



## Clinical trial results:

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

#### Summary

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

#### Results information

Result version number	v1
This version publication date	08 March 2016
First version publication date	06 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	EFC11569
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	26 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2014
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates

Background therapy:

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

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Korea, Republic of: 42
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Hungary: 65
Country: Number of subjects enrolled	Denmark: 100
Country: Number of subjects enrolled	Russian Federation: 149
Country: Number of subjects enrolled	South Africa: 92
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 217
Worldwide total number of subjects	720
EEA total number of subjects	174

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	434
From 65 to 84 years	282
85 years and over	4

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

Alirocumab and placebo for alirocumab were provided in identically matched auto-injectors and packaged identically.

Ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe, had the same appearance and feel and were labeled with a double-blind label.

### Arms

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

Arm description:

Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks.

Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level  $\geq 70$  mg/dL (1.81 mmol/L) at Week 8.

Arm type	Experimental
Investigational medicinal product name	Placebo (for ezetimibe)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

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

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

Dosage and administration details:

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

<b>Arm title</b>	Ezetimibe 10 mg
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Arm description:

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

weeks.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

<b>Number of subjects in period 1</b>	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg
Started	479	241
Completed first 52-week treatment period	408	208
Treated	479	241
Completed	0	0
Not completed	479	241
Physician decision	1	2
Other than specified here	15	8
Consent withdrawn by subject	-	1
Adverse event	36	13
Treatment ongoing	406	206
Subject moved	6	2
Poor compliance to protocol	13	7
Related to Autoinjector Administration	2	2

## Baseline characteristics

### Reporting groups

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

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

Reporting group title	Ezetimibe 10 mg
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Reporting group description:

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

Reporting group values	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg	Total
Number of subjects	479	241	720
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.7	61.3	-
standard deviation	$\pm 9.4$	$\pm 9.2$	-
Gender categorical Units: Subjects			
Female	119	71	190
Male	360	170	530
Calculated LDL-C in mmol/L			
Calculated LDL-C from Friedewald formula.			
Units: mmol/L			
arithmetic mean	2.81	2.71	-
standard deviation	$\pm 0.945$	$\pm 0.884$	-
Calculated LDL-C in mg/dL Units: mg/dL			
arithmetic mean	108.6	104.6	-
standard deviation	$\pm 36.5$	$\pm 34.1$	-

## End points

### End points reporting groups

Reporting group title	Alirocumab 75/up to 150 mg Q2W
Reporting group description: Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level $\geq 70$ mg/dL (1.81 mmol/L) at Week 8.	
Reporting group title	Ezetimibe 10 mg
Reporting group description: Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104 weeks.	
Subject analysis set title	Ezetimibe 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects exposed to Ezetimibe 10 mg added to stable LMT (mean exposure of 58 weeks).	
Subject analysis set title	Alirocumab 75 /up to 150 mg Q2W
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects exposed to Alirocumab 75 /up to 150 mg Q2W added to stable LMT (mean exposure of 58 weeks).	

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

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

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

### Statistical analyses

<b>Statistical analysis title</b>	Alirocumab vs. Ezetimibe
Statistical analysis description: Alirocumab group was compared to ezetimibe group using an appropriate contrast statement.	
Comparison groups	Ezetimibe 10 mg v Alirocumab 75/up to 150 mg Q2W
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[1]</sup>
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.4
upper limit	-25.3

Notes:

[1] - Threshold for significance  $\leq 0.05$

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

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 - On-treatment Analysis
End point description: Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis). Modified ITT population (mITT): all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment.	
End point type	Secondary
End point timeframe: From Baseline to Week 52	

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

### Statistical analyses

<b>Statistical analysis title</b>	Alirocumab vs. ezetimibe
Statistical analysis description: A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.	

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	699
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.9
upper limit	-26.2

Notes:

[2] - Threshold for significance  $\leq 0.05$

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

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

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

### Statistical analyses

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

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.7
upper limit	-25.1

Notes:

[3] - Threshold for significance  $\leq 0.05$

### 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
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End point description:

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

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe
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Statistical analysis description:

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

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	699
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	-25.6

Notes:

[4] - Threshold for significance <0.05

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

End point title	Percent Change From Baseline in Apolipoprotein B (Apo-B) at Week 24 - ITT analysis
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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 analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
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Statistical analysis description:

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

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

Notes:

[5] - Threshold for significance  $\leq 0.05$

### 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
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End point description:

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

Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline Apo B value on-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
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Statistical analysis description:

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

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
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Number of subjects included in analysis	663
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	$< 0.0001$ [6]
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Method	Mixed models analysis
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Parameter estimate	LS Mean Difference
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Point estimate	-23
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-26.5
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upper limit	-19.6
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Notes:

[6] - Threshold for significance  $\leq 0.05$

### 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 analyzed: subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment.
End point type	Secondary
End point timeframe:	From Baseline to Week 52

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

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab vs. ezetimibe
Statistical analysis description:	Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.9
upper limit	-18.9

Notes:

[7] - Threshold for significance ≤0.05.

