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 51 (5.88%)	4 / 51 (7.84%)	3 / 103 (2.91%)
occurrences (all)	3	4	4
Nausea			
subjects affected / exposed	2 / 51 (3.92%)	5 / 51 (9.80%)	3 / 103 (2.91%)
occurrences (all)	2	5	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 51 (1.96%)	3 / 51 (5.88%)	0 / 103 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 51 (5.88%)	1 / 51 (1.96%)	5 / 103 (4.85%)
occurrences (all)	6	1	7
Myalgia			
subjects affected / exposed	7 / 51 (13.73%)	11 / 51 (21.57%)	7 / 103 (6.80%)
occurrences (all)	7	15	10
Pain in extremity			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	2 / 103 (1.94%)
occurrences (all)	0	1	2
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 51 (5.88%)	0 / 51 (0.00%)	1 / 103 (0.97%)
occurrences (all)	4	0	1
Nasopharyngitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 51 (0.00%)	5 / 103 (4.85%)
occurrences (all)	3	0	5

Non-serious adverse events	Evolocumab QM		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 102 (41.18%)		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 102 (11.76%)		
occurrences (all)	12		
Paraesthesia			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Injection site erythema			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	8 / 102 (7.84%)		
occurrences (all)	9		
Myalgia			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	12		
Pain in extremity			
subjects affected / exposed	12 / 102 (11.76%)		
occurrences (all)	19		
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2012	- added testing for prior or existing HCV infection in high risk individuals and evaluation of viral load in those who show evidence thereof - strengthened the definition of statin-intolerance by requiring subjects to have failed 2 statins instead of 1 - clarified that subjects with a known sensitivity to the "active substances or their excipients" were excluded - added urine pregnancy testing at day 1, week 4, and week 8 for women of childbearing potential - implemented minor clarifications and error corrections
10 October 2012	- added the GAUSS-2 study acronym and short title - made minor modification of LDL-C inclusion limits in accordance with NCEP ATP III risk categories - added new evolocumab formulation and autoinjectors to allow administration of investigational product in a home-use setting - revised schedule of assessment and description of procedures in Section 7 to replace weeks 4 and 6 visits with home-use IP administration - added reporting requirements for product/device complaints - updated program status in evolocumab background section - provided instruction regarding missed ezetimibe doses - added subjects with a history of HCV infection to the ones at high risk of HCV injection to the HCV antibody testing and viral load monitoring, if positive - updated sections on collection and reporting of adverse events and serious adverse events, including adding device-related adverse events, and the eSAE contingency form - moved change from baseline in VLDL-C at week 12 from tertiary to secondary endpoints - added transient ischemic attacks and non-coronary revascularization as exploratory endpoints - implemented minor clarifications and error corrections
10 December 2012	- added the LDL-C endpoint of mean percent change from baseline at weeks 10 and 12 as a co-primary endpoint - added the means of weeks 10 and 12 as co-secondary endpoints to all secondary endpoints for the same reason as above - added alert threshold for elevated triglycerides - added publication references for primary result publications of phase 2 studies MENDEL and LAPLACE - introduced the simplified terminology of once monthly (QM) dosing - implemented minor clarifications and error corrections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported