EU Clinical Trials Register

Clinical trial results:
A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy

Summary

EudraCT number	2011-004130-34
Trial protocol	HU DK DE
Global end of trial date	28 July 2015

Results information

Result version number	v2 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015
Version creation reason	• New data added to full data set Addition of results: analysis of efficacy data at time points beyond the Week 52 time point (primary completion) as well as final analysis of safety data at the end of the study (Week 112)

Trial information

Trial identification

Sponsor protocol code	EFC11569

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01644188
WHO universal trial number (UTN)	U1111-1121-4315
Other trial identifiers	Study name: ODYSSEY COMBO II

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	28 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab (SAR236553/REGN727) as add-on therapy to stable maximally tolerated daily statin therapy in comparison with ezetimibe 10 mg after 24 weeks of treatment in subjects with hypercholesterolemia at high cardiovascular (CV) risk.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates

Background therapy:

All subjects had to receive a statin at maximally tolerated dose (simvastatin, atorvastatin and rosuvastatin). Background statin therapy was not to be changed (including dose) at least 4 weeks prior to the screening visit and throughout the whole study duration barring exceptional circumstances.

Evidence for comparator: -

Actual start date of recruitment	09 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Korea, Republic of: 42
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Hungary: 65
Country: Number of subjects enrolled	Denmark: 100
Country: Number of subjects enrolled	Russian Federation: 149
Country: Number of subjects enrolled	South Africa: 92
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 217

Worldwide total number of subjects	720
EEA total number of subjects	174

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)	434
From 65 to 84 years	282
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 126 centers in 10 countries. Overall, 1112 subjects were screened between August 2012 and May 2013, 392 of whom were screen failures. Screen failures ware mainly due to exclusion criteria met.

Pre-assignment

Screening details:

Randomization was stratified according to prior history of myocardial infarction (MI) or ischemic stroke, intensity of statin treatment and geographical region. Assignment to arms was done centrally using Interactive Voice/Web Response System in 2:1 ratio (alirocumab: ezetimibe) after confirmation of selection criteria. 720 subjects were randomized

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Alirocumab and placebo for alirocumab were provided in identically matched auto-injectors and packaged identically. Ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe, had the same appearance and feel and were labeled with a double-blind label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Alirocumab 75/up to 150 mg Q2W

Arm description:

Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level ≥70 mg/dL (1.81 mmol/L) at Week 8.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553, REGN727
Other name	Praluent
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh, or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

Investigational medicinal product name	Placebo (for Ezetimibe)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One over-encapsulated tablet once daily at approximately the same time of the day with or without food.

Arm title	Ezetimibe 10 mg

Arm description:

Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104 weeks.

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

Dosage and administration details:

One over-encapsulated tablet once daily at approximately the same time of the day with or without food.

Investigational medicinal product name	Placebo (for alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh, or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

Number of subjects in period 1	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg
Started	479	241
Treated	479	241
Completed	357	166
Not completed	122	75
Last visit outside protocol visit window	14	16
Related to Auto-injector Administration	2	2
Consent withdrawn by subject	14	7
Physician decision	1	3
Lost to follow-up	1	-
Selection criteria finally not met	2	-
Death	4	3
Adverse event	44	20
Other than specified	6	7
Subject moved	7	2
Poor compliance to protocol	26	14
Site closure	1	1

Baseline characteristics

Reporting groups

Reporting group title	Alirocumab 75/up to 150 mg Q2W
Reporting group description:	

Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level ≥70 mg/dL (1.81 mmol/L) at Week 8.

Reporting group title	Ezetimibe 10 mg
Reporting group description:	

Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104 weeks.

Reporting group values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg	Total
Number of subjects	479	241	720
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.7	61.3	
standard deviation	± 9.4	± 9.2	-
Gender categorical			
Units: Subjects			
Female	119	71	190
Male	360	170	530
Calculated LDL-C in mg/dL			
Calculated LDL--C in mg/dL from Friedewald formula (LDL cholesterol = Total cholesterol – HDL cholesterol - [Triglyceride/5]).			
Units: mg/dL			
arithmetic mean	108.6	104.6	
standard deviation	± 36.5	± 34.1	-
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	2.812	2.71	
standard deviation	± 0.945	± 0.884	-

End points

End points reporting groups

Reporting group title	Alirocumab 75/up to 150 mg Q2W

Reporting group description:

Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level ≥70 mg/dL (1.81 mmol/L) at Week 8.

Reporting group title	Ezetimibe 10 mg

Reporting group description:

Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104 weeks.

Subject analysis set title	Alirocumab 75 /up to 150 mg Q2W
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects exposed to Alirocumab 75 /up to 150 mg Q2W added to stable LMT (mean exposure of 58 weeks).

Subject analysis set title	Ezetimibe 10 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects exposed to Ezetimibe 10 mg added to stable LMT (mean exposure of 58 weeks).

Primary: Percent Change From Baseline in Calculated LDL-C at Week 24 -Intent-to-treat (ITT) Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 -Intent-to-treat (ITT) Analysis

End point description:

Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment.

End point type	Primary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-50.6 (± 1.4)	-20.7 (± 1.9)		

Statistical analyses

Statistical analysis title	Alirocumab vs. Ezetimibe

Statistical analysis description:

Alirocumab group was compared to ezetimibe group using an appropriate contrast statement.

Comparison groups	Ezetimibe 10 mg v Alirocumab 75/up to 150 mg Q2W
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.4
upper limit	-25.3

Notes:

[1] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 24 - On-treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 - On-treatment Analysis

End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Modified ITT population (mITT): all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	464	235		
Units: percent change				
least squares mean (standard error)	-52.4 (± 1.3)	-21.8 (± 1.8)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg

Number of subjects included in analysis	699
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.9
upper limit	-26.2

Notes:

[2] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT analysis

End point description:

Adjusted LS means and standard errors at Week 12 from a MMRM including all available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment (ITT analysis). ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-51.2 (± 1.3)	-21.8 (± 1.8)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.7
upper limit	-25.1

Notes:

[3] - Threshold for significance ≤0.05

Secondary: Percent Change from Baseline in Calculated LDL-C at Week 12 - On-treatment analysis

End point title	Percent Change from Baseline in Calculated LDL-C at Week 12 - On-treatment analysis

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). mITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	464	235		
Units: percent change				
least squares mean (standard error)	-52.4 (± 1.2)	-22.7 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	699
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	-25.6

Notes:

[4] - Threshold for significance <0.05

Secondary: Percent Change From Baseline in Apolipoprotein B (Apo-B) at Week 24 - ITT analysis

End point title	Percent Change From Baseline in Apolipoprotein B (Apo-B) at Week 24 - ITT analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
Subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment (Apo B ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	228		
Units: percent change				
least squares mean (standard error)	-40.7 (± 1.1)	-18.3 (± 1.5)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	680
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	-18.8

Notes:

[5] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Apo B at Week 24 - On-treatment analysis

End point title	Percent Change From Baseline in Apo B at Week 24 - On-treatment analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first).
Subjects of the mITT population with one baseline and at least one post-baseline Apo B value on-treatment (Apo B mITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	221		
Units: percent change				
least squares mean (standard error)	-42.1 (± 1)	-19.1 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.5
upper limit	-19.6

Notes:

[6] - Threshold for significance ≤0.05

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
Subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or

off-treatment (non-HDL-C ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-42.1 (± 1.2)	-19.2 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.9
upper limit	-18.9

Notes:

[7] - Threshold for significance ≤0.05.

Secondary: Percent Change From Baseline in Non-HDL-C at Week 24 - On-treatment Analysis

End point title	Percent Change From Baseline in Non-HDL-C at Week 24 - On-treatment Analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first).
Subjects of the mITT population with one baseline and at least one post-baseline Non-HDL-C value on-treatment (non-HDL-C mITT population).

End point type	Secondary

End point timeframe:

From Baseline up to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	464	235		
Units: percent change				
least squares mean (standard error)	-43.7 (± 1.1)	-20.2 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	699
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-23.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.2
upper limit	-19.7

Notes:

[8] - Threshold for significance ≤0.05

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

End point title	Percent Change From Baseline in Total Cholesterol (TC) at Week 24 - ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline TC value on- or off-treatment (total-C ITT population).	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-29.3 (± 0.9)	-14.6 (± 1.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	-11.7

Notes:

[9] - Threshold for significance ≤0.05.

Secondary: Percent Change From Baseline in Apo-B at Week 12 - ITT analysis

End point title	Percent Change From Baseline in Apo-B at Week 12 - ITT analysis
End point description:	
Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Apo-B ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	228		
Units: percent change				
least squares mean (standard error)	-39.7 (± 1)	-17.2 (± 1.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	680
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.7
upper limit	-19.2

Notes:

[10] - Threshold for significance ≤0.05.

