Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy

Summary

EudraCT number	2011-005109-56
Trial protocol	SE GB AT CZ NL NO ES DK
Global end of trial date	05 December 2014

Results information

Result version number	v1
This version publication date	01 February 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	EFC12492

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01623115
WHO universal trial number (UTN)	U1111-1121-4275
Other trial identifiers	STUDY NAME: ODYSSEY FH I

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	15 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2014
Global end of trial reached?	Yes
Global end of trial date	05 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab (SAR236553/REGN727) as add-on therapy to stable maximally tolerated daily statin therapy with or without other lipid-modifying therapy (LMT) in comparison with placebo after 24 weeks of treatment in subjects with heterozygous familial hypercholesterolemia (heFH).

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

Actual start date of recruitment	13 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	South Africa: 91
Country: Number of subjects enrolled	Israel: 29

Country: Number of subjects enrolled	Russian Federation: 43
Country: Number of subjects enrolled	United States: 109
Worldwide total number of subjects	486
EEA total number of subjects	182

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	405
From 65 to 84 years	80
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 89 centers in 14 countries. A total of 597 subjects were screened between July 2012 and April 2013, 111 of whom were screen failures.

Pre-assignment

Screening details:

Randomization was stratified according to prior history of myocardial infarction or ischemic stroke, intensity of statin treatment and geographic region. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in 1:2 (placebo:alirocumab) after confirmation of selection criteria. 486 subjects were randomized.

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo for alirocumab every 2 weeks (Q2W) on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.

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

Dosage and administration details:

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

Arm title	Alirocumab 75/Up to 150 mg Q2W

Arm description:

Alirocumab 75 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks. Alirocumab dose up--titrated to 150 mg from Week 12 when LDL--C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553, REGN727
Other name	
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 auto-injector.

Number of subjects in period 1	Placebo	Alirocumab 75/Up to 150 mg Q2W
Started	163	323
Completed	1	6
Not completed	162	317
Subjects moved	-	3
Physician decision	1	-
Other than specified here	5	11
Consent withdrawn by subject	-	1
Randomized but not treated	-	1
Study drug auto-injector administration	-	1
Treatment ongoing	144	280
Adverse event	8	12
Poor compliance to protocol	4	8

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo for alirocumab every 2 weeks (Q2W) on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.	
Reporting group title	Alirocumab 75/Up to 150 mg Q2W
Reporting group description:	
Alirocumab 75 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks. Alirocumab dose up--titrated to 150 mg from Week 12 when LDL--C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.	

Reporting group values	Placebo	Alirocumab 75/Up to 150 mg Q2W	Total
Number of subjects	163	323	486
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 51.7 ± 12.3	 52.1 ± 12.9	 -
Gender categorical Units: Subjects			
Female	69	143	212
Male	94	180	274
Calculated LDL--C in mmol/L			
Calculated LDL-C from Friedewald formula			
Units: mmol/L arithmetic mean standard deviation	 3.739 ± 1.213	 3.749 ± 1.325	 -
Calculated LDL--C in mg/dL Units: mg/dL arithmetic mean standard deviation	 144.4 ± 46.8	 144.8 ± 51.1	 -

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo for alirocumab every 2 weeks (Q2W) on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.	
Reporting group title	Alirocumab 75/Up to 150 mg Q2W
Reporting group description:	
Alirocumab 75 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks. Alirocumab dose up--titrated to 150 mg from Week 12 when LDL--C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects exposed to placebo Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 59 weeks).	
Subject analysis set title	Alirocumab 75/Up to 150 mg Q2W
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects exposed to Alirocumab 75 mg/Up to 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 59 weeks).	

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	9.1 (± 2.2)	-48.8 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:	
Alirocumab group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-57.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.3
upper limit	-52.6

Notes:

[1] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	321		
Units: percent change				
least squares mean (standard error)	8.8 (± 2.2)	-49.3 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab 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	Placebo v Alirocumab 75/Up to 150 mg Q2W

Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-58.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.5
upper limit	-52.7

Notes:

[2] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	5.7 (± 2)	-43.5 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-49.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.9
upper limit	-44.5

Notes:

[3] - Threshold for significance was ≤ 0.05.

