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

Summary

EudraCT number	2013-000935-29
Trial protocol	CZ DE GB IT DK NL NO
Global end of trial date	21 November 2017

Results information

Result version number	v1 (current)
This version publication date	23 November 2018
First version publication date	23 November 2018

Trial information

Trial identification

Sponsor protocol code	20120332

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01984424
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	21 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this 3-part study was to evaluate the effect of 24 weeks of evolocumab (AMG 145) administered subcutaneously (SC) every month (QM), compared with ezetimibe (part B), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic participants who were unable to tolerate an effective dose of a statin due to muscle-related side effects (MRSE) (part B), as confirmed by a lead-in, double-blind, placebo-controlled, crossover statin rechallenge (part A).

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 Code of Federal Regulations parts 11, 50, 54, 56, and 312. All participants 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 participants 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	10 December 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	Australia: 17
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 32
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 62

Worldwide total number of subjects	218
EEA total number of subjects	121

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)	144
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 511 participants were enrolled in the 3-part study at 53 centers (parts A and B) and 48 centers (part C) in the United States of America, Europe, Australia, New Zealand, Canada, and South Africa from December 2013 to November 2017. Results are reported for participants enrolled in part B and part C.

Pre-assignment

Screening details:

492 participants were randomized into part A. 199 of 202 participants that completed part A, along with additional 19 new participants, were randomized 2:1 (stratified by screening LDL-C level) to receive evolocumab or ezetimibe in 24-week, double-blind part B. A total of 209 participants from part B enrolled in 2-year, open-label extension part C.

Period 1

Period 1 title	Study part B
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Participants received either evolocumab SC or placebo SC and either ezetimibe orally (PO) or matching placebo PO. Participants disposition accounting for SC IP in part B are reported.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ezetimibe in part B

Arm description:

Participants received ezetimibe 10 milligram (mg) PO once a day (QD) and placebo matching to evolocumab SC injection QM for 24 weeks.

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

Dosage and administration details:

Participants received placebo matching to evolocumab SC injection QM for 24 weeks.

Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received ezetimibe 10 mg tablet PO QD for 24 weeks.

Arm title	Evolocumab in part B

Arm description:

Participants received evolocumab 420 mg SC injection QM and placebo matching to ezetimibe PO QD for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo matching to ezetimibe PO QD for 24 weeks.

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

Dosage and administration details:

Participants received evolocumab 420 mg SC injection QM for 24 weeks.

Number of subjects in period 1	Ezetimibe in part B	Evolocumab in part B
Started	73	145
Participants who received SC IP	73	145
Completed	69	138
Not completed	4	7
Consent withdrawn by subject	3	-
Physician decision	-	1
Adverse event, non-fatal	1	5
Lost to follow-up	-	1

Period 2

Period 2 title	Study part C
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ezetimibe in part B and Evolocumab in part C

Arm description:

Participants who completed SC IP in part B were eligible and 2 participants who did not complete IP in part B were enrolled in part C and were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC every 2 weeks (Q2W) for up to 104 weeks.

Arm type	Experimental

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

Dosage and administration details:

Participants were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC Q2W for up to 104 weeks.

Arm title	Evolocumab in part B and part C

Arm description:

Participants who completed SC IP in part B were eligible and 2 participants who did not complete IP in part B were enrolled in part C and were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC Q2W for up to 104 weeks.

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

Dosage and administration details:

Participants were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC Q2W for up to 104 weeks.

Number of subjects in period 2	Ezetimibe in part B and Evolocumab in part C	Evolocumab in part B and part C
Started	69	138
Participants who received Evolocumab	70	139
Completed	65	133
Not completed	5	6
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	3
Lost to follow-up	1	2
Joined	1	1
Enrolled without completing IP during part B	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Ezetimibe in part B
Reporting group description:	
Participants received ezetimibe 10 milligram (mg) PO once a day (QD) and placebo matching to evolocumab SC injection QM for 24 weeks.	
Reporting group title	Evolocumab in part B
Reporting group description:	
Participants received evolocumab 420 mg SC injection QM and placebo matching to ezetimibe PO QD for 24 weeks.	