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

End point title	Percent Change From Baseline in Non-HDL-C at Week 24 - On-treatment Analysis
End point description:	Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline

Non-HDL-C value on-treatment.

End point type	Secondary
End point timeframe:	
From Baseline up to Week 52	

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

### Statistical analyses

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

Notes:

[8] - Threshold for significance  $\leq 0.05$

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

End point title	Percent Change From Baseline in Total Cholesterol (TC) at Week 24 - ITT Analysis
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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 analyzed: subjects of the ITT population with one baseline and at least one post-baseline TC value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

## Statistical analyses

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

Notes:

[9] - Threshold for significance  $\leq$ 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	

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

## Statistical analyses

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

Notes:

[10] - Threshold for significance  $\leq 0.05$ .

## 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	

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

## Statistical analyses

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

Notes:

[11] - Threshold for significance  $\leq 0.05$

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

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

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

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab vs. ezetimibe
Statistical analysis description: Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	-11.6

Notes:

[12] - Threshold for significance  $\leq 0.05$

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

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

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

## Statistical analyses

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

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[13]</sup>
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.3
upper limit	-26.1

Notes:

[13] - Threshold for significance  $\leq 0.05$

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

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

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

End point type	Secondary
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End point timeframe:

Up to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
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Statistical analysis description:

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

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
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Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	7.9

Notes:

[14] - Threshold for significance  $\leq 0.05$

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

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

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

End point type	Secondary
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End point timeframe:

Up to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
----------------------------	--------------------------

Statistical analysis description:

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

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

Notes:

[15] - Threshold for significance  $\leq 0.05$

### 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
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End point description:

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

End point type	Secondary
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End point timeframe:

From baseline to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
----------------------------	--------------------------

Statistical analysis description:

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

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

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[16]</sup>
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-21.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.4
upper limit	-17

Notes:

[16] - Threshold for significance  $\leq 0.05$

### 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
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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 analyzed: subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
----------------------------	--------------------------

Statistical analysis description:

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

Comparison groups	Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[17]</sup>
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	8.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	10.7

Notes:

[17] - Threshold for significance  $\leq 0.05$

### 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
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End point description:

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

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

### Statistical analyses

Statistical analysis title	Alirocumab vs. ezetimibe
----------------------------	--------------------------

Statistical analysis description:

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

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

Notes:

[18] - Threshold for significance  $\leq 0.05$

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

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End point title	Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1) at Week 24 - ITT Analysis
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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 analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo A-1 value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 52

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

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**Statistical analyses**

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No statistical analyses for this end point

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

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

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

Lipoprotein(a) ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 12

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

### Statistical analyses

No statistical analyses for this end point

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

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

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

### Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis			
End point description:	Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Apo A-1 ITT population.			
End point type	Secondary			
End point timeframe:	From Baseline to Week 52			

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

### 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 primary completion date regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

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

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

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

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

Reporting group title	Ezetimibe 10 mg
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Reporting group description:

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

<b>Serious adverse events</b>	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 479 (18.79%)	43 / 241 (17.84%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Carcinoma			

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small Cell Lung Cancer Stage Iiia			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Stromal Tumour			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Adenocarcinoma			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small Cell Lung Cancer			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Lung			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral Artery Occlusion			

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hypertension</b>			
subjects affected / exposed	2 / 479 (0.42%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Peripheral Arterial Occlusive Disease</b>			
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Peripheral Artery Aneurysm</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>General disorders and administration site conditions</b>			
<b>Sudden Cardiac Death</b>			
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
<b>Non-Cardiac Chest Pain</b>			
subjects affected / exposed	2 / 479 (0.42%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Chest Pain</b>			
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Sudden Death</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Immune system disorders</b>			

Hypersensitivity			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional State			

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

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

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Wound</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Spinal Compression Fracture</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
<b>Acute Myocardial Infarction</b>			
subjects affected / exposed	10 / 479 (2.09%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 11	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Angina Unstable</b>			
subjects affected / exposed	8 / 479 (1.67%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Angina Pectoris</b>			
subjects affected / exposed	8 / 479 (1.67%)	6 / 241 (2.49%)	
occurrences causally related to treatment / all	1 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Atrioventricular Block</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Atrial Fibrillation</b>			
subjects affected / exposed	4 / 479 (0.84%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Arteriosclerosis Coronary Artery</b>			

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac Failure		
subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac Arrest		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Atrioventricular Block Second Degree		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular Block Complete		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial Flutter		
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac Failure Congestive		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Congestive Cardiomyopathy		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Defect Conduction Intraventricular		

