Clinical trial results:
Long-term Safety and Tolerability of REGN727/SAR236553 in High Cardiovascular Risk Patients with Hypercholesterolemia not Adequately Controlled with Their Lipid Modifying Therapy: a Randomized, Double-blind, Placebo-controlled Study

Summary

EudraCT number	2011-002806-59
Trial protocol	BE FI SE ES PT DE CZ NO GB NL HU IT DK BG
Global end of trial date	19 November 2014

Results information

Result version number	v1 (current)
This version publication date	16 April 2016
First version publication date	16 April 2016

Trial information

Trial identification

Sponsor protocol code	LTS11717

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01507831
WHO universal trial number (UTN)	U1111-1121-3928
Other trial identifiers	Study Name: ODYSSEY LONG TERM

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	24 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of SAR236553(REGN727) in high cardiovascular (CV) risk subjects with hypercholesterolemia not adequately controlled with their lipid modifying therapy (LMT).

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 received a stable dose of statin (rosuvastatin, simvastatin or atorvastatin) with or without other LMT as clinically indicated throughout the duration of study.

Evidence for comparator: -

Actual start date of recruitment	06 January 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	Netherlands: 68
Country: Number of subjects enrolled	Norway: 48
Country: Number of subjects enrolled	Poland: 146
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Spain: 92
Country: Number of subjects enrolled	Sweden: 32
Country: Number of subjects enrolled	United Kingdom: 484
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Bulgaria: 78
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Finland: 20
Country: Number of subjects enrolled	France: 87
Country: Number of subjects enrolled	Germany: 139

Country: Number of subjects enrolled	Hungary: 78
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Argentina: 28
Country: Number of subjects enrolled	Canada: 63
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Mexico: 50
Country: Number of subjects enrolled	Romania: 44
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	South Africa: 215
Country: Number of subjects enrolled	Ukraine: 38
Country: Number of subjects enrolled	United States: 485
Worldwide total number of subjects	2341
EEA total number of subjects	1422

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)	1474
From 65 to 84 years	859
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 320 centers in 27 countries. Overall, 5144 subjects were screened between January 2012 and March 2013, 2801 of whom were screen failures. Screen failures were mainly due to exclusion criteria met. In addition 2 subjects received study drug but did not undergo randomization. They were excluded from analysis.

Pre-assignment

Screening details:

Randomization was stratified as per diagnosis of heterozygous familial hypercholesterolemia (heFH), prior history of myocardial infarction (MI) or ischemic stroke, intensity of statin treatment and geographic region. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:2 ratio (placebo:alirocumab).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Q2W

Arm description:

Placebo (for alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable lipid modifying therapy (LMT) for 78 weeks.

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

Dosage and administration details:

Placebo matched to alirocumab administered as SC injection in the abdomen, thigh, or outer area of the upper arm by self-injection or by another designated person.

Arm title	Alirocumab 150 mg Q2W

Arm description:

Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.

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

Dosage and administration details:

Alirocumab administered as SC injection in the abdomen, thigh, or outer area of the upper arm by self-injection or by another designated person.

Number of subjects in period 1	Placebo Q2W	Alirocumab 150 mg Q2W
Started	788	1553
Treated	788	1550
Completed	595	1113
Not completed	193	440
Physician decision	-	4
Adverse Event	48	113
Selection criteria finally not met	-	1
Poor compliance to protocol	38	60
Site closure	-	3
Last visit outside protocol visit window	51	143
Consent withdrawn by subject	34	72
Randomized but not treated	-	3
Death	6	2
Subject moved	5	19
Unspecified	3	6
Lost to follow-up	3	-
Related to study drug administration	5	14

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Placebo (for alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable lipid modifying therapy (LMT) for 78 weeks.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.	

Reporting group values	Placebo Q2W	Alirocumab 150 mg Q2W	Total
Number of subjects	788	1553	2341
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.6	60.4	
standard deviation	± 10.4	± 10.4	-
Gender categorical			
Units: Subjects			
Female	314	570	884
Male	474	983	1457
Calculated LDL-C in mg/dL			
Calculated LDL-C in mg/dL from Friedewald formula (LDL-C = Total cholesterol - High-density lipoprotein cholesterol - [Triglyceride/5]).			
Units: mg/dL			
arithmetic mean	121.9	122.7	
standard deviation	± 41.4	± 42.6	-
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	3.157	3.178	
standard deviation	± 1.073	± 1.102	-

End points

End points reporting groups

Reporting group title	Placebo Q2W
Reporting group description:	
Placebo (for alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable lipid modifying therapy (LMT) for 78 weeks.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.	