Reporting group values	Ezetimibe in part B	Evolocumab in part B	Total
Number of subjects	73	145	218
Age, Customized Units: Subjects			
< 65 years	52	92	144
≥ 65 years	21	53	74
Age Continuous Units: years			
arithmetic mean	58.5	59.0	
standard deviation	± 9.4	± 11.1	-
Sex: Female, Male Units: Subjects			
Female	39	67	106
Male	34	78	112
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Black or African American	3	3	6
Native Hawaiian or Other Pacific Islander	0	0	0
White	69	138	207
Other	0	2	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	73	143	216
Unknown or Not Reported	0	0	0
Stratification Factor: Screening LDL-C Units: Subjects			
< 180 mg/deciliter (dL)	21	40	61
≥ 180 mg/dL	52	105	157
LDL-C Concentation Units: mg/dL			
arithmetic mean	221.9	218.8	
standard deviation	± 70.2	± 73.1	-
Total Cholesterol Concentration			

Units: mg/dL			
arithmetic mean	308.0	306.5	
standard deviation	± 73.8	± 75.4	-
High-density Lipoprotein Cholesterol (HDL-C)			
Units: mg/dL			
arithmetic mean	50.2	49.7	
standard deviation	± 15.5	± 15.4	-
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration			
Units: mg/dL			
arithmetic mean	35.7	37.1	
standard deviation	± 14.3	± 15.6	-
Non-high-density Lipoprotein Cholesterol (non-HDL-C) Concentration			
Units: mg/dL			
arithmetic mean	257.8	256.9	
standard deviation	± 76.3	± 73.8	-
Apolipoprotein B Concentration			
N=71 and 144, respectively. Whereas, N is number of participants analysed.			
Units: mg/dL			
arithmetic mean	155.0	158.3	
standard deviation	± 42.4	± 41.5	-
Total Cholesterol/HDL-C Ratio			
Units: ratio			
arithmetic mean	6.709	6.668	
standard deviation	± 2.746	± 2.349	-
Apolipoprotein B/Apolipoprotein A1 Ratio			
N=71 and 144, respectively.			
Units: ratio			
arithmetic mean	1.063	1.063	
standard deviation	± 0.416	± 0.340	-
Triglyceride Concentration			
Units: mg/dL			
median	162.5	176.0	
inter-quartile range (Q1-Q3)	127.0 to 231.0	128.0 to 233.5	-
Lipoprotein(a) Concentration			
N=71 and 144, respectively.			
Units: nanomoles per liter (nmol/L)			
median	38.0	29.0	
inter-quartile range (Q1-Q3)	18.0 to 164.0	12.5 to 152.5	-

End points

End points reporting groups

Reporting group title	Ezetimibe in part B
Reporting group description:	
Participants received ezetimibe 10 milligram (mg) PO once a day (QD) and placebo matching to evolocumab SC injection QM for 24 weeks.	
Reporting group title	Evolocumab in part B
Reporting group description:	
Participants received evolocumab 420 mg SC injection QM and placebo matching to ezetimibe PO QD for 24 weeks.	
Reporting group title	Ezetimibe in part B and Evolocumab in part C
Reporting group description:	
Participants who completed SC IP in part B were eligible and 2 participants who did not complete IP in part B were enrolled in part C and were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC every 2 weeks (Q2W) for up to 104 weeks.	
Reporting group title	Evolocumab in part B and part C
Reporting group description:	
Participants who completed SC IP in part B were eligible and 2 participants who did not complete IP in part B were enrolled in part C and were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC Q2W for up to 104 weeks.	

