



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Alirocumab in Patients with Primary Hypercholesterolemia Not Treated With a Statin

#### Summary

EudraCT number	2013-002659-14
Trial protocol	BE NL ES DK
Global end of trial date	30 June 2017

#### Results information

Result version number	v2 (current)
This version publication date	15 July 2018
First version publication date	09 February 2017
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li></ul> Addition of results covering the 2nd period of the study.

#### Trial information

##### Trial identification

Sponsor protocol code	EFC13786
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02023879
WHO universal trial number (UTN)	U1111-1146-3517
Other trial identifiers	Study Name: ODYSSEY CHOICE II

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by a regimen including an Alirocumab starting dose of 150 mg every 4 weeks (Q4W) as add-on to non-statin lipid modifying background therapy or as monotherapy in comparison with placebo in subjects with primary hypercholesterolemia not treated with a statin.

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 were to maintain a stable diet throughout the entire study duration, including the screening period. Subjects receiving background non-statin lipid modifying therapy (LMT) (ezetimibe or fenofibrate) had to continue their treatment without change (including dose) from screening through the end of 24-week double-blind (DB) treatment period barring exceptional circumstances.

Evidence for comparator: -

Actual start date of recruitment	16 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Denmark: 21
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	233
EEA total number of subjects	117

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)	125
From 65 to 84 years	104
85 years and over	4

## Subject disposition

### Recruitment

#### Recruitment details:

The study was conducted at 43 centers in 8 countries. A total of 402 subjects were screened between December-2013 and May-2014, of whom 233 were randomized for double-blind (DB) treatment period and 169 were screen failures. Out of 233 randomized for DB period, 205 subjects entered the optional open-label (OL) extension period.

### Pre-assignment

#### Screening details:

Randomization was stratified by statin intolerant status and background therapy (non-statin lipid therapy vs diet). Randomization followed a 1:2:1 ratio for placebo, Alirocumab 75 mg and Alirocumab 150 mg instead of 1:1:2 as initially planned due to systematic error in treatment allocation algorithm discovered after all subjects were randomized.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo Q2W

#### Arm description:

Placebo (for Alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable non-statin lipid modifying therapy (LMT) or diet alone for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
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>Arm title</b>	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)
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#### Arm description:

Alirocumab 75 mg SC injection Q2W added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C  $\geq 70$  mg/dL (1.81 mmol/L) or  $\geq 100$  mg/dL (2.59 mmol/L) depending on cardiovascular risk or  $< 30\%$  LDL-C reduction from baseline.

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

#### Dosage and administration details:

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

<b>Arm title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W
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**Arm description:**

Alirocumab 150 mg SC injection Q4W alternating with placebo (for alirocumab) QW4 added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C  $\geq 70$  mg/dL (1.81 mmol/L) or  $\geq 100$  mg/dL (2.59 mmol/L) depending on cardiovascular risk or  $<30\%$  LDL-C reduction from baseline.

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

**Dosage and administration details:**

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

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

**Dosage and administration details:**

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

Number of subjects in period 1	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W
Started	58	116	59
Treated	58	115	58
Completed	54	107	50
Not completed	4	9	9
Consent withdrawn by subject	1	-	1
Physician decision	-	1	-
Adverse events	2	2	5
Randomized but not treated	-	1	1
Other	1	3	1
Protocol deviation	-	2	1

**Period 2**

Period 2 title	Period 2: Open Label Extension Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Alirocumab 150 mg Q4W (after Placebo Q2W)
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### Arm description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Placebo (for Alirocumab) Q2W for 24 weeks. The alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

### Dosage and administration details:

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

<b>Arm title</b>	Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W)
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### Arm description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 75 mg Q2W/150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

### Dosage and administration details:

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

<b>Arm title</b>	Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W)
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### Arm description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 150 mg Q4W/ 150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

### Dosage and administration details:

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

Number of subjects in period 2 <sup>[1]</sup>	Alirocumab 150 mg Q4W (after Placebo Q2W)	Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W)	Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W)
Started	51	106	48
Completed	46	89	43
Not completed	5	17	5
Other than specified above	2	7	2
Adverse event	1	7	3
Poor compliance to protocol	1	1	-
Subject Moved	1	2	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The open-label extension period was optional for subjects who completed the double-blind treatment period.