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

End point title	Percent Change From Baseline in Calculated LDL-C at Week 12 - On-Treatment Analysis

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	321		
Units: percent change				
least squares mean (standard error)	5.7 (± 2)	-43.9 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-49.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.2
upper limit	-44.8

Notes:

[4] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	309		
Units: percent change				
least squares mean (standard error)	4.7 (± 1.6)	-41.1 (± 1.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-45.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.8
upper limit	-41.8

Notes:

[5] - Threshold for significance was ≤ 0.05.

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

End point title	Percent Change From Baseline in Apo- B at Week 24 - On-Treatment Analysis

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	308		
Units: percent change				
least squares mean (standard error)	4.5 (± 1.7)	-41.4 (± 1.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-45.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.9
upper limit	-41.8

Notes:

[6] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	9.6 (± 2)	-42.8 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-52.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.2
upper limit	-47.6

Notes:

[7] - Threshold for significance was ≤ 0.05.

Secondary: Percent Change From Baseline in non-HDL-C at Week 24 - On-Treatment Analysis

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	321		
Units: percent change				
least squares mean (standard error)	9.4 (± 2)	-43.3 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-52.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.5
upper limit	-47.8

Notes:

[8] - Threshold for significance was ≤ 0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	7.3 (± 1.5)	-31.4 (± 1.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-38.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.4
upper limit	-35

Notes:

[9] - Threshold for significance was ≤ 0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	309		
Units: percent change				
least squares mean (standard error)	3.1 (± 1.5)	-34.5 (± 1.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-37.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.2
upper limit	-33.9

Notes:

[10] - Threshold for significance was ≤0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	5.3 (± 1.8)	-38.4 (± 1.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-43.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48
upper limit	-39.4

Notes:

[11] - Threshold for significance was ≤0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	4.1 (± 1.4)	-28.3 (± 1)		

Statistical analyses

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

Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-32.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.7
upper limit	-29.2

Notes:

[12] - Threshold for significance was ≤0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	9 (± 2.6)	-47.1 (± 1.9)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-56.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.4
upper limit	-50

Notes:

[13] - Threshold for significance was ≤ 0.05.

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percentage of subjects				
number (not applicable)	2.4	72.2		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	156

Confidence interval	
level	95 %
sides	2-sided
lower limit	48.9
upper limit	498.1

Notes:

[14] - Threshold for significance was ≤ 0.05.

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	321		
Units: percentage of subjects				
number (not applicable)	2.4	73		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	156.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	49.7
upper limit	493.7

Notes:

[15] - Threshold for significance was ≤ 0.05.

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

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

End point description:

Adjusted percentages at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment were included in the imputation model (ITT analysis). ITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percentage of subjects				
number (not applicable)	0.8	59.8		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	244.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.4
upper limit	1744.4

Notes:

[16] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	321		
Units: percentage of subjects				
number (not applicable)	0.8	60.1		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	240
Confidence interval	
level	95 %
sides	2-sided
lower limit	33.9
upper limit	1700.7

Notes:

[17] - Threshold for significance was ≤ 0.05.

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

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

	ITT Analysis

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
arithmetic mean (standard error)	-7.5 (± 2)	-25.2 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.6
upper limit	-12.9

Notes:

[18] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	0.8 (± 1.2)	8.8 (± 0.9)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	11

Notes:

[19] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
arithmetic mean (standard error)	6.3 (± 2.2)	-9.6 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	-10.6

Notes:

[20] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	309		
Units: percent change				
least squares mean (standard error)	0.3 (± 1)	5 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [21]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	7.2

Notes:

[21] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
arithmetic mean (standard error)	-3.9 (± 1.8)	-21.2 (± 1.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.5
upper limit	-13

Notes:

[22] - Threshold for significance was ≤ 0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
least squares mean (standard error)	2.1 (± 1.2)	6.4 (± 0.8)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0031 [23]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	7.2

Notes:

[23] - Threshold for significance was ≤0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	322		
Units: percent change				
arithmetic mean (standard error)	1.7 (± 2.2)	-8 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [24]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	-4.4

Notes:

[24] - Threshold for significance was ≤0.05.