Primary: Percent Change From Baseline in LDL-C at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in LDL-C at the Mean of Weeks 22 and 24 in Part B
End point description:	
Co-primary endpoint. The full analysis set (FAS) population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).	
End point type	Primary
End point timeframe:	
Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B	

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: Percent change				
least squares mean (standard error)	-16.70 (± 1.91)	-54.50 (± 1.39)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24

Statistical analysis description:

The null hypothesis was that there was no mean difference in the percent change from baseline at weeks 22 and 24 of part B in LDL-C between evolocumab 420 mg and ezetimibe, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-37.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.31
upper limit	-33.28
Variability estimate	Standard error of the mean
Dispersion value	2.29

Notes:

[1] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[2] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

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

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

End point description:

Co-primary endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Primary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: Percent change				
least squares mean (standard error)	-16.69 (± 2.11)	-52.76 (± 1.52)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24

Statistical analysis description:

The null hypothesis was that there was no mean difference in the percent change from baseline at week 24 of part B in LDL-C between evolocumab 420 mg and ezetimibe, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-36.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.07
upper limit	-31.08
Variability estimate	Standard error of the mean
Dispersion value	2.53

Notes:

[3] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[4] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Change From Baseline in LDL-C at the Mean of Weeks 22 and 24 in Part B

End point title	Change From Baseline in LDL-C at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: mg/dL				
least squares mean (standard error)	-31.0 (± 3.8)	-106.8 (± 2.7)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-75.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.7
upper limit	-67
Variability estimate	Standard error of the mean
Dispersion value	4.5

Notes:

[5] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[6] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

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

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

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: mg/dL				
least squares mean (standard error)	-31.2 (± 4.0)	-102.9 (± 2.9)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-71.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.3
upper limit	-62.2
Variability estimate	Standard error of the mean
Dispersion value	4.8

Notes:

[7] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[8] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percentage of Participants Who Achieved LDL-C of Less Than 70 mg/dL at the Mean of Weeks 22 and 24 in Part B

End point title	Percentage of Participants Who Achieved LDL-C of Less Than 70 mg/dL at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	145		
Units: Percentage of participants				
number (confidence interval 95%)	1.4 (0.3 to 7.7)	29.9 (22.9 to 38.1)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	28.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.1
upper limit	36.7

Notes:

[9] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[10] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Based on Cochran-Mantel Haenszel test stratified by the stratification factor (screening LDL-C).

Secondary: Percentage of Participants Who Achieved LDL-C of Less Than 70 mg/dL at Week 24 in Part B

End point title	Percentage of Participants Who Achieved LDL-C of Less Than 70 mg/dL at Week 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	145		
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 6.3)	27.4 (20.1 to 36.1)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	27.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.7
upper limit	36.1

Notes:

[11] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[12] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Based on Cochran-Mantel Haenszel test stratified by the stratification factor (screening LDL-C).

Secondary: Percent Change From Baseline in Total Cholesterol at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in Total Cholesterol at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: Percent change				
least squares mean (standard error)	-11.43 (± 1.41)	-38.04 (± 1.03)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-26.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.95
upper limit	-23.27
Variability estimate	Standard error of the mean
Dispersion value	1.69

Notes:

[13] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[14] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Total Cholesterol at Week 24 in Part B

End point title	Percent Change From Baseline in Total Cholesterol at Week 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A)

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: Percent change				
least squares mean (standard error)	-11.57 (± 1.52)	-36.64 (± 1.10)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-25.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.67
upper limit	-21.48
Variability estimate	Standard error of the mean
Dispersion value	1.82

Notes:

[15] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[16] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in non-HDL-C at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in non-HDL-C at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: Percent change				
least squares mean (standard error)	-14.38 (± 1.72)	-47.44 (± 1.25)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001 [18]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-33.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.12
upper limit	-28.99
Variability estimate	Standard error of the mean
Dispersion value	2.06

Notes:

[17] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[18] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

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

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

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: Percent change				
least squares mean (standard error)	-14.62 (± 1.83)	-45.72 (± 1.32)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-31.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.44
upper limit	-26.76
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[19] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[20] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Apolipoprotein B at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in Apolipoprotein B at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	136		
Units: Percent change				
least squares mean (standard error)	-11.42 (± 1.82)	-45.28 (± 1.31)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001 [22]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-33.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.15
upper limit	-29.58
Variability estimate	Standard error of the mean
Dispersion value	2.17

Notes:

[21] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[22] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change from Baseline in Apolipoprotein B at Week 24 in Part B

End point title	Percent Change from Baseline in Apolipoprotein B at Week 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	116		
Units: Percent change				
least squares mean (standard error)	-11.74 (± 1.94)	-43.50 (± 1.40)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.0001 [24]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-31.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.35
upper limit	-27.16
Variability estimate	Standard error of the mean
Dispersion value	2.33

Notes:

[23] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[24] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Total Cholesterol/HDL-C Ratio at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in Total Cholesterol/HDL-C Ratio at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: Percent change				
least squares mean (standard error)	-11.48 (± 1.75)	-41.39 (± 1.27)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.0001 [26]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-29.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.06
upper limit	-25.77
Variability estimate	Standard error of the mean
Dispersion value	2.1

Notes:

[25] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[26] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Total Cholesterol/HDL-C Ratio at Week 24 in Part B

End point title	Percent Change From Baseline in Total Cholesterol/HDL-C Ratio at Week 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: Percent change				
least squares mean (standard error)	-12.84 (± 1.85)	-40.04 (± 1.33)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.0001 [28]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-27.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.58
upper limit	-22.82
Variability estimate	Standard error of the mean
Dispersion value	2.22

Notes:

[27] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[28] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	136		
Units: Percent change				
least squares mean (standard error)	-11.86 (± 1.89)	-45.99 (± 1.36)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.0001 [30]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-34.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.59
upper limit	-29.67
Variability estimate	Standard error of the mean
Dispersion value	2.26

Notes:

[29] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[30] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 24 in Part B

End point title	Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 24 in Part B

End point description:

Co-secondary tier 1 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	116		
Units: Percent change				
least squares mean (standard error)	-12.62 (± 1.97)	-44.60 (± 1.41)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001 [32]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-31.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.64
upper limit	-27.32
Variability estimate	Standard error of the mean
Dispersion value	2.36

Notes:

[31] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[32] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Lipoprotein(a) at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in Lipoprotein(a) at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	136		
Units: Percent change				
least squares mean (standard error)	-1.63 (± 2.80)	-22.71 (± 2.03)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.0001 [34]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-21.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.65
upper limit	-14.51
Variability estimate	Standard error of the mean
Dispersion value	3.33

Notes:

[33] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[34] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Lipoprotein(a) at Week 24 in Part B

End point title	Percent Change From Baseline in Lipoprotein(a) at Week 24 in Part B

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	116		
Units: Percent change				
least squares mean (standard error)	0.17 (± 3.05)	-21.06 (± 2.19)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.0001 [36]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-21.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.42
upper limit	-14.05
Variability estimate	Standard error of the mean
Dispersion value	3.64

Notes:

[35] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[36] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Triglycerides at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in Triglycerides at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: Percent change				
least squares mean (standard error)	-0.95 (± 3.94)	-5.39 (± 2.84)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.37 [38]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-4.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.74
upper limit	4.87
Variability estimate	Standard error of the mean
Dispersion value	4.72

Notes:

[37] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[38] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in Triglycerides at Week 24 in Part B

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

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: Percent change				
least squares mean (standard error)	-1.07 (± 4.97)	-2.88 (± 3.54)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.37 [40]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.64
upper limit	10.01
Variability estimate	Standard error of the mean
Dispersion value	6

Notes:

[39] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[40] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in HDL-C at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in HDL-C at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: Percent change				
least squares mean (standard error)	1.66 (± 1.71)	7.85 (± 1.24)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.0083 [42]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	6.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.15
upper limit	10.22
Variability estimate	Standard error of the mean
Dispersion value	2.05

Notes:

[41] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[42] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

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

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

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	117		
Units: Percent change				
least squares mean (standard error)	2.90 (± 1.89)	7.40 (± 1.36)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.0083 [44]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	8.98
Variability estimate	Standard error of the mean
Dispersion value	2.27

Notes:

[43] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[44] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in VLDL-C at the Mean of Weeks 22 and 24 in Part B