## 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 non-statin lipid modifying therapy (LMT) or diet alone for 24 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)
Reporting group description: Alirocumab 75 mg SC injection Q2W added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C $\geq 70$ mg/dL (1.81 mmol/L) or $\geq 100$ mg/dL (2.59 mmol/L) depending on cardiovascular risk or $< 30\%$ LDL-C reduction from baseline.	
Reporting group title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W
Reporting group description: Alirocumab 150 mg SC injection Q4W alternating with placebo (for alirocumab) QW4 added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C $\geq 70$ mg/dL (1.81 mmol/L) or $\geq 100$ mg/dL (2.59 mmol/L) depending on cardiovascular risk or $< 30\%$ LDL-C reduction from baseline.	

Reporting group values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W
Number of subjects	58	116	59
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	63.1 $\pm 10.7$	62.5 $\pm 9.9$	64.2 $\pm 10$
Gender categorical Units: Subjects			
Female	27	47	29
Male	31	69	30
Race Units: Subjects			
Asian	1	4	3
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	1	3	1
White	56	108	55
Ethnicity Units: Subjects			
Hispanic or Latino	1	7	4
Not Hispanic or Latino	57	109	54
Unknown or Not Reported	0	0	1
Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol [Total-C] - High-Density Lipoprotein Cholesterol [HDL-C] - [Triglyceride/5]).			
Units: mg/dL			



arithmetic mean	158.5	154.5	163.9
standard deviation	± 47.3	± 44.6	± 69.1
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	4.106	4.002	4.245
standard deviation	± 1.226	± 1.154	± 1.789

<b>Reporting group values</b>	Total		
Number of subjects	233		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	103		
Male	130		
Race			
Units: Subjects			
Asian	8		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	5		
White	219		
Ethnicity			
Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	220		
Unknown or Not Reported	1		
Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol [Total-C] - High-Density Lipoprotein Cholesterol [HDL-C] - [Triglyceride/5]).			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean			
standard deviation	-		

## 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 non-statin lipid modifying therapy (LMT) or diet alone for 24 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)
Reporting group description: Alirocumab 75 mg SC injection Q2W added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C $\geq 70$ mg/dL (1.81 mmol/L) or $\geq 100$ mg/dL (2.59 mmol/L) depending on cardiovascular risk or $< 30\%$ LDL-C reduction from baseline.	
Reporting group title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W
Reporting group description: Alirocumab 150 mg SC injection Q4W alternating with placebo (for alicrocumab) QW4 added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C $\geq 70$ mg/dL (1.81 mmol/L) or $\geq 100$ mg/dL (2.59 mmol/L) depending on cardiovascular risk or $< 30\%$ LDL-C reduction from baseline.	
Reporting group title	Alirocumab 150 mg Q4W (after Placebo Q2W)
Reporting group description: Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Placebo (for Alirocumab) Q2W for 24 weeks. The alicrocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.	
Reporting group title	Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W)
Reporting group description: Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 75 mg Q2W/150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.	
Reporting group title	Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W)
Reporting group description: Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 150 mg Q4W/ 150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.	

### 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 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population that included 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 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	4.7 (± 2.3)	-53.5 (± 1.6)	-51.7 (± 2.3)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description: Alirocumab 150 mg Q4W/up to 150 mg Q2W was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[1]</sup>
Method	Mixed models analysis
Parameter estimate	Least square (LS) mean difference
Point estimate	-56.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.9
upper limit	-49.9

Notes:

[1] - Threshold for significance at 0.05 level.

## 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 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection) (on-treatment analysis). Modified ITT (mITT) population that included 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 24	

<b>End point values</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	115	57	
Units: percent change				
least squares mean (standard error)	5.1 (± 2.1)	-55.3 (± 1.5)	-54.6 (± 2.1)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
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 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[2]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-59.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.6
upper limit	-53.8

Notes:

[2] - Threshold for significance at 0.05 level.