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Myocardial Infarction</b>			
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Myocardial Ischaemia</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Silent Myocardial Infarction</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Supraventricular Tachycardia</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ventricular Extrasystoles</b>			
subjects affected / exposed	0 / 479 (0.00%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Coronary Artery Disease</b>			
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ventricular Fibrillation</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ventricular Tachycardia</b>			

subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
<b>Headache</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dizziness</b>			
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dementia Alzheimer's Type</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cerebrovascular Accident</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Carotid Artery Stenosis</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Carotid Artery Disease</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Brain Injury</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cerebroscclerosis</b>			

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Transient Global Amnesia		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Syncope		
subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Sensory Disturbance		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intracranial Aneurysm		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Loss Of Consciousness		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic Stroke		
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myelitis Transverse		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Transient Ischaemic Attack		

subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
<b>Anaemia</b>			
subjects affected / exposed	1 / 479 (0.21%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ear and labyrinth disorders</b>			
<b>Cupulolithiasis</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			
<b>Cataract</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cataract Nuclear</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Retinal Detachment</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
<b>Abdominal Distension</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrooesophageal Reflux Disease</b>			

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal Mucocoele		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal Haemorrhage		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric Ulcer Haemorrhage		
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric Haemorrhage		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal Pain		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal Hernia		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoids		
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis		

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Large Intestine Polyp</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Inguinal Hernia</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vomiting</b>			
subjects affected / exposed	2 / 479 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
<b>Cholelithiasis</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cholecystitis Acute</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Urticaria</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
<b>Renal Tubular Necrosis</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal Failure Acute			
subjects affected / exposed	2 / 479 (0.42%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 479 (0.21%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Osteoarthritis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Column Stenosis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment Syndrome			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis Infective			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulitis		
subjects affected / exposed	3 / 479 (0.63%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchopneumonia		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis Viral		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary Tuberculosis		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative Wound Infection		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia Staphylococcal		
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis E		
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonitis		

subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Osteomyelitis Chronic</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Myringitis Bullous</b>			
subjects affected / exposed	0 / 479 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumonia</b>			
subjects affected / exposed	7 / 479 (1.46%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pyelonephritis Acute</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Scrotal Abscess</b>			
subjects affected / exposed	1 / 479 (0.21%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Alirocumab 75/up to 150 mg Q2W	Ezetimibe 10 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 479 (16.08%)	38 / 241 (15.77%)	
<b>Injury, poisoning and procedural complications</b>			
Accidental Overdose			
subjects affected / exposed	30 / 479 (6.26%)	16 / 241 (6.64%)	
occurrences (all)	44	22	
<b>Nervous system disorders</b>			

Dizziness subjects affected / exposed occurrences (all)	21 / 479 (4.38%) 22	13 / 241 (5.39%) 15	
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	31 / 479 (6.47%) 35	14 / 241 (5.81%) 15	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2013	<ul style="list-style-type: none"><li>- Changes in the exclusion criteria related to diabetic control status, history of human immunodeficiency virus, previous participation in any clinical trial of alirocumab or any other anti-PCSK9 monoclonal antibody, laboratory findings during the screening period, and known hypersensitivity to monoclonal antibody.</li><li>- Change in the reporting of AEs.</li><li>- Change in the screening period duration and the window for the training visit.</li><li>- Added the information on a possible contingency strategy in the event the manufacturer faces any performance or supply issues of the auto-injector in order to ensure the continuity of the study treatment without interruption.</li><li>- Clarification for some safety laboratory parameters.</li><li>- Clarification was provided regarding the type of cardiovascular (CV) events to be submitted to the Clinical Events Committee (CEC) for adjudication</li><li>- Added a new section of contraception in the Concomitant medication section.</li><li>- Precision in the definition of IMP and the way of handling treatment interruption.</li><li>- Added information on the collection of family medical history to be consistent with what was collected in the e-CRF and with regard to the population enrolled in the study.</li></ul>
26 February 2014	<ul style="list-style-type: none"><li>- Statistical section was changed.</li><li>- Addition of the blinding procedures related to pharmacokinetic analysis.</li><li>- Updated language on cardiovascular events to be reported to the CEC for adjudication and including a clarification on cerebrovascular events.</li><li>- Added the following sentence "LDL-C was also be measured (via the beta-quantification method) at Week 0 and Week 24".</li><li>- Updated language on collection of information on partner pregnancy as per other protocol in the ODYSSEY phase 3 program.</li><li>- Updated language on how to record injection site reactions that were not related to study drug.</li><li>- Categorization of AEs: updated language on how to record injection site reactions that were not related to study drug.</li></ul>

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.

Reported results are from first step analysis conducted after all subjects completed 52 Weeks visit.

Notes:

### Online references

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