Primary: Percentage of Subjects Who Experienced Adverse Events (AEs)

End point title	Percentage of Subjects Who Experienced Adverse Events
End point description:	
Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'treatment-emergent period' (the time from the first dose of study drug up to the last dose of study drug +70 days). Safety population: all randomized subjects who received at least one dose or part of a dose of a study drug (treated).	
End point type	Primary
End point timeframe:	
Up to 10 weeks after last study drug administration (maximum of 86 weeks)	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Safety analyses were descriptive in nature.	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	788	1550		
Units: percentage of subjects				
number (not applicable)				
Any AE	82.5	81		
Any Serious AE	19.5	18.7		
Any AE leading to death	1.3	0.5		
Any AE leading to treatment discontinuation	5.8	7.2		

Statistical analyses

No statistical analyses for this end point

Secondary: 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	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	0.8 (± 1)	-61 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-61.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.3
upper limit	-59.4

Notes:

[2] - 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) (on-treatment analysis). Modified ITT (mITT) population: 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percent change				
least squares mean (standard error)	0.7 (± 1)	-62.8 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

A hierarchial 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 hierarchial testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-63.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.9
upper limit	-61.2

Notes:

[3] - 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 MMRM model including 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: Percent Change				
least squares mean (standard error)	1.5 (± 1)	-63.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-64.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.2
upper limit	-62.4

Notes:

[4] - 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). mITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percent change				
least squares mean (standard error)	1.4 (± 1)	-64.2 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-65.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.9
upper limit	-63.2

Notes:

[5] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Measured LDL-C at Week 24 - ITT Analysis
End point description:	
Measured LDL-C values via beta quantification method. Adjusted LS means and standard errors at Week 24 from MMRM model including 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 measured LDL-C value on- or off-treatment.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	652	1278		
Units: percent change				
least squares mean (standard error)	3.5 (± 1.1)	-57.8 (± 0.8)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	1930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-61.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64
upper limit	-58.5

Notes:

[6] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Apolipoprotein (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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	1468		
Units: percent change				
least squares mean (standard error)	1.2 (± 1)	-52.8 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.3
upper limit	-51.7

Notes:

[7] - 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 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). 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	1444		
Units: percent change				
least squares mean (standard error)	1.2 (± 0.9)	-54.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-55.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.7
upper limit	-53.2

Notes:

[8] - 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: Percent Change				
least squares mean (standard error)	0.7 (± 0.9)	-51.6 (± 0.6)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-52.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.4
upper limit	-50.2

Notes:

[9] - 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). 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 to Week 52	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percent change				
least squares mean (standard error)	0.6 (± 0.9)	-53.1 (± 0.6)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-53.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.7
upper limit	-51.6

Notes:

[10] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Total Cholesterol (Total-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 Total-C value on- or off-treatment (Total-C ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	-0.3 (± 0.7)	-37.8 (± 0.5)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-37.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.1
upper limit	-35.9

Notes:

[11] - 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	1468		
Units: percent change				
least squares mean (standard error)	0.5 (± 0.9)	-55.5 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.3
upper limit	-53.7

Notes:

[12] - 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	0.9 (± 0.8)	-53.7 (± 0.6)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-54.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.6
upper limit	-52.6

Notes:

[13] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Total-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. Total-C ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	0.2 (± 0.6)	-38.8 (± 0.4)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.4
upper limit	-37.5

Notes:

[14] - Threshold for significance ≤ 0.05.

Secondary: Percentage of Very High Cardiovascular (CV) Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis

End point title	Percentage of Very High Cardiovascular (CV) Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis

End point description:

Very high CV risk: Heterozygous Familial Hypercholesterolemia(heFH) subjects with coronary heart disease(CHD) or CHD risk equivalents or non- Familial Hypercholesterolemia(FH). High CV risk: heFH subjects without CHD or CHD risk equivalents. CHD risk equivalent: peripheral arterial disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate, 30 to <60 ml/minute/1.73 m^2 of body-surface area), or diabetes mellitus + 2 or more additional risk factors (hypertension; ankle-brachial index of ≤0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or family history of premature CHD). Adjusted percentages at Week 24 were obtained from 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 imputation model. ITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percentage of subjects				
number (not applicable)	8.5	80.7		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	71.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.6
upper limit	99.1

Notes:

[15] - Threshold for significance ≤ 0.05.

Secondary: Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis

End point title	Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis

End point description:

Adjusted percentages at Week 24 were from 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). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percentage of subjects				
number (not applicable)	8.5	82.8		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	2300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	93.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	66.1
upper limit	132

Notes:

[16] - Threshold for significance ≤ 0.05.

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

End point title	Percentage of Subjects Reaching 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 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percentage of subjects				
number (not applicable)	8	79.3		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	74.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	53.3
upper limit	104.4

Notes:

[17] - Threshold for significance ≤ 0.05.

Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-Treatment Analysis

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

End point description:

Adjusted percentages at Week 24 from multiple imputation approach model including available post-baseline data from Week 4 to Week 52 (i.e. up to 21 days after last injection). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percentage of subjects				
number (not applicable)	8	81.2		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	97.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	68.2
upper limit	138.9

Notes:

[18] - 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 were obtained from multiple imputation approach followed by robust regression 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:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
arithmetic mean (standard error)	-3.7 (± 1)	-29.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.1
upper limit	-23.1

Notes:

[19] - 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	-0.6 (± 0.5)	4 (± 0.4)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	5.9

Notes:

[20] - 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 multiple imputation approach followed by robust regression 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
arithmetic mean (standard error)	1.8 (± 1.2)	-15.6 (± 0.8)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.1
upper limit	-14.6

Notes:

[21] - Threshold for significance ≤ 0.05.

Secondary: Percent Change From Baseline in Apo A1 at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Apo A1 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 A1 value on- or off-treatment (Apo A1 ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	1468		
Units: percent change				
least squares mean (standard error)	1.2 (± 0.6)	4 (± 0.4)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	4.2

Notes:

[22] - Threshold for significance ≤ 0.05.

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 multiple imputation approach followed by robust regression 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
arithmetic mean (standard error)	-3.1 (± 1)	-28.2 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-25.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.4
upper limit	-22.7

Notes:

[23] - Threshold for significance ≤ 0.05.

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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	0.2 (± 0.5)	5.8 (± 0.4)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	6.8

Notes:

[24] - Threshold for significance ≤ 0.05.

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 multiple imputation approach followed by robust regression 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	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
arithmetic mean (standard error)	1.2 (± 1.1)	-16.7 (± 0.8)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	2310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-17.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.5
upper limit	-15.3

Notes:

[25] - Threshold for significance ≤ 0.05.

Secondary: Percent Change From Baseline in Apo A1 at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Apo A1 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 A1 ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	753	1468		
Units: percent change				
least squares mean (standard error)	0.6 (± 0.5)	4.6 (± 0.3)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	5.2

Notes:

[26] - Threshold for significance ≤ 0.05.

Other pre-specified: 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 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	Other pre-specified

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	4.4 (± 1.2)	-56.8 (± 0.8)		

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). mITT population.

End point type	Other pre-specified

End point timeframe:

From Baseline to Week 52

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percent change				
least squares mean (standard error)	4.6 (± 1.1)	-59.9 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 78 - ITT Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 78 - ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 78 from MMRM model including all available post-baseline data from Week 4 to Week 78 regardless of status on- or off-treatment. ITT population.

End point type	Other pre-specified

End point timeframe:

From Baseline to Week 78

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	780	1530		
Units: percent change				
least squares mean (standard error)	3.6 (± 1.3)	-52.4 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 78 - On-Treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 78 - On-Treatment Analysis

End point description:

Adjusted LS means and standard errors at Week 78 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 78 (i.e. up to 21 days after last injection). mITT population.

End point type	Other pre-specified

End point timeframe:

From Baseline to Week 78

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	1523		
Units: percent change				
least squares mean (standard error)	3.9 (± 1.2)	-58 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Who Experienced Cardiovascular (CV) Events

End point title	Percentage of Subjects Who Experienced Cardiovascular (CV) Events

End point description:

CV events included coronary heart disease (CHD) death; non-fatal myocardial infarction (MI); fatal and non-fatal ischemic stroke; unstable angina requiring hospitalization; congestive heart failure (CHF) requiring hospitalization; ischemia-driven coronary revascularization procedure. Reported events are CV events as confirmed by an independent Clinical Events Committee (CEC) that occurred during the treatment emergent period (i.e. from first dose up to the last dose of study drug + 70 days). Safety population.

End point type	Other pre-specified

End point timeframe:

Up to 10 weeks after last study drug administration (maximum of 86 weeks)

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	788	1550		
Units: percentage of subjects				
number (not applicable)	5.1	4.6		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Subjects Who Experienced Major Adverse CV Events

End point title	Percentage of Subjects Who Experienced Major Adverse CV Events

End point description:

Major adverse CV events were defined as all adverse CV events except Congestive heart failure (CHF) requiring hospitalization; and ischemia-driven coronary revascularization procedure. Safety population.

End point type	Post-hoc

End point timeframe:

Up to 10 weeks after last study drug administration (maximum of 86 weeks)

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	788	1550		
Units: percentage of subjects				
number (not applicable)	3.3	1.7		

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 the final visit (Week 86 post-treatment follow-up visit) regardless of seriousness or relationship to investigational product.

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 study drug up to the last dose of study drug + 70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo Q2W

Reporting group description:

Placebo (for alirocumab) SC injection Q2W added to stable LMT for 78 weeks.

Reporting group title	Alirocumab 150 Q2W

Reporting group description:

Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.

Serious adverse events	Placebo Q2W	Alirocumab 150 Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	154 / 788 (19.54%)	290 / 1550 (18.71%)	
number of deaths (all causes)	8	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Myeloid Leukaemia			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-Cell Lymphoma			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
subjects affected / exposed	2 / 788 (0.25%)	8 / 1550 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Ovarian Tumour			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroid Melanoma			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon Cancer			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ductal Adenocarcinoma Of Pancreas			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endometrial Cancer			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Cancer Stage I			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Squamous Cell Carcinoma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo Maligna			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip Squamous Cell Carcinoma			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine Carcinoma Metastatic			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's Lymphoma Metastatic			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
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 / 788 (0.13%)	0 / 1550 (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	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleomorphic Liposarcoma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	3 / 788 (0.38%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer Metastatic			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer Recurrent			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Adenocarcinoma			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cancer			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Cancer			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Lung			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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 Skin			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of The Oral Cavity			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue Cancer Metastatic			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Aneurysm			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Aneurysm Rupture			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic Dissection			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep Vein Thrombosis			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity Necrosis			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Artery Aneurysm			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic Shock			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac Artery Occlusion			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 788 (0.13%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Stenosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			
subjects affected / exposed	2 / 788 (0.25%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Vascular Disorder			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian Artery Stenosis			

subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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			
Chest Pain			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Restenosis			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device Failure			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Malfunction			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multi-Organ Failure			
subjects affected / exposed	4 / 788 (0.51%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 788 (0.25%)	13 / 1550 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Restenosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine Release Syndrome			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Hypersensitivity			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Galactorrhoea			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metrorrhagia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Haemorrhage			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 788 (0.13%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Chronic			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	6 / 788 (0.76%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	2 / 788 (0.25%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Oedema			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 788 (0.13%)	6 / 1550 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
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	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol Abuse			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar Disorder			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional State			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 788 (0.25%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression Suicidal			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Disorder Due To A General Medical Condition			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			

subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Attack			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram Qt Prolonged			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram St Segment Depression			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin Increased			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Abdominal Injury			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental Overdose			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial Injury			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle Fracture			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional Overdose			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Injury			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Rupture			
subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Rupture			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Strain			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haematoma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haematuria			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Respiratory Failure			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Injury			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Haematoma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Intracranial Haemorrhage			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic Cardiomyopathy			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroglossal Cyst			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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	6 / 788 (0.76%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute Myocardial Infarction			
subjects affected / exposed	11 / 788 (1.40%)	9 / 1550 (0.58%)	
occurrences causally related to treatment / all	0 / 13	1 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina Pectoris			
subjects affected / exposed	6 / 788 (0.76%)	9 / 1550 (0.58%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	9 / 788 (1.14%)	29 / 1550 (1.87%)	
occurrences causally related to treatment / all	0 / 9	0 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Stenosis			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis Coronary Artery			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	7 / 788 (0.89%)	9 / 1550 (0.58%)	
occurrences causally related to treatment / all	0 / 8	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Second Degree			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	3 / 788 (0.38%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Failure Chronic			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	3 / 788 (0.38%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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	3 / 788 (0.38%)	10 / 1550 (0.65%)	
occurrences causally related to treatment / all	0 / 3	2 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coronary Artery Occlusion			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	2 / 788 (0.25%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dressler's Syndrome			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Heart Disease			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	4 / 788 (0.51%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	2 / 788 (0.25%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleuropericarditis			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick Sinus Syndrome			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
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	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Bradycardia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			
subjects affected / exposed	2 / 788 (0.25%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered State Of Consciousness			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Stem Infarction			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid Arteriosclerosis			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid Artery Stenosis			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar Infarction			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			

subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelination			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frontotemporal Dementia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Stroke			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			

subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 788 (0.13%)	5 / 1550 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar Infarction			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miller Fisher Syndrome			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonic Epilepsy			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve Root Compression			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic Neuritis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's Disease			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	6 / 788 (0.76%)	11 / 1550 (0.71%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 788 (0.00%)	7 / 1550 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron Deficiency Anaemia			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous Haematoma			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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			
Vertigo			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo Positional			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Age-Related Macular Degeneration			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blepharochalasis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Retinopathy			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine Ophthalmopathy			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular Hole			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open Angle Glaucoma			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Artery Occlusion			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Haemorrhage			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Vein Occlusion			
subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Vein Thrombosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Impairment			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous Detachment			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Adhesions			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Hernia			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Hernia Obstructive			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	1 / 788 (0.13%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic Pancreatitis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barrett's Oesophagus			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 788 (0.38%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diverticulum Intestinal				
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Duodenal Ulcer Haemorrhage				
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dyspepsia				
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastritis				
subjects affected / exposed	2 / 788 (0.25%)	1 / 1550 (0.06%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastroduodenal Haemorrhage				
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Haemorrhoids				
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hiatus Hernia				
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal Obstruction				

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Polyp			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Chronic			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Relapsing			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic Ulcer Haemorrhage			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			

subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Steatosis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular Injury			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis Allergic			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity Vasculitis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder Spasm			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Ureteric			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Interstitial			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Nephropathy			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertonic Bladder			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	1 / 788 (0.13%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Artery Stenosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	3 / 788 (0.38%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Chronic			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Pain			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric Stenosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Stenosis			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			

subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyrotoxic Crisis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankylosing Spondylitis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Degeneration			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 788 (0.00%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar Spinal Stenosis			
subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	3 / 788 (0.38%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	3 / 788 (0.38%)	8 / 1550 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia Rheumatica			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator Cuff Syndrome			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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	0 / 788 (0.00%)	1 / 1550 (0.06%)	
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	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral Foraminal Stenosis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 788 (0.13%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis Viral			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot Infection			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (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	0 / 788 (0.00%)	4 / 1550 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 788 (0.25%)	5 / 1550 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 788 (0.00%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Viral Infection			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin Abscess			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter Gastritis			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision Site Infection			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 788 (0.25%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme Disease			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			

subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 788 (0.13%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 788 (0.89%)	6 / 1550 (0.39%)	
occurrences causally related to treatment / all	0 / 7	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Staphylococcal			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Sepsis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative Wound Infection			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 788 (0.13%)	5 / 1550 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 788 (0.00%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Pseudomonal			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Abscess			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	2 / 788 (0.25%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 788 (0.13%)	2 / 1550 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 788 (0.13%)	3 / 1550 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic Acidosis			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipomatosis			

subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 788 (0.13%)	0 / 1550 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 788 (0.00%)	1 / 1550 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo Q2W	Alirocumab 150 Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	366 / 788 (46.45%)	707 / 1550 (45.61%)	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 788 (5.58%)	76 / 1550 (4.90%)	
occurrences (all)	47	103	
General disorders and administration site conditions			
Injection Site Reaction			
subjects affected / exposed	33 / 788 (4.19%)	91 / 1550 (5.87%)	
occurrences (all)	42	184	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	45 / 788 (5.71%)	89 / 1550 (5.74%)	
occurrences (all)	49	112	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	52 / 788 (6.60%)	80 / 1550 (5.16%)	
occurrences (all)	60	87	
Back Pain			

subjects affected / exposed	52 / 788 (6.60%)	84 / 1550 (5.42%)	
occurrences (all)	57	90	
Myalgia			
subjects affected / exposed	23 / 788 (2.92%)	84 / 1550 (5.42%)	
occurrences (all)	31	94	
Infections and infestations			
Bronchitis			
subjects affected / exposed	40 / 788 (5.08%)	83 / 1550 (5.35%)	
occurrences (all)	45	102	
Influenza			
subjects affected / exposed	43 / 788 (5.46%)	88 / 1550 (5.68%)	
occurrences (all)	53	103	
Nasopharyngitis			
subjects affected / exposed	103 / 788 (13.07%)	209 / 1550 (13.48%)	
occurrences (all)	143	267	
Upper Respiratory Tract Infection			
subjects affected / exposed	68 / 788 (8.63%)	114 / 1550 (7.35%)	
occurrences (all)	79	136	
Urinary Tract Infection			
subjects affected / exposed	54 / 788 (6.85%)	87 / 1550 (5.61%)	
occurrences (all)	84	121	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2011	Additional assessments were added for a possible significant lowering of LDL-C by alirocumab, including adrenal function monitoring and neurological examinations. The monitoring plan for LDL-C <25 mg/dL (0.65 mmol/L) was revised accordingly; Hepatitis C testing was added to the end of the treatment visit because some data suggested that proprotein convertase subtilisin kexin type 9 (PCSK9) negatively regulates CD81 levels ; An ophthalmologic sub-study in a sub-set of subjects and color vision testing in all subjects was added due to the observation of optic nerve degeneration and chorioretinal lesions in 26-week toxicology studies in rats and monkeys, respectively; Measured LDL-C via beta quantification method was added at key efficacy time points due to potential inaccuracies of calculated LDL-C, when the LDL-C level reaches <50 mg/dL (1.30 mmol/L); The exclusion criteria related to LDL-C was changed to <100 mg/dL (2.59 mmol/L), since this exclusion criterion was used in the phase 2 studies, it was viewed as more appropriate to keep the same inclusion criterion in LTS11717, when using the dose of 150 mg every 2 weeks.
11 May 2012	The exclusion criteria of LDL-C >160 mg/dL (4.14 mmol/L) at screening and subject only on statin monotherapy without additional LMT were deleted. Such subjects could be included, but an explanation for no second LMT was to be provided; A guideline was added for medical work up for cases of low hemoglobin (post-baseline decrease of ≥15 g/dL), and an algorithm was added for the identification of cases of hemolytic anemia; Clearer guidance was provided on follow-up of anti-alirocumab antibodies to maintain the integrity of the double-blind in the study; Criterion to meet an LDL-C rescue alert was modified; Clinical criteria for diagnosis of heFH for study eligibility was clarified; A CHD risk equivalent was added to include moderate chronic kidney disease as defined by estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73 m2 for 3 months or more consistently with the 2011 Guidelines for the Management of Dyslipidaemias by The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society; Recent information on rare cases of hypersensitivity was added as well as details on monitoring, reporting, and collecting information to better document potential allergy events.
12 November 2012	Exclusion criterion related to LDL-C was changed from <100 mg/dL (2.59 mmol/L) to <70 mg/dL (1.81 mmol/L), thereby including a subject population that more completely represents the expected future clinical use of the compound; Assessments regarding vitamins A, D, and K as other fat soluble vitamins and gonadal hormones assessments were clarified to ensure the integrity of the blood sample and information collected; The description of adrenal function monitoring was updated to recommend early morning sampling to best evaluate this parameter.
26 February 2014	The primary efficacy analysis population was changed to the ITT population and the statistical analysis methodology for the primary and secondary efficacy analysis endpoints was changed to ITT analysis performed on the ITT population and including all lipid values (on-treatment and off-treatment); The language regarding the recording of injection site reactions not related to IMP was updated to clarify the reporting of local injection site reactions.

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 (eCRF) form.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25773378