## 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

<b>End point values</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	3.2 (± 2.5)	-50.8 (± 1.7)	-41.7 (± 2.4)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[3]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-44.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.8
upper limit	-38.1

Notes:

[3] - Threshold for significance at 0.05 level.

## 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 24 (i.e. up to 21 days after last injection). mITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

<b>End point values</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	115	57	
Units: percent change				
least squares mean (standard error)	3.6 (± 2.3)	-51.5 (± 1.6)	-44.8 (± 2.3)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[4]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-48.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.8
upper limit	-41.9

Notes:

[4] - Threshold for significance at 0.05 level.

## Secondary: Percent Change From Baseline in Calculated LDL-C to Averaged Weeks 9 to 12 - ITT- Analysis

End point title	Percent Change From Baseline in Calculated LDL-C to Averaged Weeks 9 to 12 - ITT- Analysis
End point description:	
Adjusted LS means and standard errors at Week 12 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment and assigning a weight of 0.25 for Week 9, 10, 11 and 12 time points. ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

<b>End point values</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	3.2 (± 2)	-53.6 (± 1.4)	-52.3 (± 2)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
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	-55.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.1
upper limit	-49.8

Notes:

[5] - Threshold for significance at 0.05 level.

## Secondary: Percent Change From Baseline in Calculated LDL-C at Averaged Week 9 to 12 - On-Treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Averaged Week 9 to 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 24 (i.e. up to 21 days after last injection) and assigning a weight of 0.25 for Week 9, 10, 11 and 12 time points. mITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

<b>End point values</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	115	57	
Units: percent change				
least squares mean (standard error)	3.6 (± 1.9)	-54.1 (± 1.3)	-55 (± 1.9)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[6]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-58.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.8
upper limit	-53.4

Notes:

[6] - Threshold for significance at 0.05 level.

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

<b>End point title</b>	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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	



<b>End point values</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	112	58	
Units: percent change				
least squares mean (standard error)	7.5 (± 2.1)	-39.7 (± 1.5)	-38.9 (± 2.2)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[7]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-46.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.4
upper limit	-40.4

Notes:

[7] - Threshold for significance at 0.05 level.

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

<b>End point title</b>	Percent Change From Baseline in Apo B at Week 24 - On-treatment Analysis
End point description:	
Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). mITT population. Number of subjects analyzed = subjects of the mITT population with available data at specified time-points.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	112	54	
Units: percent change				
least squares mean (standard error)	7.7 (± 2)	-41.2 (± 1.4)	-40.9 (± 2.1)	

## Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[8]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-48.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.3
upper limit	-42.8

Notes:

[8] - Threshold for significance at 0.05 level.

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

End point title	Percent Change From Baseline in Non-HDL-C at Week 24 - ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 24 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	4.8 (± 2.1)	-45.3 (± 1.5)	-44.2 (± 2.1)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
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	-49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.9
upper limit	-43.2

Notes:

[9] - Threshold for significance at 0.05 level.

## 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 24 (i.e. up to 21 days after last injection). mITT population.	
End point type	Secondary
End point timeframe: From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	115	57	
Units: percent change				
least squares mean (standard error)	5 (± 1.9)	-46.9 (± 1.3)	-46.7 (± 1.9)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	113
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	-51.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.1
upper limit	-46.4

Notes:

[10] - Threshold for significance at 0.05 level.

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

End point title	Percent Change From Baseline in Total-C at Week 24 - ITT Analysis
End point description: Adjusted LS means and standard errors at Week 24 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.	
End point type	Secondary
End point timeframe: From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	3 (± 1.6)	-34 (± 1.1)	-32.3 (± 1.6)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
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	-35.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.8
upper limit	-30.8

Notes:

[11] - Threshold for significance at 0.05 level.

## 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.	
End point type	Secondary
End point timeframe: From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	112	58	
Units: percent change				
least squares mean (standard error)	7 (± 2.2)	-38.4 (± 1.6)	-31.3 (± 2.2)	

## Statistical analyses

<b>Statistical analysis title</b>	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[12]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-38.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.3
upper limit	-32.1

Notes:

[12] - Threshold for significance at 0.05 level.

## 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
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	3 (± 2.2)	-43.4 (± 1.5)	-34.9 (± 2.2)	

## Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
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Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
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	-37.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.9
upper limit	-31.8

Notes:

[13] - Threshold for significance at 0.05 level.

### 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	1.8 (± 1.6)	-32.6 (± 1.2)	-24.5 (± 1.6)	

### Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[14]</sup>
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.9
upper limit	-21.7

Notes:

[14] - Threshold for significance at 0.05 level.

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

Moderate CV risk: 10-year fatal cardiovascular disease (CVD) risk Systemic Coronary Risk Evaluation (SCORE)  $\geq 1$  and <5%.

High CV risk: 10-year fatal CVD risk SCORE  $\geq 5\%$  or moderate chronic kidney disease or type 1 or type 2 diabetes mellitus without target organ damage or familial hypercholesterolemia.

Very high CV risk: history of documented coronary heart disease, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion >50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis, or renal artery stent procedure; or type 1 or type 2 diabetes mellitus with target organ damage.

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 24 regardless of status on- or off-treatment were included. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percentage of subjects				
number (not applicable)	1.8	70.3	63.9	

**Statistical analyses**

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
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Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
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Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[15]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	279.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.1
upper limit	2690.1

Notes:

[15] - Threshold for significance at 0.05 level.

### Secondary: Percentage of Very High CV Risk Subjects Achieving Calculated LDL-C< 70 mg/dL (<1.81 mmol/L) or Moderate or High CV Risk Subjects Achieving 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 Achieving Calculated LDL-C< 70 mg/dL (<1.81 mmol/L) or Moderate or High CV Risk Subjects Achieving Calculated LDL-C< 100 mg/dL (<2.59 mmol/L) at Week 24 - On-treatment Analysis
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End point description:

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

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	115	57	
Units: percentage of subjects				
number (not applicable)	1.8	72.7	67.7	

### Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
----------------------------	--

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
-------------------	--

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[16]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	354.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.2
upper limit	3479.5

Notes:

[16] - Threshold for significance at 0.05 level.

### 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 from last observation carried forward (LOCF) approach including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. ITT population.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percentage of subjects				
number (not applicable)	0	60	50	

### Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a LOCF approach followed by logistic regression model.

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
-------------------	--

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[17]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	126
Confidence interval	
level	95 %
sides	2-sided
lower limit	20
upper limit	9999

Notes:

[17] - Threshold for significance at 0.05 level. Confidence interval should be read as 20.0 to >9999.

### 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 from LOCF approach including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). mITT population.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	115	57	
Units: percentage of subjects				
number (not applicable)	0	61.7	50.9	

### Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a LOCF approach followed by logistic regression model.

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
-------------------	--

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[18]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	141.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.2
upper limit	9999

Notes:

[18] - Threshold for significance at 0.05 level. Confidence interval should be read as 20.0 to >9999.

### 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 followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
arithmetic mean (standard error)	4.1 (± 3.7)	-21.8 (± 2.6)	-15.5 (± 3.7)	

### Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
----------------------------	--

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
-------------------	--

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 <sup>[19]</sup>
Method	Regression, Robust
Parameter estimate	Adjusted mean difference
Point estimate	-19.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.8
upper limit	-9.4

Notes:

[19] - Threshold for significance at 0.05 level.

### 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 a multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
arithmetic mean (standard error)	2.2 (± 3.4)	-16.5 (± 2.4)	-5.7 (± 3.3)	

### Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo
----------------------------	--

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W
-------------------	--

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0892 <sup>[20]</sup>
Method	Regression, Robust
Parameter estimate	Adjusted mean difference
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	1.2

Notes:

[20] - Threshold for significance at 0.05 level.

### 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.
End point type	Secondary
End point timeframe:	From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	-2.4 (± 1.9)	7.4 (± 1.4)	7.7 (± 2)	

### 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.
End point type	Secondary
End point timeframe:	From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
least squares mean (standard error)	-0.8 (± 1.9)	6.8 (± 1.3)	8.6 (± 1.9)	

## Statistical analyses

No statistical analyses for this end point

## 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 followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
arithmetic mean (standard error)	1.1 (± 3.8)	-10.6 (± 2.7)	-9.2 (± 3.9)	

## 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 a multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	115	58	
Units: percent change				
arithmetic mean (standard error)	2.1 (± 3.9)	-11.3 (± 2.7)	-3 (± 3.8)	

### Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.