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

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

End point values	Placebo	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	309		
Units: percent change				
least squares mean (standard error)	0.1 (± 1)	2.9 (± 0.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0187 [25]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	5.2

Notes:

[25] - Threshold for significance was ≤ 0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the primary completion date regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported adverse events and death are treatment-emergent that is AEs that developed/worsened and deaths that occurred during the 'treatment-emergent period' (from the first dose of double-blind IMP injection up to the day of the last dose of double-blind IMP injection +70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects exposed to placebo Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 59 weeks).

Reporting group title	Alirocumab 75/Up to 150 mg Q2W

Reporting group description:

Subjects exposed to Alirocumab 75 mg/Up to 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 59 weeks).

Serious adverse events	Placebo	Alirocumab 75/Up to 150 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 163 (9.20%)	39 / 322 (12.11%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acinic Cell Carcinoma Of Salivary Gland			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Neoplasm Of Thyroid Gland			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			

subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small Cell Lung Cancer Metastatic			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate Cancer Recurrent			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cancer Metastatic			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid Adenoma			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Stenosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous Fistula			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Gait Disturbance			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Miscarriage Of Partner			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy Of Partner			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International Normalised Ratio Increased			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Lumbar Puncture Syndrome			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			

subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 163 (0.00%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina Pectoris			
subjects affected / exposed	0 / 163 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 163 (0.61%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 163 (0.61%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			

subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 163 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 163 (0.61%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 163 (0.00%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Occlusion			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac Thrombus			

subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral Valve Incompetence			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular Extrasystoles			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 163 (0.61%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal Artery Embolism			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatitis Alcoholic			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema Nummular			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary Bladder Polyp			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 163 (0.61%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 163 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 163 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Fluid Retention			
subjects affected / exposed	1 / 163 (0.61%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Alirocumab 75/Up to 150 mg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 163 (28.22%)	94 / 322 (29.19%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 163 (5.52%)	13 / 322 (4.04%)	
occurrences (all)	9	18	
General disorders and administration site conditions			
Injection Site Reaction			
subjects affected / exposed	16 / 163 (9.82%)	38 / 322 (11.80%)	
occurrences (all)	53	112	
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 163 (4.91%)	19 / 322 (5.90%)	
occurrences (all)	9	20	
Nasopharyngitis			
subjects affected / exposed	11 / 163 (6.75%)	32 / 322 (9.94%)	
occurrences (all)	14	43	
Upper Respiratory Tract Infection			
subjects affected / exposed	11 / 163 (6.75%)	17 / 322 (5.28%)	
occurrences (all)	13	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2013	Change in reporting of adverse events: - Addition of neurological and ophthalmologic events in the list of adverse events of special interest (AESIs). - Addition of pregnancy of male subject's partner as an AESI with immediate notification to comply with an update in company procedures. - Safety reporting timelines were cahnged from "within 1 working day" to "within 24 hours" for serious adverse events and adverse events of special interest with immediate notification. - Change in the screening period duration and the window for the training visit. - Addition of information on a possible contingency strategy in the event the manufacturer faced any performance or supply issues of the auto-injector in order to ensure the continuity of the study treatment without interruption. - Clarification for some safety laboratory parameters. Red blood cell distribution width (RDW) and reticulocyte count added as hematology laboratory parameters. Reticulocyte count no longer assessed reflexively but rather systematically on all study samples. - Clarification was provided regarding the type of cardiovascular (CV) events to be submitted to the Clinical Events Committee (CEC) for adjudication. - Added a clarification on how to handle subjects randomized and not treated with the IMP. - Added information on the collection of family medical history. - Clarified the wording related to the possibility for a HeFH patient having completed the Double-blind treatment period to enter an open label extension (OLE).
26 February 2014	- Statistical section was changed. - Addition of the blinding procedures related to pharmacokinetic analysis. - Updated language on cardiovascular events to be reported to the CEC for adjudication and including a clarification on cerebrovascular events. - Added the following sentence "LDL-C was also be measured (via the beta-quantification method) at Week 0 and Week 24". - Updated language on collection of information on partner pregnancy as per other protocol in the ODYSSEY phase 3 program. - Updated language on how to record injection site reactions that were not related to study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: