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	

Results information

Result version number	v1
This version publication date	09 February 2017
First version publication date	09 February 2017

Trial information

Trial identification

Sponsor protocol code	EFC13786

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	Interim
Date of interim/final analysis	27 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by 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 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:

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)	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 screened between December, 2013 and May, 2014, of whom 233 subjects were randomized and 169 were screen failures. Screen failures were mainly due to exclusion criteria met.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Q2W

Arm description:

Placebo (for alirocumab) 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.

Arm title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)

Arm description:

Alirocumab 75 mg 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 ≥70 mg/dL (1.81 mmol/L) or ≥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.

Arm title	Alirocumab 150 mg Q4W/Up to 150 mg Q2W

Arm description:

Alirocumab 150 mg Q4W alternating with placebo (for alirocumab) Q4W 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 LDL-C levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥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

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Placebo (for alirocumab) 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 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 ≥70 mg/dL (1.81 mmol/L) or ≥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 Q4W alternating with placebo (for alirocumab) Q4W 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 LDL-C levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥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	63.1	62.5	64.2
standard deviation	± 10.7	± 9.9	± 10
Gender categorical			
Units: Subjects			
Female	27	47	29
Male	31	69	30
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

Reporting group values	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		
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) 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 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 ≥70 mg/dL (1.81 mmol/L) or ≥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 Q4W alternating with placebo (for alirocumab) Q4W 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 LDL-C levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline.	

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

Statistical analysis title	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 [1]
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

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 (± 2.1)	-55.3 (± 1.5)	-54.6 (± 2.1)	

Statistical analyses

Statistical analysis title	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 [2]
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

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 (± 2.5)	-50.8 (± 1.7)	-41.7 (± 2.4)	

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 [3]
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

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)	3.6 (± 2.3)	-51.5 (± 1.6)	-44.8 (± 2.3)	

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).

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 [4]
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

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)	-53.6 (± 1.4)	-52.3 (± 2)	

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 [5]
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

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)	3.6 (± 1.9)	-54.1 (± 1.3)	-55 (± 1.9)	

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).

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 [6]
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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM 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)	7.5 (± 2.1)	-39.7 (± 1.5)	-38.9 (± 2.2)	

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	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
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

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 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 [8]
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

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 [9]
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

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	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
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

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 [11]
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

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	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
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

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)	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
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 [13]
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 [14]
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

End point description:

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

High CV risk: 10-year fatal CVD risk SCORE ≥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

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

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
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
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

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 [16]
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

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 [17]
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

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 [18]
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

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

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 [19]
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

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 [20]
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

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

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

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

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)	2.6 (± 1.5)	5.9 (± 1.1)	7.6 (± 1.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the primary completion date (32 weeks) regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported AEs & deaths are treatment-emergent, i.e.,AEs developed/worsened & deaths that occurred "on-treatment" (from 1st dose of double-blind injection up to day of last dose[active or placebo depending on Q2W or Q4W regimen]+70 days or up to the day before the first injection in open-label extension period for subjects entering extension period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo Q2W

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 150 mg Q4W/Up to 150 mg Q2W

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 75 mg Q2W/Up to 150 mg Q2W (Calibrator)

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).

Serious adverse events	Placebo Q2W	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 58 (6.90%)	7 / 58 (12.07%)	6 / 115 (5.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	0 / 115 (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
Prostate Cancer			

subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	0 / 115 (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
Multiple Fractures			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	0 / 115 (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 disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
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 Arterial Occlusive Disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	0 / 115 (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 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	0 / 115 (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%)	1 / 58 (1.72%)	0 / 115 (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	1 / 58 (1.72%)	0 / 58 (0.00%)	0 / 115 (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
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
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 disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	0 / 115 (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
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	1 / 58 (1.72%)	0 / 115 (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
Epistaxis			

subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	0 / 115 (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			
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	0 / 115 (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
Infections and infestations			
Arthritis Bacterial			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 58 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo Q2W	Alirocumab 150 mg Q4W/Up to 150 mg Q2W	Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 58 (34.48%)	25 / 58 (43.10%)	51 / 115 (44.35%)
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	6 / 115 (5.22%)
occurrences (all)	1	0	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 58 (6.90%)	4 / 58 (6.90%)	1 / 115 (0.87%)
occurrences (all)	4	4	1
Headache			
subjects affected / exposed	3 / 58 (5.17%)	5 / 58 (8.62%)	10 / 115 (8.70%)
occurrences (all)	4	5	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 58 (0.00%)	4 / 58 (6.90%)	5 / 115 (4.35%)
occurrences (all)	0	4	5
Injection Site Reaction			
subjects affected / exposed	0 / 58 (0.00%)	8 / 58 (13.79%)	4 / 115 (3.48%)
occurrences (all)	0	25	6
Oedema Peripheral			
subjects affected / exposed	4 / 58 (6.90%)	0 / 58 (0.00%)	3 / 115 (2.61%)
occurrences (all)	4	0	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 58 (5.17%)	1 / 58 (1.72%)	5 / 115 (4.35%)
occurrences (all)	4	1	5
Nausea			
subjects affected / exposed	2 / 58 (3.45%)	3 / 58 (5.17%)	6 / 115 (5.22%)
occurrences (all)	2	3	6
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 58 (0.00%)	3 / 58 (5.17%)	1 / 115 (0.87%)
occurrences (all)	0	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 58 (3.45%)	7 / 58 (12.07%)	7 / 115 (6.09%)
occurrences (all)	2	8	7
Back Pain			

subjects affected / exposed	0 / 58 (0.00%)	2 / 58 (3.45%)	6 / 115 (5.22%)
occurrences (all)	0	2	6
Muscle Spasms			
subjects affected / exposed	0 / 58 (0.00%)	3 / 58 (5.17%)	8 / 115 (6.96%)
occurrences (all)	0	3	8
Myalgia			
subjects affected / exposed	3 / 58 (5.17%)	3 / 58 (5.17%)	7 / 115 (6.09%)
occurrences (all)	3	3	10
Pain In Extremity			
subjects affected / exposed	1 / 58 (1.72%)	3 / 58 (5.17%)	4 / 115 (3.48%)
occurrences (all)	1	3	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 58 (5.17%)	5 / 58 (8.62%)	10 / 115 (8.70%)
occurrences (all)	3	7	11
Urinary Tract Infection			
subjects affected / exposed	1 / 58 (1.72%)	4 / 58 (6.90%)	4 / 115 (3.48%)
occurrences (all)	1	4	4
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 58 (6.90%)	3 / 58 (5.17%)	4 / 115 (3.48%)
occurrences (all)	5	5	4

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.

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.

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:

Online references

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