End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	112	58	
Units: percent change				
least squares mean (standard error)	3.4 (± 1.5)	8.2 (± 1.1)	10 (± 1.5)	

### 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
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	112	58	
Units: percent change				
least squares mean (standard error)	2.6 ( $\pm$ 1.5)	5.9 ( $\pm$ 1.1)	7.6 ( $\pm$ 1.5)	

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 32, 36, 48, 72, 96, 120, 144, 168 On-Treatment Analysis in Open Label Extension Treatment Phase

End point title	Percent Change From Baseline in Calculated LDL-C at Week 32, 36, 48, 72, 96, 120, 144, 168 On-Treatment Analysis in Open Label Extension Treatment Phase
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End point description:

Mean percent changes (and standard deviations) observed during the open-label extension period are provided. Open-label extension population included all randomized subjects who received at least one dose or part of dose of open-label IMP. Here, "n (number analyzed)" signifies the number of subjects evaluable for each specified time-point.

End point type	Other pre-specified
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End point timeframe:

Baseline, Week 32, 36, 48, 72, 96, 120, 144 and Week 168

<b>End point values</b>	Alirocumab 150 mg Q4W (after Placebo Q2W)	Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W)	Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	106	48	
Units: percent change				
arithmetic mean (standard deviation)				
Week 32 (n=48, 98, 45)	-37.3 (± 18.8)	-41.1 (± 21.2)	-46.9 (± 13.3)	
Week 36 (n=48, 96, 46)	-36.1 (± 22.0)	-39.2 (± 21.2)	-43.1 (± 13.7)	
Week 48 (n=47, 91, 44)	-46.5 (± 24.2)	-49.2 (± 18.7)	-48.7 (± 21.7)	
Week 72 (n=50, 94, 47)	-50.8 (± 20.6)	-53.7 (± 19.5)	-52.3 (± 21.3)	
Week 96 (n=48, 90, 44)	-49.8 (± 20.4)	-52.8 (± 19.6)	-46.8 (± 22.0)	
Week 120 (n=46, 81, 37)	-50.6 (± 20.9)	-53.7 (± 18.7)	-51.8 (± 24.1)	
Week 144 (n=38, 72, 29)	-52.7 (± 17.6)	-48.7 (± 23.7)	-49.4 (± 20.9)	
Week 168 (n=4, 13, 4)	-47.8 (± 24.2)	-66.2 (± 17.1)	-60.0 (± 4.6)	

### 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 informed consent form up to study completion (up to 176 weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs/deaths are treatment-emergent ie; AEs that developed/worsened and deaths that occurred 'on treatment'; from 1st dose up to last dose (active/placebo depending on Q2W/Q4W dosing) in DB period+70 days, truncated at the day before 1st dose in OL period for subjects entering in OL period; from 1st dose up to last dose in OL period+70 days.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	Placebo Q2W
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Reporting group description:

Subjects exposed to placebo SC injection Q2W added to stable non-statin LMT or diet alone (mean exposure of 23 weeks).

Reporting group title	Alirocumab 75 mg Q2W/Up150 mg Q2W
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Reporting group description:

Subjects exposed to alirocumab 75 mg Q2W/up to 150 mg Q2W SC injection added to stable non-statin LMT or diet alone (mean exposure of 23 weeks).

Reporting group title	Alirocumab 150 mg Q4W/Up150 mg Q2W
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Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W/up to 150 mg Q2W SC injection added to stable non-statin LMT or diet alone (mean exposure of 22 weeks).

Reporting group title	Alirocumab 150 mg Q4W (After Placebo Q2W)
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Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W SC injection added to stable non-statin LMT or diet alone (mean exposure of 128 weeks) after having received Placebo Q2W for 24 weeks.

Reporting group title	Alirocumab 150 mg Q4W (After Alirocumab 75 Q2W/Up150 Q2W)
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Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W SC injection added to stable non-statin LMT or diet alone (mean exposure of 117 weeks) after having received Alirocumab 75 mg Q2W/Up to 150 mg Q2W for 24 weeks.