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

End point title	Percent Change From Baseline in Non-HDL-C at Week 12 - ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Non-HDL-C ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-42.6 (± 1.1)	-20.6 (± 1.5)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.6
upper limit	-18.3

Notes:

[11] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Total Cholesterol (TC) at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Total Cholesterol (TC) at Week 12 - ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Total-C ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-29.4 (± 0.8)	-15.1 (± 1.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	-11.6

Notes:

[12] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 52 - ITT Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 52 - ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 52 from a MMRM model including all available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment.
ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	-49.5 (± 1.5)	-18.3 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.3
upper limit	-26.1

Notes:

[13] - Threshold for significance ≤0.05

Secondary: Percentage of Subjects Achieving Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT analysis

End point title	Percentage of Subjects Achieving Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT analysis

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment were included in the imputation model. ITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percentage of subjects				
number (not applicable)	77	45.6		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a Logistic regression model

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	7.9

Notes:

[14] - Threshold for significance ≤0.05

Secondary: Percentage of Subjects Achieving Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-treatment analysis

End point title	Percentage of Subjects Achieving Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-treatment analysis

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from week 4 to week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	464	235		
Units: percentage of subjects				
number (not applicable)	78.9	47.4		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	699
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	8.8

Notes:

[15] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Lipoprotein(a) at Week 24 - ITT analysis

End point title	Percent Change From Baseline in Lipoprotein(a) at Week 24 - ITT analysis
End point description:	
Adjusted means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. ITT population.	
End point type	Secondary
End point timeframe:	
From baseline to Week 52	

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
arithmetic mean (standard error)	-27.8 (± 1.4)	-6.1 (± 2)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-21.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.4
upper limit	-17

Notes:

[16] - Threshold for significance ≤0.05

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

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

	Analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
Subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment(HDL-C ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard deviation)	8.6 (± 0.8)	0.5 (± 1.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	10.7

Notes:

[17] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis

End point description:

Adjusted means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
ITT population.

End point type	Secondary

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
arithmetic mean (standard error)	-13 (± 1.5)	-12.8 (± 2)		

Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9117 [18]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	4.6

Notes:

[18] - Threshold for significance ≤0.05

Secondary: Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1) at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1) at Week 24 - ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
Subjects of the ITT population with one baseline and at least one post-baseline Apo A-1 value on- or off-treatment (Apo A-1 ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	228		
Units: percent change				
least squares mean (standard error)	5 (± 0.6)	-1.3 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Lipoprotein(a) at Week 12 - ITT analysis

End point description:

Adjusted means and standard errors at Week 12 from from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
arithmetic mean (standard error)	-22.1 (± 1.2)	1.1 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-

baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
HDL-C ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	8.7 (± 0.7)	2.8 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis

End point description:

Adjusted means and standard errors at Week 12 from from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
arithmetic mean (standard error)	-13 (± 1.5)	-12.8 (± 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
Apo A-1 ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	240		
Units: percent change				
least squares mean (standard error)	1.5 (± 0.5)	-2.9 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 52 – On-Treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 52 – On-Treatment Analysis

End point description:

Adjusted LS means and standard errors at Week 52 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). mITT population.

End point type	Other pre-specified

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 /up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	464	235		
Units: Percent change				
least squares mean (standard error)	-51.8 (± 1.5)	-19.7 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 104 – ITT Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 104 – ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 104 from MMRM including all available post-baseline data from Week 4 to Week 104 regardless of status on- or off-treatment. ITT population.	
End point type	Other pre-specified
End point timeframe:	
From Baseline to Week 104	

End point values	Alirocumab 75 /up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	467	240		
Units: Percent change				
least squares mean (standard error)	-44.2 (± 1.7)	-15.2 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 104 – On-Treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 104 – On-Treatment Analysis
End point description:	
Adjusted LS means and standard errors at Week 104 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 104 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). mITT population.	
End point type	Other pre-specified
End point timeframe:	
From Baseline to Week 104	

End point values	Alirocumab 75 /up to 150 mg Q2W	Ezetimibe 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	464	235		
Units: Percent change				
least squares mean (standard error)	-48.9 (± 1.7)	-17 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to final visit (Week 112) in the study regardless of seriousness or relationship to study drugs.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during 'the treatment-emergent period' (from the first dose of double-blind investigational medicinal product (IMP) administration [capsule or injection, whichever came first] up the day of the last double-blind IMP injection + 70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Alirocumab 75 /Up to 150 mg Q2W

Reporting group description:

Subjects exposed to Alirocumab 75 /up to 150 mg Q2W added to stable LMT (mean exposition of 90 weeks).

Reporting group title	Ezetimibe 10 mg

Reporting group description:

Subjects exposed to Ezetimibe 10 mg added to stable LMT (mean exposition of 90 weeks).