End point title	Percent Change From Baseline in VLDL-C at the Mean of Weeks 22 and 24 in Part B

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Weeks 22 and 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	136		
Units: Percent change				
least squares mean (standard error)	-2.15 (± 3.22)	-6.81 (± 2.33)		

Statistical analyses

Statistical analysis title	Treatment Difference at Mean of Weeks 22 and 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.37 [46]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-4.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.25
upper limit	2.94
Variability estimate	Standard error of the mean
Dispersion value	3.85

Notes:

[45] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[46] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Secondary: Percent Change From Baseline in VLDL-C at Week 24 in Part B

End point title	Percent Change From Baseline in VLDL-C at Week 24 in Part B

End point description:

Co-secondary tier 2 endpoint. The FAS population include all randomized participants in part B who received at least 1 dose of part B IP (SC or PO).

End point type	Secondary

End point timeframe:

Baseline (part A Day 1 for those who entered part A, and part B Day 1 for those who bypassed part A) and Week 24 of part B

End point values	Ezetimibe in part B	Evolocumab in part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: Percent change				
least squares mean (standard error)	-2.66 (± 3.88)	-3.90 (± 2.78)		

Statistical analyses

Statistical analysis title	Treatment Difference at Week 24
Comparison groups	Ezetimibe in part B v Evolocumab in part B
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.37 [48]
Method	Repeated Measures Model
Parameter estimate	Least Square Mean Treatment Difference
Point estimate	-1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.45
upper limit	7.98
Variability estimate	Standard error of the mean
Dispersion value	4.67

Notes:

[47] - Treatment difference calculated with ezetimibe in part B reporting group as the reference.

[48] - Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05. Model includes treatment group, stratification factor (screening LDL-C), scheduled visit and interaction of treatment with scheduled visit.

Other pre-specified: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs) in Part C

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs) in Part C

End point description:

An adverse event (AE) is defined as any untoward medical occurrence or worsening of a pre-existing medical condition in a participant. A serious AE is defined as an AE that meets at least 1 of following serious criteria: fatal, life threatening (immediate risk of death), requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect and other medically important serious event. AEs that occurred after IP administration in part C until 30 days after end of IP or EOS were considered treatment emergent in part C. Adverse device effect included AEs resulting from insufficient or inadequate instructions for use, or any malfunction of device, or use error or from intentional misuse of device. The long-term analysis set (LAS) population included all participants enrolled in part C of study who received at least 1 dose of open-label IP and was used in all analyses for part C of study.

End point type	Other pre-specified

End point timeframe:

From the first dose of IP in part C until 30 days after the end of IP or end of study (EOS), whichever was earlier (up to 104 weeks)

End point values	Ezetimibe in part B and Evolocumab in part C	Evolocumab in part B and part C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[49]	139[50]		
Units: Participants				
TEAEs	55	111		
TESAEs	14	36		
Device related TEAEs	1	1		
TEAEs leading to discontinuation of IP	3	4		
Fatal AE	0	1		

Notes:

[49] - One participant enrolled in to this group of part C without completing IP during part B.

[50] - One participant enrolled in to this group of part C without completing IP during part B.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants who Experienced the Maximum Toxicity Grade [Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3] Shift From Baseline in the Clinical Laboratory Parameters During Part C

End point title	Number of Participants who Experienced the Maximum Toxicity Grade [Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3] Shift From Baseline in the Clinical Laboratory Parameters During Part C

End point description:

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters were taken every 3 months and at the EOS or safety follow-up visit during part C of the study. The results were based on the shift of laboratory parameters from study baseline grade 0 to 2 to postbaseline grade 3 to 4 during part C. All baseline values were collected at the start of the study, ie, baseline values from the start of part A for participants who entered part A, and from the start of part B for participants who bypassed part A. Laboratory shift values for specific analytes were provided using the CTCAE version 4.03 toxicity criteria. The LAS population included all participants enrolled in part C of the study who received at least 1 dose of open-label IP and was used in all analyses for part C of the study. AST = aspartate aminotransferase and INR = international normalized ratio.