Reporting group title	Alirocumab 150 mg Q4W (After Alirocumab 150 Q4W/Up150 Q2W)
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Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W SC injection added to stable non-statin LMT or diet alone (mean exposure of 119 weeks) after having received Alirocumab 150 mg Q4W/Up to 150 mg Q2W for 24 weeks.

Serious adverse events	Placebo Q2W	Alirocumab 75 mg Q2W/Up150 mg Q2W	Alirocumab 150 mg Q4W/Up150 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 58 (6.90%)	7 / 115 (6.09%)	7 / 58 (12.07%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Fallopian Tube Neoplasm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Squamous Cell Carcinoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			

subjects affected / exposed	1 / 58 (1.72%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Cancer			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Crisis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic Shock			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Occlusion			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Stenosis			

subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Ischaemia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Disorder			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral Injury			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw Fracture			

subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Fractures			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haematoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haematoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Haemothorax			



subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Renal Injury			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Valve Stenosis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			

subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Incompetence			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar Infarction			

subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential Tremor			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-Ischaemic Encephalopathy			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal Detachment			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Faecaloma	subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage	subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal Haematoma	subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction	subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus	subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders				
Biliary Colic				
	subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis				
	subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders				
Acute Kidney Injury				
	subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nephrolithiasis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Basedow's Disease			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rheumatoid Arthritis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Osteoarthritis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Bacterial			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Infection			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 115 (0.87%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			

subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Alirocumab 150 mg Q4W (After Placebo Q2W)	Alirocumab 150 mg Q4W (After Alirocumab 75 Q2W/Up150 Q2W)	Alirocumab 150 mg Q4W (After Alirocumab 150 Q4W/Up150 Q2W)
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 51 (29.41%)	28 / 106 (26.42%)	14 / 48 (29.17%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	1 / 51 (1.96%)	2 / 106 (1.89%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Fallopian Tube Neoplasm			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			



subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Squamous Cell Carcinoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	1 / 51 (1.96%)	2 / 106 (1.89%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Cancer			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Crisis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 51 (0.00%)	2 / 106 (1.89%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic Shock			

subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Occlusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Stenosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Ischaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 106 (1.89%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral Injury			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 51 (3.92%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Humerus Fracture			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw Fracture			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Fractures			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haematoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Fracture			

subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haematoma			
subjects affected / exposed	1 / 51 (1.96%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Haemothorax			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Renal Injury			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 51 (0.00%)	3 / 106 (2.83%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Angina Pectoris			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			

subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Aortic Valve Stenosis</b>			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Atrial Fibrillation</b>			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac Failure Congestive</b>			
subjects affected / exposed	1 / 51 (1.96%)	2 / 106 (1.89%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardio-Respiratory Arrest</b>			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiomyopathy</b>			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Coronary Artery Disease</b>			
subjects affected / exposed	0 / 51 (0.00%)	2 / 106 (1.89%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Mitral Valve Incompetence</b>			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Myocardial Infarction</b>			

subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar Infarction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential Tremor			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-Ischaemic Encephalopathy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 51 (0.00%)	2 / 106 (1.89%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 51 (0.00%)	3 / 106 (2.83%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal Detachment			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			



subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal Haematoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary Colic			

subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Basedow's Disease			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myalgia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Osteoarthritis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Bacterial			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 106 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Infection			