Serious adverse events	Alirocumab 75 /Up to 150 mg Q2W	Ezetimibe 10 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 479 (25.89%)	60 / 241 (24.90%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Stromal Tumour			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Adenocarcinoma			

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Malignant Melanoma		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases To Central Nervous System		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Non-Small Cell Lung Cancer		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Non-Small Cell Lung Cancer Metastatic		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Non-Small Cell Lung Cancer Stage Iiia		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Oesophageal Carcinoma		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oestrogen Receptor Positive Breast Cancer		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pancreatic Carcinoma		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pituitary Tumour Benign		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Prostate Cancer		
subjects affected / exposed	3 / 479 (0.63%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal Neoplasm		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous Cell Carcinoma Of Lung		
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Squamous Cell Carcinoma Of Skin		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular disorders		
Aortic Dissection		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Femoral Artery Occlusion		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertension		

subjects affected / exposed	3 / 479 (0.63%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Peripheral Arterial Occlusive Disease

subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0

Peripheral Artery Aneurysm

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Peripheral Vascular Disorder

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Thrombophlebitis Superficial

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Venous Thrombosis Limb

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

General disorders and administration site conditions

Asthenia

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Chest Pain

subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Implant Site Haematoma

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Non-Cardiac Chest Pain				
subjects affected / exposed	6 / 479 (1.25%)	2 / 241 (0.83%)		
occurrences causally related to treatment / all	0 / 7	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sudden Cardiac Death				
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 1	0 / 1		
Sudden Death				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory, thoracic and mediastinal disorders				
Chronic Obstructive Pulmonary Disease				
subjects affected / exposed	4 / 479 (0.84%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 8	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dyspnoea				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pleuritic Pain				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Pneumonia Aspiration		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary Embolism		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary Oedema		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sleep Apnoea Syndrome		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Vocal Cord Polyp		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Psychiatric disorders		
Anxiety		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Completed Suicide		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Confusional State		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Depression		

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Bacterial Test Positive			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International Normalised Ratio Increased			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Restenosis			
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hand Fracture		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hip Fracture		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Incisional Hernia		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Laceration		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Meniscus Injury		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple Fractures		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Patella Fracture		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pubis Fracture		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rib Fracture		

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Road Traffic Accident

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Skeletal Injury

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Spinal Compression Fracture

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Wound

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Cardiac disorders

Acute Coronary Syndrome

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Acute Myocardial Infarction

subjects affected / exposed	12 / 479 (2.51%)	3 / 241 (1.24%)
occurrences causally related to treatment / all	0 / 13	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0

Angina Pectoris

subjects affected / exposed	10 / 479 (2.09%)	6 / 241 (2.49%)
occurrences causally related to treatment / all	0 / 11	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0

Angina Unstable

subjects affected / exposed	9 / 479 (1.88%)	6 / 241 (2.49%)		
occurrences causally related to treatment / all	0 / 9	0 / 6		
deaths causally related to treatment / all	0 / 0	0 / 0		
Arrhythmia				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Arteriosclerosis Coronary Artery				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrial Fibrillation				
subjects affected / exposed	4 / 479 (0.84%)	2 / 241 (0.83%)		
occurrences causally related to treatment / all	0 / 5	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrial Flutter				
subjects affected / exposed	2 / 479 (0.42%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrioventricular Block				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrioventricular Block Complete				
subjects affected / exposed	2 / 479 (0.42%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrioventricular Block Second Degree				
subjects affected / exposed	1 / 479 (0.21%)	2 / 241 (0.83%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac Arrest				

subjects affected / exposed	4 / 479 (0.84%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Cardiac Failure			
subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	4 / 479 (0.84%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congestive Cardiomyopathy			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Defect Conduction Intraventricular			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial Infarction			
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			

subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Silent Myocardial Infarction

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Supraventricular Tachycardia

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Ventricular Extrasystoles

subjects affected / exposed	0 / 479 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Ventricular Fibrillation

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Ventricular Tachycardia

subjects affected / exposed	2 / 479 (0.42%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Nervous system disorders

Brain Injury

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Carotid Artery Disease

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Carotid Artery Stenosis

subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Cerebral Haemorrhage

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Cerebrosclerosis

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Dementia Alzheimer's Type

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Dizziness

subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Facial Paresis

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Headache

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Hypoxic-Ischaemic Encephalopathy

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0

Intracranial Aneurysm

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	3 / 479 (0.63%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis Transverse			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory Disturbance			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 479 (0.42%)	4 / 241 (1.66%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Global Amnesia			

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Transient Ischaemic Attack

subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Blood and lymphatic system disorders