End point type	Other pre-specified

End point timeframe:

From the first dose of IP in part C until 30 days after the end of IP or EOS, whichever was earlier (up to 104 weeks)

End point values	Ezetimibe in part B and Evolocumab in part C	Evolocumab in part B and part C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[51]	139[52]		
Units: Participants				
AST (shift from grade 0 to 3)	0	1		
Creatine kinase (shift from grade 0 to 4)	0	1		
Creatine kinase (shift from grade 1 to 3)	0	1		
Creatine kinase (shift from grade 1 to 4)	0	1		
Creatine kinase (shift from grade 2 to 3)	0	1		
Creatinine (shift from grade 2 to 3)	1	0		
Sodium (shift from grade 1 to 3)	0	1		
Total bilirubin (shift from grade 0 to 3)	1	0		
INR (shift from grade 2 to 3)	0	1		

Notes:

[51] - One participant enrolled in to this group of part C without completing IP during part B.

[52] - One participant enrolled in to this group of part C without completing IP during part B.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Positive Anti-Evolocumab Antibody Formation in Part C

End point title	Number of Participants With Positive Anti-Evolocumab Antibody Formation in Part C

End point description:

Blood samples were collected annually and at the end of study or safety follow-up visit during part C of the study for the measurement of anti-evolocumab binding antibodies. The LAS population included all participants enrolled in part C of the study who received at least 1 dose of open-label IP and was used in all analyses for part C of the study.

End point type	Other pre-specified

End point timeframe:

From the first dose of IP in part C until 30 days after the end of IP or EOS, whichever was earlier (up to 104 weeks)

End point values	Ezetimibe in part B and Evolocumab in part C	Evolocumab in part B and part C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[53]	139[54]		
Units: Participants				
Binding antibody positive	0	0		
Neutralizing antibody positive	0	0		

Notes:

[53] - One participant enrolled in to this group of part C without completing IP during part B.

[54] - One participant enrolled in to this group of part C without completing IP during part B.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of IP in part B until the EOS visit in part C or early termination from the study, up to 128 weeks

Adverse event reporting additional description:

The FAS population and LAS population were analyzed for AEs in part B and part C of study, respectively.
MedDRA dictionary version 18.1 was used for part B and 20.1 for part C.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1 20.1

Reporting groups

Reporting group title	Evolocumab in Part B

Reporting group description:

Participants received evolocumab 420 mg SC injection QM and placebo matching to ezetimibe orally QD for 24 weeks.

Reporting group title	Ezetimibe in Part B and Evolocumab in Part C

Reporting group description:

Participants who completed SC IP in part B were eligible and 2 participants who did not complete IP in part B were enrolled in part C and were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC Q2W for up to 104 weeks.

Reporting group title	Ezetimibe in Part B

Reporting group description:

Participants received ezetimibe 10 mg orally QD and placebo matching to evolocumab SC injection QM for 24 weeks.

Reporting group title	Evolocumab in Part B and Part C

Reporting group description:

Participants who completed SC IP in part B were eligible and 2 participants who did not complete IP in part B were enrolled in part C and were allowed to choose quarterly during scheduled study center visits between evolocumab 420 mg SC QM or evolocumab 140 mg SC Q2W for up to 104 weeks.

Serious adverse events	Evolocumab in Part B	Ezetimibe in Part B and Evolocumab in Part C	Ezetimibe in Part B
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 145 (6.21%)	14 / 70 (20.00%)	10 / 73 (13.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Chronic lymphocytic leukaemia			

subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Lipoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Prostate cancer stage I			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Prostatic adenoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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 crisis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Peripheral artery occlusion			

subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Surgical and medical procedures			
Spinal fusion surgery			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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			
Vocal cord cyst			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Psychiatric disorders			
Bipolar I disorder			

subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Foreign body in respiratory tract			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Hip fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Ligament sprain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Pelvic fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Post procedural urine leak			

subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Road traffic accident			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 145 (0.69%)	4 / 70 (5.71%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 145 (1.38%)	0 / 70 (0.00%)	0 / 73 (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

Atrial flutter			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Cardiac failure			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Coronary artery perforation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Heart valve incompetence			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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 cardiomyopathy			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Myocardial infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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			

Carotid artery stenosis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Dizziness			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Hypoaesthesia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Migraine with aura			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Myasthenia gravis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Neuralgia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
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			

Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Vomiting			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Cholelithiasis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Calculus urinary			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Haematuria			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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

Nephrolithiasis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Back pain			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 145 (0.00%)	2 / 70 (2.86%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Neck pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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	1 / 145 (0.69%)	1 / 70 (1.43%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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			
Arthritis infective			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Diverticulitis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Gastroenteritis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Meningitis viral			
subjects affected / exposed	1 / 145 (0.69%)	0 / 70 (0.00%)	0 / 73 (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
Pneumonia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Urinary tract infection			
subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 145 (0.00%)	0 / 70 (0.00%)	0 / 73 (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
Wound infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 145 (0.00%)	1 / 70 (1.43%)	0 / 73 (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 in Part B and Part C		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 139 (25.90%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive lobular breast carcinoma			

subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lipoma				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal adenocarcinoma				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer stage I				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatic adenoma				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral artery occlusion				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Spinal fusion surgery				
subjects affected / exposed	0 / 139 (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	3 / 139 (2.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine prolapse			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Vocal cord cyst			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foreign body in respiratory tract			

subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	2 / 139 (1.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Post procedural urine leak				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Congenital cystic kidney disease				

subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	2 / 139 (1.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery perforation				

subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heart valve incompetence				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic cardiomyopathy				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Myocardial ischaemia				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
subjects affected / exposed	0 / 139 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 139 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine with aura			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus urinary			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical spinal stenosis			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Obesity			
subjects affected / exposed	0 / 139 (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	Evolocumab in Part B	Ezetimibe in Part B and Evolocumab in Part C	Ezetimibe in Part B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 145 (59.31%)	34 / 70 (48.57%)	44 / 73 (60.27%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 145 (6.90%)	3 / 70 (4.29%)	7 / 73 (9.59%)
occurrences (all)	12	3	8
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 145 (8.28%)	0 / 70 (0.00%)	5 / 73 (6.85%)
occurrences (all)	12	0	5
Influenza like illness			
subjects affected / exposed	1 / 145 (0.69%)	2 / 70 (2.86%)	4 / 73 (5.48%)
occurrences (all)	1	3	5
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 145 (2.07%)	2 / 70 (2.86%)	4 / 73 (5.48%)
occurrences (all)	3	2	4
Diarrhoea			
subjects affected / exposed	6 / 145 (4.14%)	2 / 70 (2.86%)	4 / 73 (5.48%)
occurrences (all)	6	3	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 145 (8.97%)	7 / 70 (10.00%)	1 / 73 (1.37%)
occurrences (all)	13	10	1
Back pain			
subjects affected / exposed	10 / 145 (6.90%)	6 / 70 (8.57%)	5 / 73 (6.85%)
occurrences (all)	10	7	6

Muscle spasms			
subjects affected / exposed	13 / 145 (8.97%)	4 / 70 (5.71%)	5 / 73 (6.85%)
occurrences (all)	15	6	6
Musculoskeletal pain			
subjects affected / exposed	5 / 145 (3.45%)	2 / 70 (2.86%)	1 / 73 (1.37%)
occurrences (all)	5	2	1
Myalgia			
subjects affected / exposed	20 / 145 (13.79%)	8 / 70 (11.43%)	16 / 73 (21.92%)
occurrences (all)	22	10	21
Pain in extremity			
subjects affected / exposed	13 / 145 (8.97%)	3 / 70 (4.29%)	1 / 73 (1.37%)
occurrences (all)	15	3	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 145 (0.69%)	1 / 70 (1.43%)	4 / 73 (5.48%)
occurrences (all)	1	1	4
Influenza			
subjects affected / exposed	7 / 145 (4.83%)	3 / 70 (4.29%)	1 / 73 (1.37%)
occurrences (all)	7	3	2
Nasopharyngitis			
subjects affected / exposed	14 / 145 (9.66%)	3 / 70 (4.29%)	2 / 73 (2.74%)
occurrences (all)	14	4	2
Sinusitis			
subjects affected / exposed	4 / 145 (2.76%)	3 / 70 (4.29%)	2 / 73 (2.74%)
occurrences (all)	5	3	2
Upper respiratory tract infection			
subjects affected / exposed	4 / 145 (2.76%)	1 / 70 (1.43%)	1 / 73 (1.37%)
occurrences (all)	4	1	1
Urinary tract infection			
subjects affected / exposed	5 / 145 (3.45%)	4 / 70 (5.71%)	3 / 73 (4.11%)
occurrences (all)	6	4	4
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 145 (0.00%)	2 / 70 (2.86%)	1 / 73 (1.37%)
occurrences (all)	0	2	3