subjects affected / exposed	0 / 51 (0.00%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 106 (0.94%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Placebo Q2W	Alirocumab 75 mg Q2W/Up150 mg Q2W	Alirocumab 150 mg Q4W/Up150 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 58 (48.28%)	61 / 115 (53.04%)	29 / 58 (50.00%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 58 (1.72%)	6 / 115 (5.22%)	0 / 58 (0.00%)
occurrences (all)	1	7	0
Laceration			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 58 (3.45%)	1 / 115 (0.87%)	2 / 58 (3.45%)
occurrences (all)	2	1	2
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	1 / 115 (0.87%) 1	4 / 58 (6.90%) 4
Headache subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5	10 / 115 (8.70%) 10	5 / 58 (8.62%) 5
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	5 / 115 (4.35%) 5	4 / 58 (6.90%) 4
Injection Site Reaction subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	4 / 115 (3.48%) 6	8 / 58 (13.79%) 25
Non-Cardiac Chest Pain subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 4	3 / 115 (2.61%) 3	0 / 58 (0.00%) 0
Oedema Peripheral subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	3 / 115 (2.61%) 3	0 / 58 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	5 / 115 (4.35%) 5	1 / 58 (1.72%) 1
Nausea subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	6 / 115 (5.22%) 6	3 / 58 (5.17%) 3
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 115 (2.61%) 4	1 / 58 (1.72%) 1
Skin and subcutaneous tissue disorders			
Dry Skin subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 115 (0.00%) 0	1 / 58 (1.72%) 1
Rash			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 115 (0.87%) 1	3 / 58 (5.17%) 3
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	2 / 115 (1.74%) 2	1 / 58 (1.72%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	8 / 115 (6.96%) 8	7 / 58 (12.07%) 8
Back Pain subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	5 / 115 (4.35%) 5	2 / 58 (3.45%) 2
Muscle Spasms subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	9 / 115 (7.83%) 9	3 / 58 (5.17%) 3
Musculoskeletal Pain subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	3 / 115 (2.61%) 3	0 / 58 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	7 / 115 (6.09%) 10	3 / 58 (5.17%) 3
Neck Pain subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	2 / 115 (1.74%) 2	0 / 58 (0.00%) 0
Osteoarthritis subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 115 (0.00%) 0	0 / 58 (0.00%) 0
Pain In Extremity subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	4 / 115 (3.48%) 4	3 / 58 (5.17%) 3
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 115 (0.87%) 1	1 / 58 (1.72%) 1
Influenza			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 115 (2.61%) 3	1 / 58 (1.72%) 1
Pharyngitis subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 115 (0.87%) 1	0 / 58 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	1 / 115 (0.87%) 1	0 / 58 (0.00%) 0
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5	4 / 115 (3.48%) 4	3 / 58 (5.17%) 5
Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	4 / 115 (3.48%) 4	4 / 58 (6.90%) 4
Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	10 / 115 (8.70%) 11	5 / 58 (8.62%) 7
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 115 (0.00%) 0	1 / 58 (1.72%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 115 (0.00%) 0	0 / 58 (0.00%) 0

<b>Non-serious adverse events</b>	Alirocumab 150 mg Q4W (After Placebo Q2W)	Alirocumab 150 mg Q4W (After Alirocumab 75 Q2W/Up150 Q2W)	Alirocumab 150 mg Q4W (After Alirocumab 150 Q4W/Up150 Q2W)
Total subjects affected by non-serious adverse events subjects affected / exposed	42 / 51 (82.35%)	71 / 106 (66.98%)	31 / 48 (64.58%)
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 6	14 / 106 (13.21%) 14	2 / 48 (4.17%) 3
Laceration			

subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	3 / 106 (2.83%) 4	0 / 48 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	8 / 106 (7.55%) 8	2 / 48 (4.17%) 2
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4  3 / 51 (5.88%) 4	5 / 106 (4.72%) 5  6 / 106 (5.66%) 8	4 / 48 (8.33%) 4  4 / 48 (8.33%) 4
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Injection Site Reaction subjects affected / exposed occurrences (all)  Non-Cardiac Chest Pain subjects affected / exposed occurrences (all)  Oedema Peripheral subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3  1 / 51 (1.96%) 3  6 / 51 (11.76%) 7  4 / 51 (7.84%) 4	7 / 106 (6.60%) 7  7 / 106 (6.60%) 12  5 / 106 (4.72%) 5  5 / 106 (4.72%) 5	3 / 48 (6.25%) 3  7 / 48 (14.58%) 37  1 / 48 (2.08%) 1  5 / 48 (10.42%) 5
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4  1 / 51 (1.96%) 1	11 / 106 (10.38%) 15  3 / 106 (2.83%) 3	2 / 48 (4.17%) 2  3 / 48 (6.25%) 4
Respiratory, thoracic and mediastinal disorders Cough			



subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 9	9 / 106 (8.49%) 11	1 / 48 (2.08%) 3
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	3 / 51 (5.88%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	0 / 51 (0.00%)	3 / 106 (2.83%)	1 / 48 (2.08%)
occurrences (all)	0	3	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 51 (1.96%)	7 / 106 (6.60%)	0 / 48 (0.00%)
occurrences (all)	1	7	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 51 (15.69%)	7 / 106 (6.60%)	3 / 48 (6.25%)
occurrences (all)	11	8	6
Back Pain			
subjects affected / exposed	4 / 51 (7.84%)	10 / 106 (9.43%)	7 / 48 (14.58%)
occurrences (all)	4	10	10
Muscle Spasms			
subjects affected / exposed	4 / 51 (7.84%)	4 / 106 (3.77%)	1 / 48 (2.08%)
occurrences (all)	6	4	1
Musculoskeletal Pain			
subjects affected / exposed	1 / 51 (1.96%)	6 / 106 (5.66%)	2 / 48 (4.17%)
occurrences (all)	1	6	2
Myalgia			
subjects affected / exposed	7 / 51 (13.73%)	6 / 106 (5.66%)	1 / 48 (2.08%)
occurrences (all)	8	7	2
Neck Pain			
subjects affected / exposed	3 / 51 (5.88%)	0 / 106 (0.00%)	0 / 48 (0.00%)
occurrences (all)	3	0	0
Osteoarthritis			
subjects affected / exposed	8 / 51 (15.69%)	7 / 106 (6.60%)	3 / 48 (6.25%)
occurrences (all)	9	10	3
Pain In Extremity			

subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	3 / 106 (2.83%) 3	1 / 48 (2.08%) 1
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 51 (5.88%)	4 / 106 (3.77%)	5 / 48 (10.42%)
occurrences (all)	5	5	8
Influenza			
subjects affected / exposed	3 / 51 (5.88%)	9 / 106 (8.49%)	4 / 48 (8.33%)
occurrences (all)	4	12	4
Pharyngitis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 106 (0.94%)	0 / 48 (0.00%)
occurrences (all)	3	1	0
Sinusitis			
subjects affected / exposed	3 / 51 (5.88%)	3 / 106 (2.83%)	1 / 48 (2.08%)
occurrences (all)	3	3	3
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 51 (13.73%)	8 / 106 (7.55%)	4 / 48 (8.33%)
occurrences (all)	11	9	4
Urinary Tract Infection			
subjects affected / exposed	4 / 51 (7.84%)	7 / 106 (6.60%)	5 / 48 (10.42%)
occurrences (all)	4	11	5
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 51 (9.80%)	16 / 106 (15.09%)	9 / 48 (18.75%)
occurrences (all)	5	25	11
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	5 / 51 (9.80%)	5 / 106 (4.72%)	1 / 48 (2.08%)
occurrences (all)	9	7	1
Hyperkalaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 106 (0.94%)	3 / 48 (6.25%)
occurrences (all)	1	1	3

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	-Changes were made to the exclusion criterion for consistency with the 2004 adult treatment panel (ATP) III guidelines. -Timing of the primary endpoint was changed (at Week 24, to be consistent with the rest of the phase 3 program). -Changes were made to the analysis of the primary and secondary endpoints (use of an ITT approach). -Added collection of measured LDL-C at Week 0 and Week 24.
25 August 2014	-Adjusted the list of key and other secondary efficacy endpoints and estimands (ITT estimand and on-treatment estimand). -Added time points (Week 9, Week 10 and Week 11) in the model for the primary efficacy analysis endpoint. -Specified sensitivity analyses to be performed on the primary efficacy endpoint.
08 July 2015	- Extended the duration of the open-label treatment period to Q2 2017 or until alirocumab was commercially available in the country. - Added a follow-up phone call for safety assessments 10 weeks after last IMP administration.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The systematic randomization error was not anticipated to have an impact on the power of the study. The sample size to detect a difference in efficacy endpoints was reached (it was increased to obtain additional safety data) and blind was maintained.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27625344>