Anaemia

subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		

Haemorrhagic Anaemia

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Ear and labyrinth disorders

Cupulolithiasis

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Eye disorders

Cataract

subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Cataract Nuclear

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Ophthalmoplegia

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Retinal Detachment				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vision Blurred				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal disorders				
Abdominal Distension				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal Hernia				
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal Pain				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Constipation				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diverticular Perforation				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diverticulum Intestinal				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastric Haemorrhage				

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastric Ulcer Haemorrhage				
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastritis				
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastroduodenitis				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal Haemorrhage				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrooesophageal Reflux Disease				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Haemorrhoids				
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Inguinal Hernia				
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Irritable Bowel Syndrome				

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Large Intestine Polyp		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal Haemorrhage		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vomiting		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatobiliary disorders		
Cholecystitis Acute		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cholelithiasis		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skin and subcutaneous tissue disorders		
Eczema Nummular		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urticaria		

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Renal and urinary disorders

Acute Kidney Injury

subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Calculus Ureteric

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Haematuria

subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Nephrolithiasis

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Renal Tubular Necrosis

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Endocrine disorders

Goitre

subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders

Arthralgia

subjects affected / exposed	2 / 479 (0.42%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Compartment Syndrome		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Flank Pain		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rotator Cuff Syndrome		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal Column Stenosis		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal Instability		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal Osteoarthritis		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infections and infestations		
Arthritis Infective		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis		

subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchopneumonia				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cellulitis Of Male External Genital Organ				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Colonic Abscess				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diverticulitis				
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastroenteritis				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastroenteritis Viral				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatitis E				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Myringitis Bullous				

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Osteomyelitis Chronic				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Peritonitis				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia				
subjects affected / exposed	9 / 479 (1.88%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 9	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia Staphylococcal				
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Postoperative Wound Infection				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pulmonary Tuberculosis				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pyelonephritis Acute				
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Scrotal Abscess				

	1 / 479 (0.21%)	0 / 241 (0.00%)	
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alirocumab 75 /Up to 150 mg Q2W	Ezetimibe 10 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 479 (38.62%)	90 / 241 (37.34%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	47 / 479 (9.81%)	19 / 241 (7.88%)	
occurrences (all)	70	33	
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 479 (6.47%)	14 / 241 (5.81%)	
occurrences (all)	38	19	
Nervous system disorders			
Dizziness			
subjects affected / exposed	28 / 479 (5.85%)	18 / 241 (7.47%)	
occurrences (all)	29	20	
Headache			

subjects affected / exposed	29 / 479 (6.05%)	13 / 241 (5.39%)	
occurrences (all)	36	14	

Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	25 / 479 (5.22%)	13 / 241 (5.39%)	
occurrences (all)	28	14	

Infections and infestations			
Influenza			
subjects affected / exposed	22 / 479 (4.59%)	16 / 241 (6.64%)	
occurrences (all)	25	17	
Nasopharyngitis			
subjects affected / exposed	23 / 479 (4.80%)	15 / 241 (6.22%)	
occurrences (all)	35	16	
Upper Respiratory Tract Infection			
subjects affected / exposed	42 / 479 (8.77%)	17 / 241 (7.05%)	
occurrences (all)	52	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2013	- Changes in the exclusion criteria related to diabetic control status, history of human immunodeficiency virus, previous participation in any clinical trial of alirocumab or any other anti-PCSK9 monoclonal antibody, laboratory findings during the screening period, and known hypersensitivity to monoclonal antibody. - Change in the reporting of AEs. - Change in the screening period duration and the window for the training visit. - Added the information on a possible contingency strategy in the event the manufacturer faces any performance or supply issues of the auto-injector in order to ensure the continuity of the study treatment without interruption. - Clarification for some safety laboratory parameters. - Clarification was provided regarding the type of cardiovascular (CV) events to be submitted to the Clinical Events Committee (CEC) for adjudication - Added a new section of contraception in the Concomitant medication section. - Precision in the definition of IMP and the way of handling treatment interruption. - Added information on the collection of family medical history to be consistent with what was collected in the e-CRF and with regard to the population enrolled in the study.
26 February 2014	- Statistical section was changed. - Addition of the blinding procedures related to pharmacokinetic analysis. - Updated language on cardiovascular events to be reported to the CEC for adjudication and including a clarification on cerebrovascular events. - Added the following sentence "LDL-C was also be measured (via the beta-quantification method) at Week 0 and Week 24". - Updated language on collection of information on partner pregnancy as per other protocol in the ODYSSEY phase 3 program. - Updated language on how to record injection site reactions that were not related to study drug. - Categorization of AEs: updated language on how to record injection site reactions that were not related to study drug.

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.

Manual reclassification was done by the Sponsor for the "other reasons" of non-completion of study as specified in the electronic case report form (eCRF).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25687353