Non-serious adverse events	Evolocumab in Part		

	B and Part C		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 139 (54.68%)		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 139 (5.76%)		
occurrences (all)	10		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 139 (4.32%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	5 / 139 (3.60%)		
occurrences (all)	7		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 139 (2.88%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 139 (7.19%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	9 / 139 (6.47%)		
occurrences (all)	9		
Muscle spasms			
subjects affected / exposed	10 / 139 (7.19%)		
occurrences (all)	10		
Musculoskeletal pain			
subjects affected / exposed	8 / 139 (5.76%)		
occurrences (all)	8		
Myalgia			

subjects affected / exposed	16 / 139 (11.51%)		
occurrences (all)	26		
Pain in extremity			
subjects affected / exposed	6 / 139 (4.32%)		
occurrences (all)	7		
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 139 (7.19%)		
occurrences (all)	13		
Influenza			
subjects affected / exposed	9 / 139 (6.47%)		
occurrences (all)	12		
Nasopharyngitis			
subjects affected / exposed	15 / 139 (10.79%)		
occurrences (all)	18		
Sinusitis			
subjects affected / exposed	7 / 139 (5.04%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	7 / 139 (5.04%)		
occurrences (all)	11		
Urinary tract infection			
subjects affected / exposed	7 / 139 (5.04%)		
occurrences (all)	11		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	7 / 139 (5.04%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2013	The main purpose of this amendment was to add Vitamin E reflex testing to part C of the protocol in cases where LDL-C is < 25 mg/dL. To clarify language for laboratory testing on Day 1 of part B in participants who complete part A. As prior version was incorrect with respect to participants who go directly to part B due to 10x upper limit of normal (ULN) creatine kinase (CK). Add the potential to use the automated mini-doser in part C of the study. Remove duplicate exclusion criteria regarding malignancy. Remove Statin Intolerance Questionnaire as it is redundant with the Short Form (36) Health Survey (SF-36). Make the Brief Pain Inventory (BPI) mandatory in part A. Add the BPI and the SF-36 to part B and add corresponding exploratory analysis and statistical language. Clarify language on MRSE that in the opinion of the investigator lead to discontinuation of IP. Update statin inclusion criteria per FDA comment.
15 January 2014	The main purpose of this amendment was to clarify that participants must bypass part A and be randomized directly into part B if they have a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy. Update duration of part A to approximately 24 weeks. Modify inclusion criterion to specify that participants with fasting LDL-C ≥ 160 mg/dL (4.14 millimoles per liter) without diagnosed coronary heart disease or risk equivalent should have 1 or more risk factors. To clarify text to reflect that participants must discontinue statins and ezetimibe for ≥ 4 weeks before LDL-C screening. To Modify timing of non-protocol testing of specific analytes to at least 12 weeks after participant's last blinded IP administration. Add Hepatitis C virus viral load testing for participants positive for Hepatitis C virus on Day 1 (part B). Remove Hemoglobin A1c from exploratory endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The efficacy and safety evaluations were presented only for part B and C of 3-part study. The AE data was not included for part A as this was designed to confirm presence of statin-related MRSE and ensure that only these participants entered part B.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27039291